

Bipolar Disorder

An Evidence-Based Clinical
Guide

Ives Cavalcante Passos
Michael Berk
Flavio Kapczinski
Editors



Springer

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We dedicate this book to our families, whose support has been instrumental in shaping our scientific careers. It is through their encouragement that we were able to pursue our work, and this book reflects the fruits of that effort.

Foreword

This book, entitled *Bipolar Disorder: An Evidence-Based Clinical Guide*, edited by Ives Cavalcante Passos, Michael Berk, and Flavio Kapczinski, is the most up-to-date and comprehensive book on bipolar disorder ever written. It is encyclopedic in scope, covering all aspects of this complex illness, including its comorbidities, pathophysiology, and treatment. It covers everything one would need to know about bipolar disorder (BD) in adults and points out many future treatment opportunities. It is a must-read for both clinicians and research investigators.

I would like to highlight several themes that recur in multiple chapters that require further emphasis and study. One would hope that the consistent call for earlier and more comprehensive clinical treatment intervention can be adopted as a new set of public health recommendations and actions that change the way patients in the community are routinely treated so that their long-term course of illness is vastly improved.

One of the most important themes is explicated by Lars Kessing (Chap. 9) on the clinical course and progression of the illness. He describes the literature indicating that bipolar disorder tends to be progressive, and that the number of episodes a person has experienced is associated with: (1) increased risk of recurrence, (2) reduced probability of recovery, (3) increased severity of episodes, (4) a lowered threshold for developing episodes, and (5) progression of cognitive deficits. Additionally, there is an increased risk of developing dementia in old age. There is much data supporting the notion that starting lithium after the first episode leads to superior outcomes compared to starting it later in the course of the illness, although this is rarely done. The scholarly Chaps. 10 and 19 on staging and on biological markers of illness progress also emphasize the importance of early recognition and treatment. These and other chapters make it clear that childhood-onset bipolar runs a more difficult course of illness both because of the early onset itself and the longer delay before receiving treatment.

Childhood-onset is associated with a more adverse course of illness than adult-onset illness. As Birmaher notes in Chap. 35: “In general, all analyses of the course of BD in youth show that worse prognosis is associated with early-onset, more severe illness (more recurrent and longer-lasting episodes, suicidality), presence of

comorbid disorders, poor adherence to treatment, history of physical or sexual abuse, low SES, more service utilization, family history of mania or substance abuse, and living in families with high ‘expressed emotion’ (high emotional over-involvement, critical comments, and hostility).”

This view is particularly important because bipolar disorder typically begins early, in childhood or adolescence. Multiple studies indicate that more than one-quarter of illness in adults in the USA begins before age 13, and in two-thirds of patients, it begins before age 19. This much higher incidence of early-onset illness in the USA than in Germany and the Netherlands (referred to here as Europe) appears related to an excess of both genetic and environmental vulnerability factors. Parents and grandparents of bipolar patients in the USA have more bipolar disorder and other psychiatric illnesses than those from Europe. Also, there is more psychosocial adversity in childhood (verbal, physical, and sexual abuse) in the USA, and each is associated with an earlier onset of bipolar disorder and a more adverse subsequent course of illness.

These findings are mirrored by Ives Cavalcante Passos in Chap. 5. He states, “Early trauma should always be considered and assessed in the clinical setting, whether to determine the risk of developing a mood disorder or to predict and prevent more severe progression of bipolar disorder. Because it is such a detrimental factor not only in the setting of bipolar disorder but for mental health in general, early trauma should be a priority target for intervention, once it is a modifiable factor.”

Thus, episodes of mood disorder themselves, childhood adversity, and bouts of substance abuse each contribute to illness progression and each, upon repetition, show greater behavioral effects or sensitization. These forms of sensitization seem to be mediated by epigenetic effects where events in the environment place chemical moieties on DNA, histones, and microRNA that can have long-lasting effects on what genes are turned on or off. In addition, many of these epigenetic changes in sperm and ova can survive after fertilization and convey vulnerability to episodes, stressors, and substance use to the next generation, even in the absence of contact with the parent.

Thus, there are multiple interactive pathways (from stressor episodes and substance abuse via genetics and epigenetics) that lead to early bipolar disorder and its myriads of problems in its trajectory into adulthood. These deserve to be formally identified as they pose immense, potentially lifelong medical and psychiatric problems. With these early episodes, there is delayed treatment leading to more severe and rapidly recurring episodes, the risk of substance abuse, disability, suicide, metabolic syndrome, a decade or more of loss of life expectancy, cognitive dysfunction, treatment resistance, and the risk of dementia in old age, as further explicated in Chaps. 9, 11, 12, 19, 23, and 35.

Childhood-onset bipolar needs to be viewed and treated as a medical emergency. What these multiple types of sensitization with their adverse outcomes mean is that the diagnosis of childhood-onset bipolar disorder should be treated as a medical emergency, with early and multiple treatment approaches, in an attempt to stave off the disastrous outcomes that so many suffer. Most of the authors of these chapters

have urged more treatment research for bipolar disorder in general and for childhood-onset disorder specifically, but to no avail. This lack of treatment research deserves further recognition and new public health, political, and advocacy efforts.

One of the bright spots is the wealth of positive data on psychotherapeutic approaches to early bipolar disorder. Chapter 33 by Miklowitz et al. on family-focused therapy (FFT) is particularly encouraging for the findings showing marked effects of FFT compared to treatment as usual in those with prodromal symptoms, especially in families with high expressed emotion. These positive data on FFT support the role of this therapy, along with related psychosocial interventions (Chaps. 29–32) and illness education, as essential components of early and longitudinal treatment of the illness. All too often these crucial treatment approaches are left out of the therapeutic paradigm.

Therapy and illness education appear as critical components of the expert clinic treatment shown in a randomized study to be more effective in preventing relapses than treatment as usual (TAU) in Denmark, where it is free and likely to be excellent. Notably, just 2 years of this expert clinic treatment resulted in a better outcome over the next 6 years, suggesting that patients learned to manage their illness better for the longer term and that early expert intervention can change the course of illness for the better. Pharmacotherapy, psychotherapy, symptom identification, and longitudinal mood charting appeared to be important aspects of the clinical program.

Engaging patients in the details of treatment and rigorous longitudinal assessments on some form of mood charting appears essential to a good treatment outcome. A form for patients to nightly chart their mood, sleep, medications, life events, side effects, and related comorbid symptoms is available at www.bipolarnews.org (click on Personal Calendar or Mood Chart). Many other computerized formats are available, and having patients use some form of mood charting is an invaluable tool in treatment assessment and revision (Chap. 38). Patients and physicians not having good feedback about the course of illness in bipolar disorder would be akin to not knowing one's blood pressure in the management of hypertension.

Chapter 20 by Kermamatian et al. provides a beautiful and systematic approach to the pharmacological treatment of mania, laying out the best initial options and then a series of sequential steps to eventually reach a good outcome. It is disappointing no such structured algorithm is offered by Birmaher et al. in Chap. 35 for children with early onset illness because the data to support such a crucial approach are lacking.

In the USA, the NIMH has the goal of early intervention in psychiatric illness as one of its stated programmatic ideals, but paradoxically has not supported or funded such important clinical treatment research for more than a decade. Instead, it has invested the bulk of its funding in genetics and molecular biology in an attempt to find the so-far non-existent magic bullet to treat the illness. This neglect of clinical treatment research is inexcusable, as there is a host of treatments for adult-onset illness (Chaps. 20–24), brought forth by the pharmaceutical industry and approved by the FDA, but there is virtually nothing on how to use these drugs to treat childhood-onset illness. Testing out well-tolerated existing drugs for adults for their

utility in heading off the adverse outcomes of childhood-onset bipolar illness would be relatively simple and inexpensive compared to the search for new agents. However, no such program exists because other priorities are touted by influential experts.

Childhood-onset bipolar disorder needs to be treated as a medical emergency and as a national and international disaster, and clinical treatment research on it is mandated by governmental agencies and private foundations around the world. Otherwise, the adverse trajectory outlined in so many of the chapters in this book will continue to destroy the lives of those in this and future generations.

Lithium is the acknowledged best treatment for heading off the progression of bipolar disorder (Kessing, Chap. 9 and Alda, Chap. 26) but is rarely used in adults in the USA and even more rarely in children. Children with early aspects of bipolar disorder, described by Birmaher (Chap. 35) as bipolar not otherwise specified (BP-NOS) and now as unspecified bipolar disorder (USBPD), are common, present levels of severity comparable to those with BP I or II, take longer to reach remission, and—depending on family history—about 50% convert to BP I or II after several years of follow-up. Likewise, prodromal symptoms are readily identified, but treatment approaches remain to be systematically delineated (Lorenzoni et al., Chap. 5). There is another subtype of BP-NOS/USBPD that requires extra vigilance to actively look for and recognize as preliminary data suggest that it has a series of atypical or unusual treatments.

This subtype was originally called Fear of Harm by Papolos et al. and is now called sleep and temperature dysregulation disorder (STDD). In addition to (1) extreme behavioral dyscontrol, one has to explicitly probe parents for (2) a history of marked sleep reluctance with horrific nightmares and (3) evidence of overheating manifest by red ears and/or red face. This STDD syndrome responds to mood stabilization with high doses of lithium along with attempts at cooling with clonidine and other peripheral cooling measures and then increasing doses of intranasal ketamine, which upon repetition further helps cooling, sleep disruption, and the severe behavioral dyscontrol. This STDD syndrome is typically poorly recognized, and children who are treated with more conventional methods most often are non-responsive and continue to suffer markedly. With this ongoing novel therapeutic approach to this atypical form of USBPD, children can have remarkable long-term therapeutic responses, but this approach needs to be further explored in controlled clinical trials.

Palma (Chap. 12) beautifully describes the comorbidities largely associated with the treatments of bipolar disorder, but what is also needed is the therapeutic approaches to the multiple comorbidities and syndromes associated with the illness itself, including anxiety disorders, substance abuse, ADHD, oppositional defiant disorder, OCD, PTSD, trichotillomania, and other habits. Berk et al. have pioneered the use of N-acetylcysteine (NAC) in mood and anxiety in bipolar patients, but NAC is also effective in a range of addictions including smoking, alcohol, stimulants, and marijuana, and habits, such as OCD, trichotillomania, non-suicidal self-injury, and the like. One potential linkage to the mechanism of action of NAC in so many diverse syndromes is its ability to decrease glutamate release in the nucleus

accumbens and striatal habit memory system. As revealed by Peter Kalivas, NAC among its many other actions increases the growth of glutamate transporters from striatal synapses into glial cells, allowing greater prefrontal cortical control over diverse illnesses and habits.

Another supplement that deserves further exploration in the early phases of bipolar disorder is acetyl-L-carnitine (LAC), which is low in the blood of patients with early-onset refractory unipolar depression and especially those with a history of childhood adversity. There are preliminary data on the antidepressant effects of LAC in patients and in the defeat stress animal model of depression, where it works faster than that of conventional antidepressants and may have a more extended duration of action. LAC appears to exert epigenetic effects in rapidly inducing the inhibitory presynaptic glutamate receptor mGluR-2 to decrease glutamate release. LAC also is an insulin receptor sensitizer, a mitochondrial enhancer that treats peripheral neuropathy, and has anti-nociceptive effects. Exploring the potential role of LAC in prodromal and early-onset bipolar illness, especially in the large group who have experienced child adversity, would appear to have a very high priority.

The potential role of L-methylfolate in these early manifestations of bipolar disorder likewise should be studied given its multiple rationales in adult depressed patients and its safety. All of the other available well-tolerated potential approaches to bipolar disorders in adults similarly deserve systematic study in prodromes and youngsters with early onset bipolar disorder. Not only does the FDA allow non-approved agents for the treatment of illness when there is a good rationale involved, but this investigator would encourage clinicians to make much wider use of off-label approaches. Given the complexity of bipolar disorder and the paucity of data on its systematic treatment especially in youngsters, it would appear that good medical treatment almost mandates the use of off-label agents. Careful assessment of how well a given treatment works for a given individual with good longitudinal monitoring provides a rational way of using and evaluating the effectiveness of unapproved agents. Response of an individual, particularly if confirmed in an off-on-off-on sequence or an unexpected extended period of wellness, should be included under the rubric of this volume as an “Evidenced-Based Clinical Guide.”

This is particularly the case for treatments such as rTMS, VNS, and ketamine that are or were originally only approved for unipolar depression, but not for bipolar disorder despite positive preliminary data. rTMS using 10 Hz stimulation (for about 25 min) over the dorsolateral prefrontal cortex is FDA-approved for unipolar depression and is now superseded by theta burst TMS (with equivalent effects with about 5 min of stimulation). When TBS is given 10 times a day for 5 days, using an fMRI-defined target location, it has remarkable effects in refractory unipolar depression. It is labeled accelerated intermittent theta burst (aiTBS) procedure. This system, called the Stanford accelerated intelligent neuromodulation therapy (SAINT), is FDA for unipolar depression but also works in bipolar depression. This has recently been confirmed in a randomized placebo-controlled study using similar parameters by Yvette Sheline et al., who saw huge effect sizes and a high remission rate in a small group of patients with refractory bipolar disorder. Hopefully, this form of aiTBS will soon be approved for bipolar patients. The same situation is

present for ketamine where intranasal esketamine is approved for unipolar but not bipolar depression despite very positive results in this population.

This book entitled “Bipolar Disorder: An Evidence-Based Clinical Guide” is a masterful compendium to understanding and treating bipolar illness. The expertise of all of its authors and their pointing out future directions hopefully will soon be applied to patients with bipolar disorder in such a way that the illness is no longer the pernicious and deadly one that it is now. There is an indirect lesson from the AIDS epidemic. AIDS used to be a death sentence, but with an enormous infusion of funding and research on early effective intervention, it is now a well-managed chronic illness with good long-term survival.

As currently treated or ignored, bipolar illness continues to be one of high recurrence, disability, impaired function, and potentially lethal via suicide or increased cardiovascular mortality. If dealt with properly, there is every reason to believe that the course of bipolar disorder could be vastly improved. An AIDS-type national and international initiative could similarly turn the tide for bipolar disorder.

Early identification and treatment are emphasized in almost every chapter in this book as a key to better outcomes. It remains to be seen how and whether the necessary funding and directed clinical treatment research can be accomplished. Congress mandated the 409(i) provision of the Best Pharmaceuticals for Children Act (BPCA). The provisions of this program need to be refocused on and mandated for childhood bipolar disorder along with the needed increase in funding allocation. There is a vast list of off-label drugs and supplements and already available FDA-approved drugs for adults that are expertly dealt with in this volume but need to be systematically studied in youngsters so that the treatment and early intervention of bipolar disorder in children goes from its current status as a guessing game to a set of empirically based recommendations.

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Robert M. Post

Preface

Bipolar disorder has a worldwide prevalence of about 2%, with subclinical variants affecting another 2% of the population. According to the World Health Organization, bipolar disorder is among the top 10 leading causes of disability-adjusted life years in young adults. Additionally, people with bipolar disorder die on average 10 years earlier, and the lifetime risk of suicide is estimated to be at least 20 times that of the general population. Consequently, bipolar disorder accounts for up to a quarter of all suicides. Although these findings illustrate the severity and complexity of this illness, we are living in exciting times in the field of bipolar disorder for several reasons.

First and foremost, over the last 25 years, novel and evidence-based pharmacological and psychosocial strategies have been added to the treatment algorithm of bipolar disorder. There are currently dozens of therapeutic strategies with particularities related to efficacy, safety, and tolerance, addressing different phases and stages of the disorder. Of note, clinicians have also observed a change in drug prescription patterns for bipolar disorder, with greater use of antipsychotics. At the same time, however, research emerged regarding the classical mood stabilizer lithium with compelling evidence of its anti-suicidal and neuroprotective effects. It is likely that lithium is the only true disease-modifying agent in psychiatry.

Second, several studies have addressed the natural history of the disease and shown that the course of bipolar disorder is heterogeneous. However, on average, the risk of recurrence increases with the number of previous episodes. In addition, data demonstrate that the number of previous episodes is associated with (1) increased duration and symptomatic severity of subsequent episodes; (2) increased risk of dementia over the long term; and (3) refractoriness to treatment. It is worth mentioning that patients with multiple episodes may present clinical progression also defined as neuroprogression.

Third, neuroscience has shed light on the molecular underpinnings of the potential decline in cognition and physical health that occurs in some people with bipolar disorder. Some studies have supported the theory that immune activation is a key component in driving the changes that take place in the brain and periphery. Moreover, recent neuroimaging consortiums have revealed the cortical and

subcortical changes associated with bipolar disorder, as well as their impact on neurocognition.

Fourth, bipolar disorder can also affect individuals in different stages of life. In children and adolescents, diagnosing bipolar disorder is a challenge due to its clinical heterogeneity and symptom overlap with other psychiatric disorders, such as attention-deficit/hyperactivity disorder and conduct disorder. Likewise, bipolar disorder in older adults is often misdiagnosed or underdiagnosed, leading to poor outcomes and increased morbidity and mortality. The treatment of bipolar disorder in older adults requires careful consideration of comorbid medical conditions, medication interactions, and age-related changes in pharmacokinetics and pharmacodynamics.

Lastly, new technologies and lifestyle approaches are gaining traction in the field of bipolar disorder. Smartphone apps and sensors have the potential to (1) enable digital interventions; (2) allow real-time collection of biological data; and (3) mitigate recall bias in clinical appointments by closely monitoring patients. Additionally, machine learning algorithms and big data have the potential to facilitate predictive psychiatry, an exciting new field where large datasets may allow us to predict clinical responses and outcomes, such as suicide attempts. Lifestyle approaches, now evidence based in depression, are gaining traction as an area of interest in bipolar disorder.

Bipolar disorder is a complex disease that requires specialized care for effective assessment and treatment. Much of the burden associated with this disorder can be mitigated by treatments guided by the best scientific evidence. In this regard, “Bipolar Disorder: An Evidence-Based Clinical Guide,” divided into six sections and totaling 41 chapters covering all relevant aspects of the disorder, will arm clinicians and researchers with the latest findings and refine the necessary skills to provide the best clinical care.

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Part I
The Natural History of Bipolar Disorder

Chapter 1

Historical Roots of Bipolar Disorder



Ives Cavalcante Passos, Pedro Kazlauckas Lucas, Aline Zimmerman, Kyara Rodrigues de Aguiar, Thiago Henrique Roza, Nicole Goulart Saviatto, Isabela Vanni, Augusto Ossamu Shintani, and Flavio Kapczinski

1.1 Introduction

The history of bipolar disorder is intertwined with the broader history of psychiatry and medicine. This chapter traces the evolution of our understanding of this complex and often debilitating condition, from its earliest descriptions in ancient texts to its modern conceptualization as a distinct psychiatric disorder. The journey through time reveals not only the changing perceptions of bipolar disorder but also the development of medical and psychological theories that have shaped current treatment approaches. By examining the historical roots of bipolar

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disorder, we gain valuable insights into how past ideas have influenced contemporary practice.

In ancient times, conditions that we now recognize as forms of bipolar disorder were often interpreted through the lens of supernatural or religious beliefs. Early references to mood disorders can be found in the writings of Hippocrates, who proposed the foundational idea of the humoral theory to explain both physical and mental illnesses. The notions of “melancholia” and “mania” were described as consequences of imbalances in the bodily humors, particularly black and yellow bile [1]. Galen refined and significantly expanded this theory, popularizing it across the Roman Empire and establishing it as a cornerstone of medical practice for many centuries [1].

As medical knowledge advanced, the concept that would eventually evolve into what we now call bipolar disorder began to take shape. Physicians such as Aretaeus of Cappadocia and later, psychiatrists like Emil Kraepelin, played pivotal roles in refining the definitions and classifications of mood disorders. Aretaeus showed that mania and melancholia can occur in the same person over time [2]. Kraepelin, in turn, is credited with distinguishing manic-depressive insanity from schizophrenia, a major milestone that contributed to the recognition of this condition as a distinct clinical entity [3]. His work highlighted the episodic nature of the disorder, which remains a key feature in its diagnosis today.

The twentieth century saw significant progress in the treatment of bipolar disorder, with the introduction of lithium therapy representing a breakthrough in the field [4]. This period witnessed the ongoing debate over the nature of mood disorders, including discussions on the differentiation between unipolar and bipolar depression [5] and condition’s heterogeneity [6, 7]. The contributions of various researchers during this time helped shape the diagnostic criteria currently used in clinical practice, offering a more nuanced understanding of the disorder’s manifestations and course.

Nowadays, bipolar disorder is recognized as a multifaceted condition with complex etiologies involving genetic, neurobiological, and environmental factors. The primary objective of this chapter is to provide a comprehensive overview of the historical developments that have led to our current understanding of bipolar disorder, highlighting key figures, theories, and treatments that have influenced the field. By reflecting on the past, this chapter aims to emphasize the importance of historical knowledge in informing contemporary and future practices. Figure 1.1 highlights the key contributions of scholars in the historical evolution of the concept of bipolar disorder.

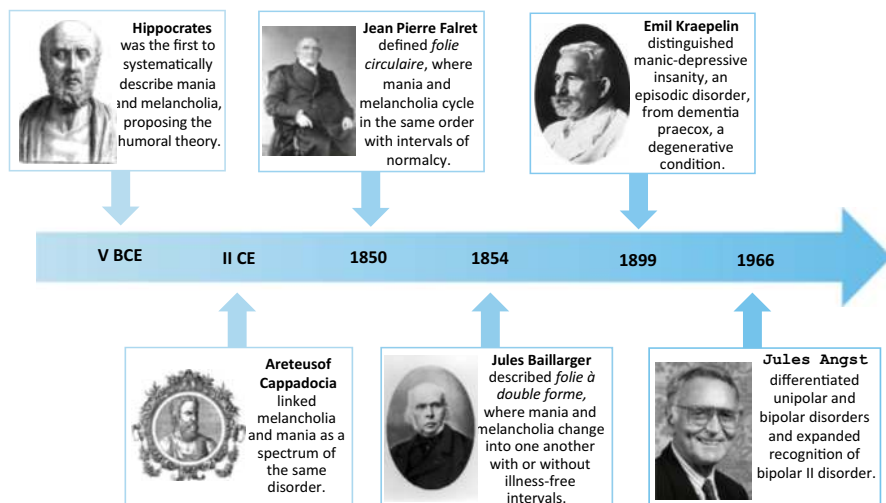


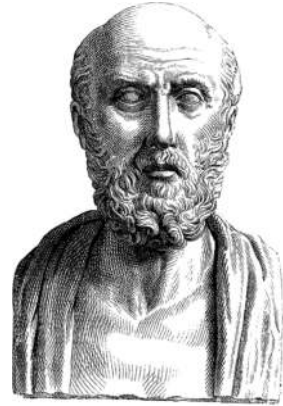
Fig. 1.1 Historical evolution of the concept of bipolar disorder

1.2 Hippocrates (Fifth Century BCE)

Before Hippocrates, the prevailing belief was that madness was caused by divine intervention, viewed as a punishment imposed on humans. However, in the fifth century BCE, supernatural beliefs and notions of possession were challenged by Greek medical writings that sought to understand mental illness from a biological perspective. Hippocratic texts, especially in his famous work “On the Sacred Disease,” conceptualized sickness in naturalistic terms.

The people ought to know that the brain is the sole origin of pleasures and joys, laughter and jests, sadness and worry as well as dysphoria and crying. Through the brain we can think, see, hear, and differentiate between feeling ashamed, good, bad, happy.... Through the brain we become insane, enraged, we develop anxiety and fears, which can come in the night or during the day, we suffer from sleeplessness, we make mistakes and have unfounded worries, we lose the ability to recognize reality, we become apathetic and we cannot participate in social life.... We suffer all those mentioned above through the brain when it is ill....[8].

Hippocrates (Fig. 1.2) and his contemporaries were among the first to describe melancholia (“melas” = black, and “cholé” = bile) and behavioral conditions that might now be recognized as hypomania, mania, and mixed states [9]. Mania and melancholia are two of the earliest documented human diseases, although in a broader way than in current definitions. They attributed the melancholic state, as well as other disorders such as dysentery and skin rashes, to an excess of black bile, one of the four basic humors described by the author (blood, black bile, yellow bile, and phlegm) [10]. According to Hippocrates, these states were clinically characterized by several symptoms, above all fear and sadness.

Fig. 1.2 Hippocrates

And by the same organ we become mad and delirious, and fears and terrors assail us, some by night, and some by day, and dreams and untimely wanderings, and cares that are not suitable, and ignorance of present circumstances, desuetude, and unskillfulness. All these things we endure from the brain, when it is not healthy, but is more hot, more cold, more moist, or more dry than natural, or when it suffers any other preternatural and unusual affection. And we become mad from its humidity...[11].

Hippocrates had a keen interest in mental and behavioral conditions and developed an early classification, categorizing them as melancholia, mania, and paranoia [12]. The humoral theory proposed by him was further refined by Galen of Pergamon. It was Aretaeus of Cappadocia, however, who strongly and systematically linked melancholia and mania as a spectrum of the same disorder [9].

1.3 Galen of Pergamon (Second Century CE)

Galen of Pergamon (Fig. 1.3), born in the ancient Greek city of Pergamon (modern-day Bergama, Turkey), was one of the most influential physicians and philosophers of antiquity. Trained in the medical schools of Pergamon, Smyrna, and Alexandria, Galen later became the personal physician to several Roman emperors in Rome. His work expanded on the Hippocratic tradition, particularly through the refinement of the humoral theory, which posited that the balance of four bodily humors—blood, phlegm, yellow bile, and black bile—was essential for both physical health and temperament. Galen's systematic approach provided a comprehensive framework that linked physiological processes with psychological conditions. The balance of the four basic humors was believed to influence personality traits or temperament types (sanguine [pleasure-seeking, sociable], melancholic [analytical, thoughtful], choleric [ambitious, assertive], and phlegmatic [restrained, quiet]). Traditionally, melancholia was associated with an excess or maldistribution of black bile and mania with the influence of yellow or black bile [1].

Fig. 1.3 Galen of Pergamon



In his treatises, particularly *On the Natural Faculties* and *On Temperaments*, Galen detailed how imbalances in these humors could lead to specific temperaments and illnesses. His descriptions of melancholia and mania, though not fully aligned with modern definitions, highlight an early recognition of mood variability linked to biological factors. By conceptualizing these states as part of a broader humoral imbalance, Galen influenced later medical theories that sought to understand the biological underpinnings of mood disorders.

1.4 Aretaeus of Cappadocia (Second Century CE)

Aretaeus of Cappadocia (Fig. 1.4) is widely regarded as one of the most prominent physicians in Greco-Roman ancient times, after Hippocrates, who strongly influenced him. He was born in Cappadocia, Asia Minor (modern-day Turkey), and studied medicine in Alexandria, developing his practice in Rome. Aretaeus of

Fig. 1.4 Aretaeus of Cappadocia



Cappadocia was a follower of the “Pneumatic School,” which was based on principles that considered the characteristics of the basic elements (cold, heat, dry, and wet), as well as the role of the pneuma (air), as causal elements of diseases [2, 13, 14]. He produced two treatises that remained unknown until the sixteenth century, “*De causis et signis morborum acutorum et diuturnorum*” (“On the causes and symptoms of acute and chronic diseases”) and “*De curatione morborum acutorum et diuturnorum*” (“On the cure of acute and chronic diseases”), each one composed of four books [13, 14]. His work is characterized by a vivid and detailed portrayal of several medical conditions, including asthma, celiac disease, pneumonia, paraplegia, tetanus, epilepsy, gout, and diabetes, among others [2, 13].

Aretaeus of Cappadocia also made significant contributions to the fields of mental health. Although conditions such as hysteria, melancholy, mania, and phrenitis had been identified and described before his time, Aretaeus further advanced psychiatric nosology and clinical observation, distinguishing some mental disorders from nervous diseases [2, 14]. Notably, he provided a detailed description of mania and melancholy, linking both conditions as part of a larger entity, which could be interpreted as the same condition, hence the roots of the concept of bipolar disorder are often associated with him [15, 16]. Aretaeus described melancholy as a “lowness of spirits” connected to mania, stating, “it seems to me that melancholia is the beginning and a part of mania,” and “in most of them [melancholics] the depressed mood remits after a variable period of time and hedonia arises, then they develop a mania.” He also described melancholy as a chronic condition marked by the possibility of recurrence [2, 15]. As for mania, he described it as “madness, derangement of mind,” which could take several forms in terms of manifestations. He described that “those who have formerly been mad are more prone to melancholy,”

writing that after the remission of mania, a patient could face an important period of melancholy [2].

According to Aretaeus, mania and melancholy shared a similar etiology, with both originating in the “black bile,” an explanation that was connected to the humoral theory commonly accepted at his time. In addition, according to his view, mania was a more severe form of melancholy “If the brain is also affected, then the melancholia increases and becomes mania” [15]. His interpretation can also be seen as a biological explanation of mental disorders, mainly considering the connection of these conditions with the brain [15, 16].

In his writings, Aretaeus associated specific personality traits with the risk of developing mania or melancholy, also connecting some seasons of the year with an increased chance of recurrence of the conditions. Among the characteristics of melancholy, Aretaeus described loss of appetite, fearfulness, sleep problems, and tiredness in the mornings, whereas in cases of mania, he observed increases in sexual behavior, aggression, disinhibition, hallucinations, and problematic patterns of alcohol consumption. He also associated a desire to die with melancholic states. It is worth mentioning that his concepts of melancholia and mania were broader than the modern concepts: depression, psychotic depression, schizoaffective disorders, mixed states, schizophrenia with affective symptomatology, and some organic psychoses were involved [12]. Aretaeus provided detailed behavioral descriptions of mania in chap. VI of his book “*On the Causes and Symptoms of Acute and Chronic Diseases*”:

Some patients with mania are cheerful, they laugh, play, dance day and night, they stroll in the market, sometimes with a garland on the head, as if they had been winner in a game: these patients do not bring worries to their relatives. But others fly into a rage.... The manifestations of mania are countless. Some manics, who are intelligent and well educated, are dealing with astronomy, although they never studied it, with philosophy, but autodidactically, they consider poetry as a gift of muses [12].

This passage reflects his observation of the diverse presentations of mania, from euphoric and creative states to irritable and aggressive episodes. Interestingly, Aretaeus of Cappadocia also wrote about the connection between love and melancholy in chap. V of the same book:

It has been reported about a man who had been assumed to suffer from an incurable melancholia, and the physicians were not able to help him. But the love of a young girl was able to cure him. In my opinion he was always in love with her but because he thought that she did not have any interest in him he became dysphoric and sad, so that he suffered from melancholia. But he did not express his feelings to the girl. When he did so, and the girl responded, his sadness, dysphoria and anger disappeared and he became happy. In this sense love was the physician [8].

1.5 Alexander of Tralles (c. 525–605 CE)

Alexander of Tralles was a Byzantine physician who lived in the sixth century CE. His major work, the *Therapeutics* (*Therapeutica*), was composed in the first half of the sixth century, possibly in Rome, where he spent much of his life [17]. During the Roman and Late Antiquity, melancholia acquired a narrower interpretation. While some physicians made a sharp distinction between mania and melancholia, there was also a gradual or inclusive perspective [18]. This inclusive perspective is to be found in Alexander of Tralles (c. 575), who observed that mania and melancholia could occur in cycles with mixed features [19]. On the cyclicity of mania and melancholia, Alexander of Tralles held that manics “present intervals and attacks such as occur in fevers that recur periodically.” The word attack, originally used to describe attacks of fever, has become commonly used in psychiatry to describe crises or episodes of mental health disorders. Similarly, the terms remission and intermission, coined to describe the course of fevers, are of common use in psychiatry [20]. In line with Aretaeus of Cappadocia, Alexander wrote on the link between mania and melancholia: “the mania is nothing more than an exaggeration of the melancholic state that leads to extreme wildness” [18]. In his work, he recognized an increased risk of suicide associated with what he may well have conceived as a single disorder [19, 21].

1.6 Théophile Bonet (1620–1689)

After Alexander of Tralles, some advances were made in understanding mood disorders, particularly within the Islamic Golden Age. Persian and Arabic scholars like Avicenna and Razes expanded upon the medical knowledge of ancient Greece and Rome, recognizing melancholia and mania as interconnected states. The concept of a continuum between these states gained traction, with prominent figures such as the European physician Théophile Bonet (Fig. 1.5) introducing terms like “*maniacomelancholicus*” to describe what may have been early interpretations of bipolar disorder. These contributions laid important groundwork for the more refined psychiatric theories that emerged in the eighteenth century.

Fig. 1.5 Théophile Bonet

1.7 Andrés Piquer-Arrufat (1711–1772)

Piquer-Arrufat (Fig. 1.6), a renowned Spanish physician, served as the principal physician to King Ferdinand VI and vice president of the Academy of Medicine in Madrid. His eclectic approach integrated traditional humoral theories with emerging neurophysiological concepts, emphasizing the importance of clinical observation and the longitudinal course of illnesses [22]. His 1759 manuscript showed the term “melancholic-manic illness” (*affectio melancholico-maniaca*). Piquer also viewed melancholia and mania as expressions of the same disorder. “Melancholia and mania are terms denoting a single disease accompanied by several disorders of mood. When the sick mind is moved by fear and sadness, we name this melancholia, and when it is by rage and audacity, mania” [23]. He also identified mixed states, seasonality, and rapid cycling, aligning with modern descriptions of bipolar disorder. Piquer was among the early proponents of the brain “damage” as an etiological factor, shifting away from humoral theories and emphasizing patient-centered care through careful clinical observation.

Fig. 1.6 Andrés Piquer-Arrufat



1.8 Johann Heinroth (1773–1843)

Johann Christian August Heinroth (Fig. 1.7) was a German psychiatrist, known as the first professor of “Mental Medicine” in the Western world, at the University of Leipzig [24]. He devoted his life to studying the complex interaction between mental illness and moral character, mostly influenced by his Protestant Christian faith [25, 26]. In his practice, he found it necessary to analyze his patients’ physical well-being, social situation, sanitary conditions, and religious life, as he believed that all those factors had an influence on the development of a mental disorder [27]. However, the most important factor, according to him, was religious life. He stated that the more a person doubted God or became weak in their belief, or if the patient had a wrongly conducted life and sinned, the more susceptible they would become to suffer from a mental illness [25, 28].

Regarding bipolar disorder, Heinroth was the first modern psychiatrist to systematically describe mixed states [29]. In his book published in 1818, “*Textbook of mental disorders or mental disorders and their treatment*” (*Lehrbuch der Störungen des Seelenlebens oder der Seelenstörungen und ihrer Behandlung*), Heinroth organized mental disorders into three primary categories: exaltations (*hyperthymias*),

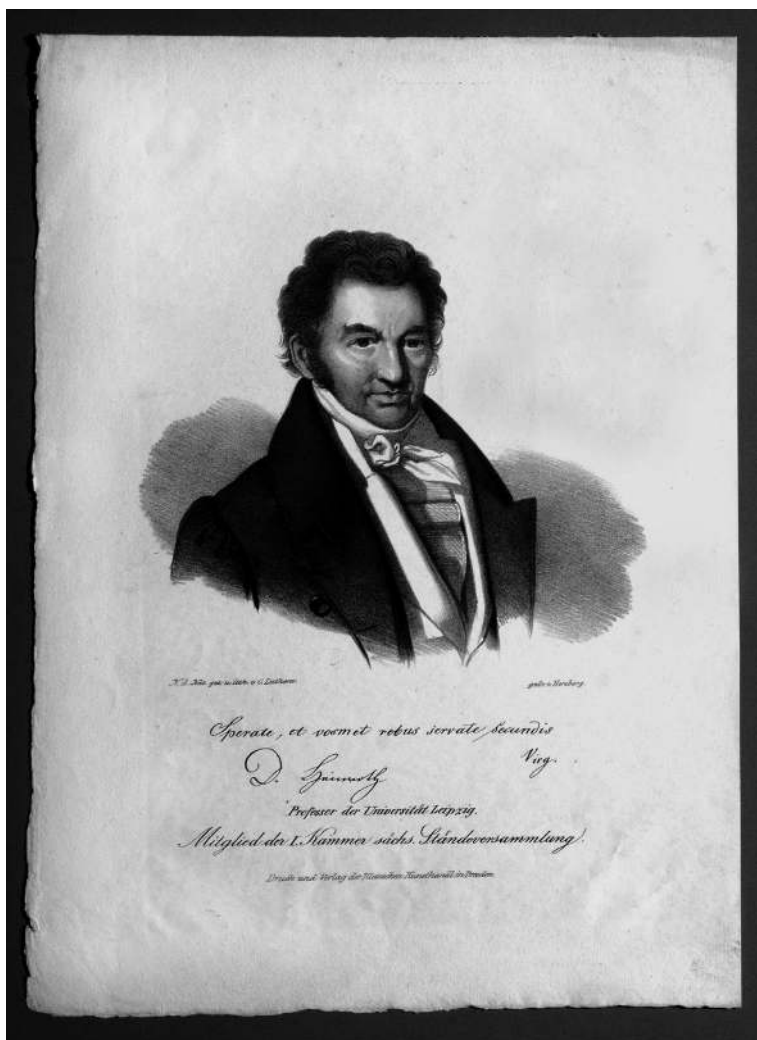


Fig. 1.7 Johann Heinroth

depressions (*asthenias*), and mixed states, which he termed hyper-asthenias [30]. Heinroth used the German word *Mischung*, meaning mixture, to describe these mixed states, which he further subdivided into three groups: “mixed mood disorders” (*animi morbi complicati*), “mixed mental disorders” (*morbi mentis mixti*), and “mixed volition disorders” (*morbi voluntatis mixti*), as shown in Table 1.1. In the categories “mixed mood disorders” and “mixed volition disorders,” one can observe conditions that align with what we now recognize as mixed affective and schizoaffective disorders according to modern definitions.

Table 1.1 A mixture of exaltation and depression according to Heinroth, 1818

<i>First group: Mixed mood disorders (animi morbi complicati)</i>
1. Ecstasis melancholica
2. Melancholia moria
3. Melancholica furens
4. Melancholia mixta catholica
<i>Second group: Mixed mental disorders (morbi mentis mixti)</i>
1. Paranoia anoa
2. Paranoia anomala
3. Paranoia anomala maniaca
4. Paranoia anomala catholica
<i>Third group: Mixed volition disorders (morbi voluntatis mixti, athymia)</i>
1. Panphobia, melancholia hypochondriaca
2. Athymia melancholica
3. Athymia paranoia
4. Athymia melancholico-maniaca

1.9 Ernst Albrecht von Zeller (1804–1877)

As the understanding of mood disorders continued to evolve, German psychiatrists like Ernst Albrecht von Zeller and Wilhelm Griesinger emerged, offering new perspectives that emphasized the concept of a unitary illness with clinical progression. Ernst Albrecht von Zeller was a German psychiatrist noted for his contributions to the early development of the concept of “unitary psychosis” (*Einheitspsychose*) [31]. He based his ideas on the work of the Belgian psychiatrist Joseph Guislain, whose book he translated into German. von Zeller’s efforts helped shape the understanding of mental illnesses in the nineteenth century, advocating the notion that various psychiatric conditions stem from a single underlying disorder [32]. He perceived various stages of insanity, typically starting with melancholia, later progressing to mania, followed by paranoia, and finally leading to dementia.

1.10 Wilhelm Griesinger (1817–1868)

Building on von Zeller’s ideas, Wilhelm Griesinger (Fig. 1.8), a pioneering figure in modern psychiatry, further developed the concept of unitary psychosis. However, he did not share Zeller’s beliefs about the nature of the human soul or character and its influence on madness. As a somaticist, he is often regarded as one of the founders of materialist psychiatry. Griesinger, who briefly worked with von Zeller in Württemberg, published his most influential work, *Pathologie und Therapie der psychischen Krankheiten* (“Pathology and Therapy of Mental Disorders”), in 1845. In this work, he postulated that all forms of major mental illnesses originated from a single disease process, with the brain being the organ invariably affected.

Fig. 1.8 Wilhelm Griesinger



Insanity itself, an anomalous condition of the faculties of knowledge and of will, is only a symptom; our classification of the group of mental diseases proceeds upon the symptomatological method. The first step towards a knowledge of the symptoms is their locality—to which organ the indications of the disease belong? What organ must necessarily and invariably be diseased where there is madness? Physiological and pathological facts show us that this organ can only be the brain [33].

In his book, he also divided mental diseases into three categories: mental depression states (*psychische Depressionszustände*), mental exaltation states (*psychische Exaltationszustände*), and mental weakness states (*psychische Schwächezustände*). Griesinger separated depression or melancholia from exaltation or mania and considered them different manifestations of a single disease process, noting that transitions between these states are quite common [12, 33]. He also described the so-called mid-forms (*Mittelformen*) “in which a change from depression in the manic exaltation occurs.” Griesinger described mixed states of melancholia and excitation as well as rapid cycling forms. He was the first to use the word “cycle” to describe these conditions, noting that “not rarely the whole disease consists of a cycle of both forms (mania and melancholia) which often regularly alternate with each other” [12]. He also described the seasonal pattern associated to the condition: “other observers and ourselves have seen cases where at a particular season a profound

melancholia supervenes and this in spring passes into mania, which again in autumn gradually sinks into melancholia.”

This view aligns with his concept of specific manifestations of a single psychosis, as postulated before by Ernst, rather than considering a discrete manic-depressive syndrome. He later reported that many cases of melancholia and mania develop into states of “mental weakness” (*psychische Schwächezustände*), suggesting that the prognosis and outcome were often unfavorable [12].

1.11 Jean-Pierre Falret (1794–1870)

Significant contributions to the modern concept of bipolar disorder were made in France. These developments took place during the mid-nineteenth century, particularly through the work of Jean-Pierre Falret and Jules Baillarger, whose competing theories marked a pivotal moment in psychiatric history.

Although ancient physicians and earlier psychiatrists recognized symptoms of mood disorders, they did not view bipolar disorder as a distinct entity. It was Jean-Pierre Falret (Fig. 1.9), a pupil of Esquirol, who first proposed this idea at La

Fig. 1.9 Jean-Pierre Falret



Salpêtrière Hospital in Paris. Falret described, in a short manuscript published in the *Gazette des Hôpitaux* (*De la folie circulaire ou forme de maladie mentale caractérisée par l'alternative régulière de la manie et de la mélancholie*) and based on lectures given in 1850 at the Salpêtrière Hospital, a condition characterized by the alternation and recurrence of episodes of melancholia and mania [16, 34, 35]. He named the condition *folie circulaire*, also known as circular insanity [15, 34]. Later, he developed more on the concept, describing that the condition also included periods of stability between the cycles of mania and depression, with this period free of symptoms (which could vary significantly in terms of duration) being an integral part of the psychopathological description of the condition [16, 35]. Jean-Pierre Falret completed his concept in the following 3 years, and published it in 1854 in the *Leçons cliniques de médecine mentale faites à l'hospice de la Salpêtrière*. Karl Kahlbaum highlighted that Griesinger's observations were pivotal in shaping Jean-Pierre Falret's concept of *folie circulaire*.

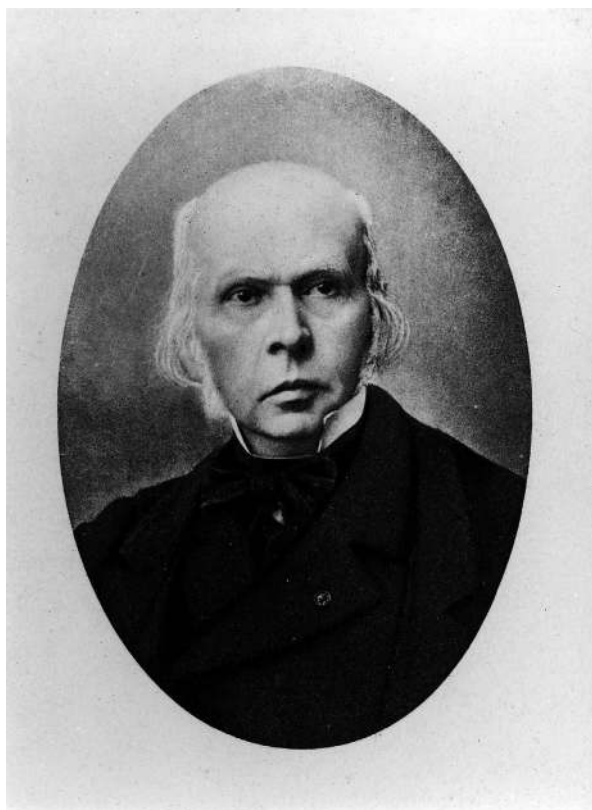
In other of his works, Falret raised the hypothesis that the condition could have a hereditary risk, also writing an important monograph about suicide and being an advocate for psychological treatments [16, 35]. In addition, he wrote on the potential forensic aspects associated with circular insanity, the importance of prognostic assessments, and the hopes that one day an effective pharmacological treatment would be found for the condition [35]. Nonetheless, Falret also made several restrictions in the clinical characteristics and course of circular insanity, writing that mania and melancholia “have to alternate for a long time, in always the same order with a relatively short interval of normalcy,” also not considering periods of mixed mood presentations [36].

1.12 Jules Baillarger (1809–1890)

On January 31, 1854, Jules Baillarger (Fig. 1.10) delivered a lecture to the *Académie Impériale de Médecine* describing a similar clinical presentation, naming it as *la folie à double forme*, also known as the insanity of double form [37]. He reported that the condition was marked by sudden or progressive changes in mental state, varying between excitation and depression. According to this description, periods of stability without the presence of symptoms could be present in the *folie à double forme*, but it was not always the case.

Immediately after Baillarger's presentation, Falret protested, claiming he had already published a description of the same disorder, called *folie circulaire*.

At our last meeting, our honorable colleague, Dr. Baillarger, read a paper on a new type of insanity [*la folie à double-forme*]. I must tell you, Gentlemen, that to me this type of insanity is not new. I have been aware of it for a long time, and for more than 10 years. I have described it in my lectures at the Salpêtrière. Many similar cases have been presented by the students there and discussed in our clinical seminars. We even gave it a name because, in our opinion, it is not a mere variant but a genuine form of mental illness. We call it circular insanity [*la folie circulaire*] because the unfortunate patients afflicted with this illness live

Fig. 1.10 Jules Baillarger

out their lives in a perpetual circle of depression and manic excitement interrupted by a period of lucidity, which is typically brief but occasionally long lasting [35].

Falret presented his lecture to the Academy on February 14. Baillarger accused Falret of using the two-week interval between their presentations to incorporate key elements of *folie à double forme* into his concept of *folie circulaire*. Falret showed considerable restraint in the dispute, whereas Baillarger persisted in repeating and elaborating on his accusations throughout his life. A thorough review of the available printed materials establishes Falret's clear precedence, indicating that the descriptions of *la folie circulaire* and *la folie à double forme* differ significantly, with Falret's description being closer to our current understanding of bipolar disorder [38].

Both concepts (*la folie circulaire* and *la folie à double-forme*) rapidly gained international attention, being well-accepted in several countries in Europe, as well as in the USA, and also receiving other similar names over the years [15, 16]. In spite of this controversy, according to Andreas Marneros and Jules Angst, "the conclusions drawn by the two very different, hostile "fathers" of the concept of bipolar disorders vary considerably: Baillarger assumed a type of disease in which mania and melancholia change into one another but the interval is of no meaning. In

contrast, Falret involved the interval between the manic and the melancholic episode in his concept; even episodes of mania and melancholia separated by a long interval belong together, forming the *folie circulaire*.” [12].

1.13 Louis-Victor Marcé (1828–1865)

Louis-Victor Marcé made significant contributions to psychiatry, particularly with his 1858 monograph on perinatal mental disorders in women [39] and his 1862 textbook on general psychiatry [39–41]. He served as *médecin-adjoint* to Jules Baillarger and Jacques-Joseph Moreau at a *maison de santé* in Ivry-sur-Seine. Marcé’s work anticipated the risks of depression during pregnancy and postpartum psychoses, pioneering the study of perinatal psychiatric disorders. Marcé’s clinical observations advanced the understanding of bipolar disorder, particularly its heterogeneity. He noted that individuals often alternated between periods of excitement and depression, but these shifts were not always extreme enough for a diagnosis of mania or melancholia. His insights contributed to the current understanding of bipolar disorder type II, recognizing that these mood changes could go unnoticed as personality quirks. He also emphasized that the intensity of agitation and depression do not always correlate, complicating diagnosis.

What is infinitely more common is to see excitation and depression without going into manic or melancholic episodes. They simply constitute differences in levels of intellectual activities to the point where the illness can go unrecognized and can be seen for long periods of time as simple bizarreness of character... One could be tempted to suppose but should not believe that there is always a perfect correlation between the intensity of the agitation and the intensity of depression. I have seen a melancholic episode with profound stupor followed by a period of excitation, characterized only by intellectual overactivity. In a similar way that a manic or excitation episode can be mild and yet correspond to a profound period of stupor, a very short manic episode can be followed by a very long melancholic episode.

In simple terms, Marcé highlighted that symptoms of excitement and depression can vary widely in intensity and duration and do not always follow a predictable pattern or present classically, making the diagnosis and understanding of these disorders more complex than clinicians of his time anticipated.

1.14 Karl Ludwig Kahlbaum (1828–1899)

Karl Ludwig Kahlbaum was a German psychiatrist known for his contributions to the classification of mental disorders and the constant attempt to link psychiatric conditions to neuropathology [42, 43]. He believed that a diagnosis in psychiatry implied that an illness had a specific etiology, set of symptoms, course, and prognosis [44]. Furthermore, Kahlbaum also emphasized the importance of considering, in addition to signs and symptoms, the assessment of the course of an illness and

longitudinal observations when making a psychiatric diagnosis. Additionally, he was a pioneer in describing catatonia (or tension insanity or, in German, *die Katatonie oder das Spannungsirresein*) [45] relating it with affective disorders, alcoholism, epilepsy, malaria, and tuberculosis [46, 47]. He also observed that similar clinical presentations do not necessarily share the same etiology, course, or outcome and emphasized efforts to differentiate organic versus functional disorders. Concerning bipolar disorder, Kahlbaum introduced the concept of cyclothymia as a relatively benign form of circular insanity. He grouped cyclothymia with dysthymia and hyperthymia as “partial mental disorder” (*partielle Seelenstörungen*) with “non-degenerative outcome.” His work later influenced Emil Kraepelin, as Kraepelin expanded Kahlbaum’s concept of cyclothymia to include cases with single manic or depressive episodes [48]. Karl Kahlbaum is also considered the first modern psychiatrist to identify schizoaffective disorders as a distinct category, referring to it as “*vesania typica circularis*” in his book [49].

1.15 Emil Kraepelin (1856–1926)

One of the most renowned psychiatrists of the last century, Emil Kraepelin (Fig. 1.11), was born in a small town in Germany in the late nineteenth century. He came from a humble but inspiring background: his father was a music teacher, and his brother was a biologist. It is easy to understand where his passion for the arts and sciences came from, leading him to study medicine and changing how we see mental disorders [50]. Kraepelin’s academic journey began at Leipzig and Würzburg, where he received his medical degree. After moving to Munich and becoming a psychiatrist, Kraepelin moved back to Leipzig, where he met the famous psychologist Wilhelm Wundt and started working on experiments in his lab. In Wundt’s laboratory, Kraepelin worked on skills in empirical research, studying the effects of drugs, alcohol, and fatigue on psychological functioning [51]. His focus on research was so extensive that Kraepelin had to sacrifice his clinical position temporarily, but this period was crucial in shaping Kraepelin’s scientific rigor and dedication [52].

Kraepelin’s main contribution to psychiatry is his work in diagnosing mental disorders. He was always interested in observing patients, their symptoms, and the course of their psychiatric illnesses, which led to him noticing that those previously considered different psychotic conditions had similarities and were not necessarily different conditions [53]. In the first edition of his textbook (1883), he proposed that mania and periodic insanity “are simply manifestations of a single pathological process... certain basic traits are found consistently, even though there are many external differences” [28]. The turning point for his career came during his tenure at the University of Dorpat in Estonia, where he began to document the course and outcomes of psychiatric conditions systematically. His textbook, which Kraepelin initially wrote to raise money for his marriage, had nine editions between 1883 and 1926 and laid the foundation for modern psychiatry by emphasizing diagnosis based on clinical observation [28].

Fig. 1.11 Emil Kraepelin

Kraepelin's ideas continued to evolve at the University of Heidelberg, where he published his textbook's second and third editions. By the fourth edition in 1893, Kraepelin had begun to outline his concept of manic-depressive insanity, categorizing melancholia and mania as part of a more extensive illness he termed "periodic insanity." The most critical edition of Kraepelin's textbook was the sixth, where he differentiated two psychoses: "manic-depressive insanity," an episodic disorder, and "dementia praecox," a progressive disease causing brain function impairment. His contributions to the understanding, diagnosis, and prognosis of manic-depressive illness were significant. However, merging unipolar and bipolar forms into a single concept of manic-depressive insanity and including all affective disorders under this umbrella was later seen as a regression. It was only with the contributions of Karl Leonhard, Jules Angst, Carlo Perris, and George Winokur that bipolar and unipolar were recognized as separate conditions.

In 1903, Kraepelin moved to Munich, where he became a professor of psychiatry and established the German Research Institute of Psychiatry. This institute became a hub for research, attracting figures such as Alois Alzheimer, who

discovered Alzheimer’s disease [52]. Kraepelin’s work on manic-depressive insanity continued to evolve, and in the eighth edition of his textbook, he detailed various subtypes and syndromes within the disorder. He also wrote about the concept of “mixed states,” underlining the complexity and variability of the illness. Kraepelin first introduced the term “*Mischzustände*” (mixed states) in the fifth edition of his textbook in 1896, although, already in 1893, he had described the “manic stupor.” By the sixth edition, in 1899, he had nearly completed their theoretical framework. His final categorization and naming came in the eighth edition in 1913, solidifying his contributions to understanding mixed states within bipolar disorder. Table 1.2 presents the development of Kraepelin’s concept of mixed states [12].

Kraepelin wrote the following about his belief that various abnormal mood states were manifestations of a single pathological process:

In the course of years, I have become more and more convinced that all [abnormal mood states] represent manifestations of a single morbid process, and that all the morbid forms... not only pass over the one into the other without recognizable boundaries, but...replace each other in one and the same [patient]...It is fundamentally and practically impossible to keep apart in any consistent way simple, periodic and circular cases; everywhere there are transitions [54, 55].

The Diagnostic and Statistical Manual of Mental Disorders (DSM), the diagnostic classification method clinicians use today, owes to Kraepelin’s methodical and systematic approach to diagnosing mental illnesses [56]. Kraepelin was an empiricist and considered the founder of phenomenological psychiatry [52].

Table 1.2 The evolution of Kraepelin’s concept of mixed states

1893	1899	1904	1913
1. “Manic stupor”(manischer stupor)	1. “Manic state with inhibition” (manische Zustände mit Hemmung) 2. “Depressive states with excitation” (depressive Zustände mit Erregung)	1. “Furious mania” (zornige Manie) 2. “Depressive excitation” (depressive Hemmung) 3. “Unproductive mania with thought poverty” (unproduktive gedankenarme Manie) 4. “Manic stupor” (manischer stupor) 5. “Depression with flight of ideas” (depression mit Ideenflucht) 6. “Manic inhibition” (manische Hemmung)	1. “Depressive or anxious mania” (depressive oder ängstliche Manie) 2. “Excited depression” (erregte depression) 3. “Mania with thought poverty” (ideenarme Manie) 4. “Manic stupor” (manischer stupor) 5. “Depression with flight of ideas” (ideenflüchtige depression) 6. “Inhibited mania” (gehemmte Manie)

1.16 Karl Leonhard (1904–1988)

Karl Leonhard, born in Germany, was a psychiatrist known for his contributions to expanding Kraepelin's dual theory. His work added a layer of complexity to the field. Leonhard was the sixth of eleven children, and his father was a protestant minister [57]. Leonhard thrived during a period of significant scientific and medical advancements, collaborating with renowned psychiatrists like Karl Kleist and Carl Wernicke. After earning his medical degree from the University of Munich in 1928, he worked as a physician in psychiatric hospitals. Karl Kleist then invited him to help develop a complex nosology of psychotic illnesses [58].

In the middle of the twentieth century, while working as a professor at the University of Berlin and later at the Charité, Leonhard focused on the nuances of bipolar disorder. He observed that the disorder was not a singular entity but a spectrum of conditions with varying presentations and courses [57]. This led him to propose a more detailed classification system for bipolar disorders, which he outlined in his work "*Classification of Endogenous Psychoses and their Differentiated Etiology*" in 1957. Leonhard's classification allowed mood disorders also to include other psychotic disorders previously unclassified. He introduced the concept of "cycloid psychoses," a group of episodic mental illnesses characterized by rapid shifts in mood and behavior. This concept helped bridge the gap between mood disorders and schizophrenia by creating a highly differentiated classification system for endogenous psychoses. He did that by studying patients for over 60 years, conducting long-term and family studies, and creating subtypes based on observable or elicitable signs [59].

Karl Leonhard supported the distinction between monopolar and bipolar mood disorders, observing that a family history of psychotic illnesses and depression had different associations with bipolar mood disorders [60]. Subsequent studies identified several differences, including earlier onset age in bipolar disorder compared to major depression, a nearly equal sex-risk ratio in bipolar disorder (as opposed to a higher prevalence in women for unipolar depression), and shorter duration of episodes and cycles between recurrences in bipolar disorder [61].

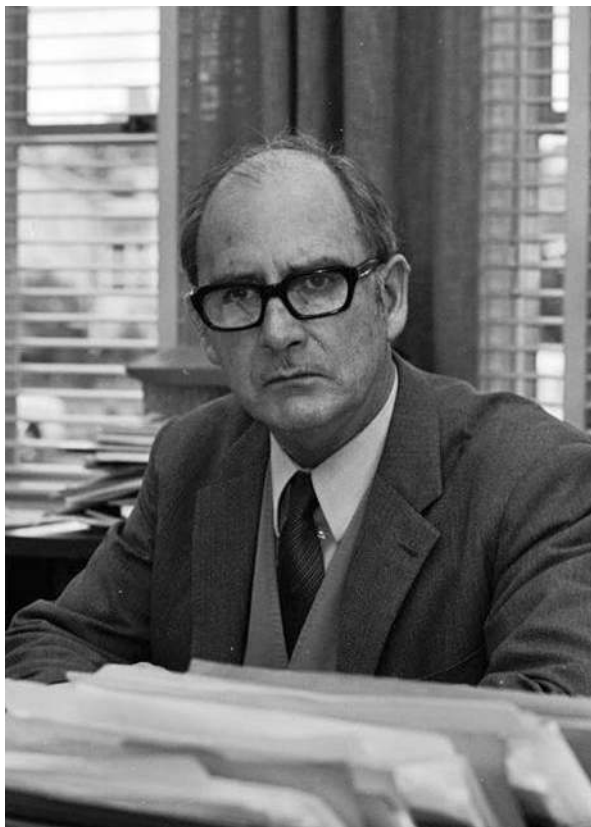
Despite his innovative ideas, Leonhard's work initially faced skepticism. At the time, the psychiatric community was still significantly influenced by psychoanalytic theories, and his biological approach was not widely accepted. However, overtime, the empirical strength of his research and the clarity of his classifications gained recognition. The contributions of Leonhard, along with Jules Angst, Carlo Perris, and George Winokur, led to the broad acceptance of the concept of bipolar disorder by the late 1960s. By 1980, the DSM officially included the terms of bipolar and mania [60].

1.17 John Cade (1912–1980)

The acceptance of bipolar disorder as a distinct clinical entity was significantly influenced by the discovery of lithium and its specific efficacy for treating the condition [28]. It all started with John Cade (Fig. 1.12), an Australian psychiatrist who fought in World War II and became a prisoner of war at Changi Prison from 1942 to 1945. Just a few years later, in 1948, while working as a psychiatrist, he observed a link between hyperthyroidism symptoms and manic symptoms, which led him to question whether the origin of manic-depressive illness could be related to endocrine dysfunctions [62].

He started a series of experiments injecting the urine of patients with depression and mania intraperitoneally into guinea pigs. He discovered that the urine of manic patients caused significantly higher mortality in the guinea pigs compared to the urine of other patients, suggesting the presence of a toxic substance. After further experiments, he hypothesized that elevated uric acid in the urine might be the reason for the increased toxicity. At that time, lithium was used to treat excess uric acid in the blood, leading Cade to consider it as a potential treatment for mania [62, 63].

Fig. 1.12 John Cade



But before trying it on patients, following the principles of Hippocrate's "*primum non nocere*" (first, do no harm), Cade tested lithium on himself to ensure the safety of the method. After confirming the absence of toxicity in himself, he began studying its effects on patients [62].

In 1949, Cade began treating patients with lithium and reported a case series of ten manic patients in which he achieved excellent results. His findings were published in an article in *The Medical Journal of Australia*, entitled "Lithium salts in the treatment of psychotic excitement." One notable case was described as follows:

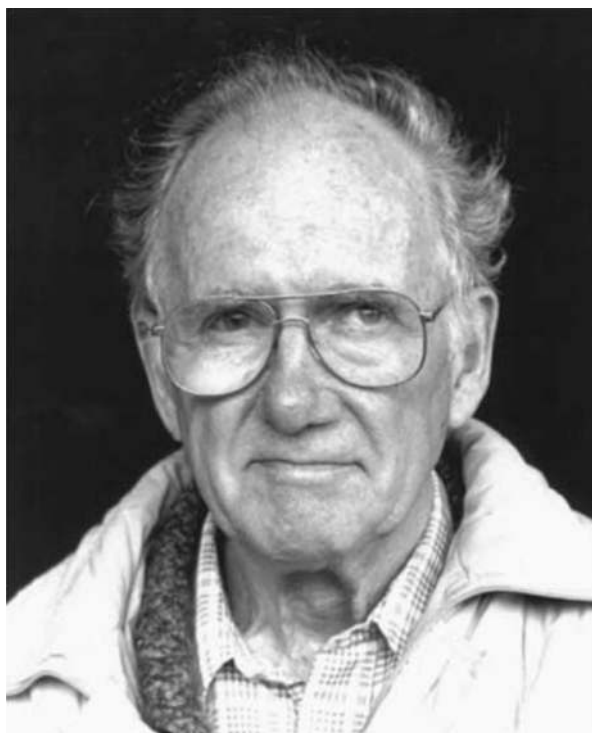
W.B., fifty-one years old, in a chronic manic state for five years, restless, dirty, destructive, mischievous, and interfering, had long been regarded as the most troublesome patient in the ward... From the start of the treatment on March 29, 1948, with lithium citrate, he steadily settled down and in three weeks was enjoying the unaccustomed surroundings of the convalescent ward... He was soon back working happily at his old job...[4].

Despite the excellent results in this case series, Cade's paper initially went unnoticed. This was due to several factors, including cases of toxicity and even deaths associated with lithium use, the greater interest and rise of new neuroleptic drugs, and skepticism among many psychiatrists about trusting a simple substance to treat such a complex condition as bipolar disorder. However, after a gap of several years, other clinical trials with lithium were conducted and produced similar results to Cade's study. Cade later defined this phenomenon as the "pharmacological rehabilitation of lithium" [62].

1.18 Mogens Schou (1918–2005)

The resurgence of lithium in psychiatric treatment can be traced back to the pivotal double-blind, placebo-controlled trial conducted in 1954 by Danish psychiatrist Mogens Schou (Fig. 1.13) and his colleagues [64]. This study marked the beginning of Schou's distinguished association with lithium. In the 1960s, he demonstrated that long-term lithium use could effectively prevent recurrences in bipolar disorder. From that point forward, Schou became a resolute advocate for lithium, engaging in numerous debates with critics who denied its prophylactic effects, often relying on speculative rather than empirical arguments. In response to these criticisms, Schou undertook a seven-year, placebo-controlled trial that confirmed lithium's prophylactic efficacy. His research earned him numerous accolades, though he once remarked that, for him, "every single patient whose life was changed radically by lithium outweighs honors and awards" [65].

Lithium salts became widely used in the mid-1960s and remained the only treatment for bipolar patients until the efficacy of valproate was demonstrated in the mid-1990s [62]. Today, lithium remains the gold standard for the maintenance treatment of bipolar disorder, despite the discovery of many other effective medications [66]. In addition to his dedication to lithium, Schou was receptive to the later introduction of new treatments, including antiepileptics and antipsychotics, recognizing the necessity of expanding the therapeutic options available to patients [65].

Fig. 1.13 Mogens Schou

1.19 Jules Angst (1926-)

Jules Angst (Fig. 1.14), a prominent Swiss psychiatrist, has made important contributions to the understanding of mood disorders, particularly bipolar disorder. In 1966, the “rebirth” of bipolar disorders was marked by Angst’s monograph, *Zur Ätiologie und Nosologie Endogener Depressiver Psychosen* (On the Aetiology and Nosology of Endogenous Depressive Psychoses) [5], which, along with Carlo Perris’s work, independently supported the differentiation between unipolar and bipolar disorders. Angst’s study at the University Hospital of Zurich, involving 326 patients treated between 1959 and 1963, led to key conclusions that have influenced the field. Among the significant findings of this study was the observation that, while there is a relationship between female gender and endogenous depression, bipolar disorders are equally represented in males and females. Additionally, Angst’s work showed that manic-depressive illness is not nosologically homogeneous, as unipolar depression differs significantly from bipolar disorders in genetics, gender, course, and premorbid personality. Furthermore, late-onset depression (Kraepelin’s “Involutionmelancholie”) seems to belong to unipolar depression, with only a weak relationship to bipolar disorders.

His research also has shaped the conceptualization of the bipolar spectrum, notably expanding the recognition of bipolar II disorder and the epidemiology of

Fig. 1.14 Jules Angst

hypomania. Angst's Zurich Cohort Study was pivotal in identifying a much higher prevalence of hypomania than previously thought, demonstrating that many individuals with brief hypomanic episodes (lasting 1–3 days) were frequently underdiagnosed [7]. His work challenged earlier rigid diagnostic categories, advocating for a broader definition of bipolarity that includes subthreshold symptoms and soft bipolarity, a concept that encompasses milder forms of the disorder like cyclothymia [67]. Angst's findings not only brought attention to the bipolar spectrum but also emphasized the importance of considering the longitudinal course of mood disorders in both clinical and research settings. His work further advanced the understanding of bipolar II disorder, a condition first distinguished from bipolar I by Dunner and colleagues in 1976 [68]. This distinction, along with Angst's findings, underscored the continuum of bipolar manifestations, from subthreshold hypomanic symptoms to more severe manic episodes, influencing the modern approach to diagnosis and treatment.

In addition to his work on the bipolar spectrum, Jules Angst also played a role in highlighting the importance of comorbidities in bipolar disorder, particularly with conditions such as anxiety disorders, substance abuse, and suicidality. His research showed that individuals with bipolar II disorder and hypomania often experience a

high degree of comorbidity with these issues, complicating both diagnosis and treatment. Angst's longitudinal studies further underscored the heterogeneity of bipolar disorder, demonstrating that many patients transition between different mood states over time, which reinforced the need for flexible and dynamic treatment approaches. His emphasis on the long-term observation of patients has been instrumental in guiding modern therapeutic strategies and diagnostic refinements, ensuring that the full range of mood disorders is addressed in clinical practice.

1.20 Contemporary Evolution

The historical journey of understanding bipolar disorder has been marked by significant milestones, each contributing to the contemporary conceptualization of this complex condition. As we reflect on this evolution, it becomes clear that the advancements in our understanding of bipolar disorder are deeply rooted in the meticulous observations and theories proposed by early scholars. These foundational ideas have laid the groundwork for modern research, which now benefits from longitudinal studies, randomized clinical trials, sophisticated technologies, and new methodologies that were unimaginable in earlier eras.

One of the most important contributions to the understanding of bipolar disorder in recent decades has been the advent of longitudinal studies. These studies have allowed researchers to track the progression of the disorder overtime, providing invaluable insights into its natural course. Jules Angst significantly expanded the understanding of the bipolar spectrum, particularly with his Zurich Cohort Study, which revealed a higher prevalence of hypomania, bipolar II disorder, and the link to suicidality. He emphasized the importance of comorbidities like anxiety and substance abuse in bipolar disorder and advocated for a broader diagnostic approach, including subthreshold symptoms and "soft bipolarity." His longitudinal research highlighted the dynamic nature of mood disorders, influencing both diagnosis and treatment strategies. Similarly, Lars Vedel Kessing's nationwide register-based studies in Denmark provided crucial insights into the progression of bipolar disorder. His work demonstrated that with an increasing number of affective episodes, there is a heightened risk of recurrence as well as an elevated risk of developing dementia [69–71]. Kessing's research also showed that lithium treatment may have protective effects against dementia, further illustrating the complex clinical progression of the disorder and offering a more nuanced understanding of its long-term impact [72]. These longitudinal and population-based studies have provided a deeper understanding of the heterogeneity and clinical course of bipolar disorder, shaping current approaches to diagnosis and management. Prodromal symptoms of bipolar disorder have been investigated in recent years as well [73, 74].

In parallel with these longitudinal studies, advances in neuroimaging have revolutionized our understanding of the biological underpinnings of bipolar disorder. The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA)

consortium has played a pivotal role in this area. By pooling data from numerous studies across the globe, ENIGMA has been able to identify consistent brain structure abnormalities in individuals with bipolar disorder. For example, the consortium has revealed volumetric reductions in subcortical brain regions such as the hippocampus, amygdala, and thalamus, as well as enlargement of the lateral ventricles [75]. Later on, the same group found that individuals with bipolar disorder also exhibit cortical gray matter thinning in the frontal, temporal, and parietal regions, with the most significant effects observed in the left pars opercularis, fusiform gyrus, and rostral middle frontal cortex. Moreover, the duration of illness was associated with reduced cortical thickness, and various commonly prescribed medications, such as lithium and antipsychotics, showed significant associations with cortical structure, highlighting the complexity of the disorder's neurobiological impact [76].

In addition to these epidemiological and neuroimaging advancements, Robert M. Post's contributions to the neurobiological understanding of bipolar disorder have been pivotal in elucidating the disorder's progression and recurrence patterns. His *kindling hypothesis*, introduced in 1992, proposed that mood episodes, initially triggered by external stressors, may overtime become autonomously generated due to neurobiological changes. This concept has been crucial in understanding the progression and recurrence of affective episodes, such as mania and depression, suggesting that repeated episodes may lower the threshold for future occurrences and increase treatment resistance [77]. Post's work on episode sensitization has significantly influenced modern approaches to early intervention, neuroprogression [78], and staging [79, 80] in bipolar disorder.

Kay Redfield Jamison has also played an important role in shaping the modern understanding of bipolar disorder. As both a clinical psychologist and an individual diagnosed with the condition, Jamison has combined her professional expertise and personal experience to advocate for a broader understanding of bipolarity and reduce the stigma surrounding mental illness. Her 1995 memoir, *An Unquiet Mind* [81], brought bipolar disorder to the forefront of public awareness, while her academic work, including co-authoring *Manic-Depressive Illness* with Frederick Goodwin [61], provided a comprehensive clinical perspective on the condition. Jamison has been a vocal advocate for viewing the potential positive aspects of bipolar disorder, such as heightened creativity, urging professionals to manage the condition without suppressing these traits [82]. Her efforts have significantly advanced the public discourse on bipolar disorder, advocating for a balanced and destigmatized understanding of the illness, and her work remains influential in both academic and public spheres [83].

In recent years, significant progress has been made in the treatment of bipolar disorder, guided by comprehensive guidelines [84, 85]. These guidelines have synthesized the growing body of evidence from randomized clinical trials to provide clinicians with evidence-based recommendations that consider both efficacy and safety across the lifespan. They emphasize a hierarchical approach to treatment, categorizing interventions into lines of treatment according to the evidence level and safety/tolerability. The guidelines also highlight the importance of personalized

treatment strategies, recommending combination therapies or adjustments based on patient history, comorbidities, and treatment response. As the treatment landscape continues to evolve, these guidelines serve as a critical tool for clinicians navigating the complexities of bipolar disorder management. Network meta-analyses have enriched this field by offering a comparative assessment of multiple pharmacological interventions [86]. These analyses allow for a more nuanced understanding of efficacy and tolerability, enabling clinicians to make more informed, individualized treatment decisions.

As we look to the future, integrating machine learning and big data into bipolar disorder research holds great promise [87]. These technologies have the potential to transform the field by enabling the prediction of illness onset [88], the identification of individuals at high risk for unfavorable outcomes such as suicide attempts, and the customization of treatment plans based on individual patient profiles [89]. By analyzing large datasets, machine learning algorithms can uncover patterns and associations that would be impossible to detect through traditional research methods, paving the way for a new era of precision psychiatry.

In conclusion, the contemporary evolution of bipolar disorder research reflects a dynamic interplay between historical insights and cutting-edge scientific advancements. As we continue to unravel the complexities of this disorder, the integration of longitudinal studies, neuroimaging, staging models, machine learning, and collaborative efforts promises to enhance our understanding and improve outcomes for those affected by bipolar disorder. While this chapter has focused on a select group of scholars and their pivotal contributions to the modern conceptualization of bipolar disorder, it is important to acknowledge that many others have also provided valuable insights. Due to space constraints, we have limited our discussion to these key figures and theories, which represent critical milestones in the evolution of our understanding of bipolar disorder and serve as the foundation for contemporary psychiatric practice.

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Chapter 2

Creativity in Bipolar Disorder at the Nexus of Art, Science, Outreach, and the Clinic



David G. Angeler

2.1 Introduction

Bipolar disorder is an affective disorder marked by substantial emotional instability. Mood swings occur as recurrent cycles of (hypo)mania and depression episodes, punctuated by periods of remission. Symptoms are differentiated among patients, and depression and (hypo)mania symptoms often co-occur in so-called mixed states. The rising global prevalence of bipolar disorder, particularly among adolescents and young adults [1], poses societal challenges. This trend, which is shaping the human potential of future generations, underscores the urgency of addressing these issues. Estimated economic costs due to dysfunction and inability are already now substantial, exemplified by annual per-patient expenses totaling ca. \$36,000 in the United States [2] and ca. £15,000 in the United Kingdom [3]. These numbers are projected to increase with the worldwide demise of mental ill health [4], let alone the costs associated with the substantial suffering of patients and their families.

Despite these trends inspiring pessimism for humanity's future, there is reason to believe that bipolar disorder also has beneficial facets that ultimately enrich societies. This chapter will discuss the frequently unprecedented role of creativity associated with bipolar disorder (bipolar creativity) that has shaped the arts, science, politics, and philosophy [5]. The discussion unfolds within a holistic framework, highlighting bipolar creativity at the intersection of various areas of human inquiry such as the arts, sciences, and philosophy. The chapter also considers practical

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pursuits, such as mental health outreach and clinical applications. Adopting an “eclectic approach” [6], the conversation embraces an ecosystem perspective, rooted in the emerging transdisciplinary Convergence Mental Health paradigm [7]. This approach examines bipolar creativity as a function of interacting processes operating within and across multiple scales, from neurological to social-ecological factors [8–10].

Building on a Convergence Mental Health approach, I will first briefly review the link between art, creativity, and bipolar disorder. Next, I will discuss the commonly accepted genetic trait-based, deterministic view of creativity and its limitations. To address these, I will present a more comprehensive, process-oriented perspective of bipolar creativity. This perspective, rooted in a Whiteheadian process ontology, will consider the complex interplay of a plethora of interacting individual, social, and ecological factors. This consideration allows for a holistic study of indeterminate bipolar creativity within the Convergence Mental Health approach. A key aim of this chapter is to highlight the paradoxical interplay of the “Bad” (suffering, costs, stigma) and the “Good” (benefits of creative, scientific, artistic, and political accomplishments) in bipolar creativity that needs to be accounted for in bipolar creativity research. This will be depicted as a “strange loop” [11, 12], the model serving a heuristic that reconciles the tension between the “Bad” and the “Good.” Case studies supporting the connection between bipolar creativity, art, and science will be presented to demonstrate the strange loop for the mental health clinic. Future basic and applied studies may build on these examples.

2.2 Bipolar Disorder and Creativity

There are many historical accounts of famous personalities known for their creative artistic accomplishments who are conjectured to have had bipolar disorder. It is important to acknowledge that bipolar disorder cannot be diagnosed *postmortem*. However, attributing a phenomenology reminding of bipolar disorder symptoms to historical figures becomes circumstantially evident through the legacy of their work. For example, *Margery Kempe* (approx. 1373–1438), an English writer and mystic in the Middle Ages is known for her book, *The Book of Margery Kempe*, which is considered the first autobiography in English, in which she describes her trials and tribulations associated with her emotional instability and episodes of ecstasy and despair. Another personality in the medieval period who is theorized to have had bipolar disorder is *Geoffrey Chaucer* (approx. 1343–1400), an English poet and author widely regarded as the father of English literature and the greatest poet of the Middle Ages. He is best known for his masterpiece, *The Canterbury Tales*, a collection of stories told by a group of pilgrims on their way to Canterbury. Lord Byron, Herman Melville, Robert Schumann, Samuel Taylor Coleridge, Vincent van Gogh, Ernest Hemingway, Virginia Woolf, Sylvia Plath, Frida Kahlo, Amy Winehouse, Mariah Carey, and Sinéad O’Connor are just a few more names of bipolar artists whose work resonates through societies, fueled by their temperaments “touched with fire” [13].

The contributions of bipolar individuals to society may stem from commonalities underlying bipolar creativity such as openness and tolerance for ambiguity, and the ability to make unconventional connections that can enrich group creativity [14, 15]. The ability to link apparently unconnected knowledge suggests that bipolar creativity is discovery, not creation per se. That is, the bipolar individual actualizes hidden potentialities but does not create and conceive ideas *ex nihilo*. Research, of which some non-exhaustive examples are shown here, has shown that shared genetic factors that are strongly hereditary correlate with bipolar creativity. This genetic basis may contribute to mediating discovery, both in the arts and in the sciences.

Power et al. [16] found a link between bipolar disorder, polygenic risk scores, and creativity when they analyzed the DNA of Icelandic citizens. This supports the results by Kyaga et al. [17], who showed that creativity and bipolar disorder were linked in certain groups of patients with a proclivity for or diagnoses of bipolar disorder, and healthy family members of schizophrenia patients, but not in individuals with unipolar depression. This highlights that the creativity associated with bipolar disorder cannot be generalized across mental health conditions. Further evidence of the link between bipolar disorder, and creativity comes from a pilot study by Burkhardt et al. [18]. These researchers found that among the 38 participants, those at risk for bipolar disorder scored significantly higher in creativity scores. The researchers documented the participants' professions, noting if they were dancers, actors, visual artists, writers, or musicians. They found that these creative individuals had a 17% higher prevalence of certain genetic variants. These specific variants are known to increase the risk of developing bipolar disorder or schizophrenia.

The same genes linked to mood swings and emotional intensity in bipolar disorder may also be responsible for the ability to foster novel and original ideas beyond the realm of art. This can be seen in the work of philosopher Friedrich Nietzsche, who is often described as speculatively bipolar and was also artistically engaged, as well as in the contributions of many scientists. However, because of the structured scientific process constraining flexibility in the translation of ideas, the creativity of bipolar scientists is often obscured [19]. Notwithstanding, scientists with the disorder, such as Austrian physicist Ludwig Boltzmann, the father of statistical mechanics, have often revolutionized entire disciplines through their research approaches [20]. Revolutionary discoveries have often been attributed to a high level of human intelligence, as is the case with Albert Einstein or René Descartes. While it is not fully understood how the creative process in bipolar disorder is causally linked with manifested intelligence, there is evidence of a genetic correlation between the disorder and intelligence traits. For instance, Smith [21] recorded the IQ of eight-year-old children and reassessed them for manic traits when the participants became young adults. The results showed a link between high childhood IQ and bipolar disorder symptoms in later life. Similarly, Gale et al. [22] found high intelligence in Swedish men to comprise a risk factor for bipolar disorder but only in a minority of cases when the disorder manifested without psychiatric comorbidities. It is nevertheless acknowledged that other thinkers and scientists with a sharp intellect,

creativity, and unconventional approach to problem-solving such as renowned physicist Richard Feynman, who was also an avid bongo player and artist, did not suffer from mental health problems. This highlights that the interplay between creativity, intelligence, and mental health conditions is highly complex, and the identification of causal relationships is difficult.

The link between creativity and bipolar disorder can be informed by an evolutionary perspective, which suggests that “nothing in biology makes sense except in the light of evolution” [23]. Specifically, genetic evolution in relation to neural [24] and genetic [25] factors can explain why bipolar disorder is common and persistent in humans, even though the condition should be eliminated by natural selection. The evolutionary perspective often implies that an increased susceptibility to certain illnesses can confer survival advantages in unrelated situations. For instance, sickle cell anemia protects against malaria. Similarly, bipolar disorder may be associated with creativity, which can be beneficial in problem-solving contexts. This illustrates a complex interplay of individual and group factors, which are intertwined and difficult to isolate. Both clinical and subclinical populations contribute to this phenomenon.

Studying bipolar creativity from an evolutionary perspective is beneficial as it provides a mechanistic understanding of cause-effect relationships; that is, how genes may affect creativity. However, this approach can be reductionist, offering only a partial, static, and deterministic view of creativity in which other factors, such as intelligence discussed above and social and ecological features, which will be examined below, are unaccounted for. This is due to the gene-creativity relationship being rooted in a substance ontological framework, a key philosophical underpinning of western science. This view sees creative development as an ordered sequence, emphasizing the role of genes in driving creativity in a bottom-up information flow. This bottom-up interpretation risks reducing creativity to a mere byproduct of its genetic traits, ignoring the reciprocal effects of higher-level processes like environmental and societal factors. For instance, stressful environments and strained relationships can trigger depressive episodes, potentially “turning off” the genetic traits underlying bipolar creativity. Dosage effects of symptoms and substantial variability in the expression of creativity among individuals and populations can operate in such a way that a small quantity might confer advantages, while larger quantities could be disadvantageous and hinder creativity in context-dependent circumstances [26, 27]. The narrative of Vincent Van Gogh illustrates that his severe illness prevented him from painting. Even during his stay at hospital Saint-Paul in Arles, he only resumed painting as his health started to improve. Bipolar creativity, shaped by phenotypic variation, genetic diversity, unique symptom profiles, including childhood trauma, and environmental factors, can be further complicated by individual personality traits and social-cultural factors [28–31]. These variables may introduce “noise,” obscuring the signal of bipolar creativity.

To fully understand the paradoxical interplay between the “Good” and the “Bad” in bipolar disorder, it is crucial to adopt a holistic perspective and account for genetic correlates and the influence of social-ecological factors. Extending the substance-based framework with a processual view can be useful for understanding bipolar creativity and its role in the arts and sciences.

2.3 Creativity as a Process

Just as biologists advocate for a processual ontology to accurately represent life's organization [32], bipolar creativity can also be more accurately depicted as a process. This process, rather than only being a trait occurrence, unfolds over time. It involves the dynamic interaction of intrinsic (genetics, mood states, symptom severity) and extrinsic (work conditions, family relations, stigma, therapeutic support) factors in bipolar populations. Alfred North Whitehead's term "conrescence" emphasizes this comprehensive "co-construction." In the context of bipolar creativity, it signifies the potential or lack thereof for an idea to be conceived, manifested, translated, and incorporated into society. This process is mediated by the transition from a multitude of potentialities to actuality and from diversity to unity. These potentialities, which tend toward infinity, represent hidden, unresolved combinations of genetic, social, and environmental factors. They influence and are influenced by the elicitation, translation, and societal incorporation of creative ideas. This illustrates one of nature's constants: the uncertainty and limited predictability of the future. For instance, a bipolar individual might conceive a potentially transformative creative idea. However, its development could falter at the idea stage due to communication or comprehension barriers. If pursued, the idea could inspire social innovation, but the timing and method of this are uncertain. The idea might become obsolete due to technological advancements, or it could be replaced by newer creative ideas. All these possibilities illustrate the potential for societal benefits to arise, or not arise, from bipolar creativity. From a processual view, creativity is neither localizable nor decomposable, and any stage in its development is merely an abstraction, disconnected from the integrated spatiotemporal process.

Creativity research exists that adheres to a Whiteheadian process ontology and that portrays creativity as a dynamic process rather than the result of genetic traits. For example, Kaufman and Beghetto [33] argued that their model can better capture the developmental and multifaceted nature of creativity. Their model distinguishes between different classes of creativity: the generation of creative expression (mini-c), recognizable manifestations of creativity (little-c), and highly impactful, eminent forms of creativity (big-c). The latter is often romanticized with the "mad genius" myth. This model makes clear that creativity is not only an act of an "insane" talent but that it also manifests in more "mundane" endeavors of daily life (interpersonal relationships, work performance, cooking lunch, or dealing with distress) [34]. It allows one to discern fundamental (generating genuinely novel knowledge) and situational (building existing knowledge) creativity forms [35, 36]. Corazza [37] introduced the Dynamic Universal Creativity Process (DUCP), which is defined as the active ensemble of all creativity episodes in the evolution of our cosmos. He showed how creativity is not only a psychological construct for humans but rather a unifying cosmological principle. Walia [38] suggested a dynamic definition of creativity that focuses on the process rather than the product and that considers the social, cultural, and historical context of creative actions. Angeler et al. [9] go one step further and describe the creative process of being embedded in broader

social-ecological systems dynamics. They proposed a dynamic, hierarchical connection between processes at the levels of neurons, ecological systems, and societies that mediate the creative process and potentially tangible artistic and scientific outcomes. The grounding of bipolar creativity as a concrescent process in social-ecological systems underscores its complexity.

The potential for research into bipolar creativity is vast. However, concerns have been raised that starting with too much complexity could obscure our understanding of bipolar creativity and its relationship with neurodivergence [7]. To understand bipolar creativity holistically, we must address several challenges. For example, we need to accommodate the paradoxical “Yin-Yang” relationship between the “curse” and “blessings” of bipolar disorder at different levels. This is a process in itself, a higher-level immaterial process that emanates from complex “bundles” of other, material (genetic correlates of creativity) and immaterial (perception, attention, memory, language, problem-solving, and decision-making) processes operating within and across hierarchical scales. There is ontic uncertainty inherent in this process, which poses insurmountable challenges for empirical assessment. Understanding bipolar creativity also requires envisioning bold, yet ethically challenging, clinical approaches to enhance creativity. This could involve identifying highly creative individuals and inducing states of (hypo)mania or depression in them, which are conducive to novel creative thinking [39]. We must consider the relationship between external environmental demands and internal regulatory processes that lead to various potential behavioral outputs, some adaptive (allostatic load) and others pathological (allostatic overload) [40]. It is crucial to manage or mitigate states associated with severe impairment and dysfunction, such as periods of intense depression or mania in bipolar disorder.

Identifying trade-offs for conducting responsible scientific and clinical research is a prerequisite. It is clear that many nuanced forms of creativity can interact dynamically among factors that are intrinsic and extrinsic to bipolar individuals and populations, making the operationalization and quantification of creativity challenging [6]. Simplified models are necessary to make the complex process of bipolar creativity more accessible. Heuristics or metaphors, such as panarchy or adaptive cycles used in resilience research [41], have been beneficial for surrogate learning and inductive thinking [42, 43]. However, these heuristics should not be taken as exact representations of nature to avoid the “fallacy of misplaced concreteness” as termed by Whitehead.

The strange loop model [11, 12] is suggested as a useful tool to depict the broad scope of the creative process in a simpler way (Fig. 2.1). This model is not a prescriptive approach to research, as there is no universal model for research into bipolar creativity [9]. The strange loop heuristic should be seen as a foundational element of bipolar creativity research based on a concrescent premise. Thus, the strength of strange loops lies in their role as a mental model or heuristic that can guide future research and clinical approaches. The following section will describe the model and support its use in bipolar creativity research with interdisciplinary examples that merge the arts and sciences, demonstrating also the potential for clinical and outreach efforts.

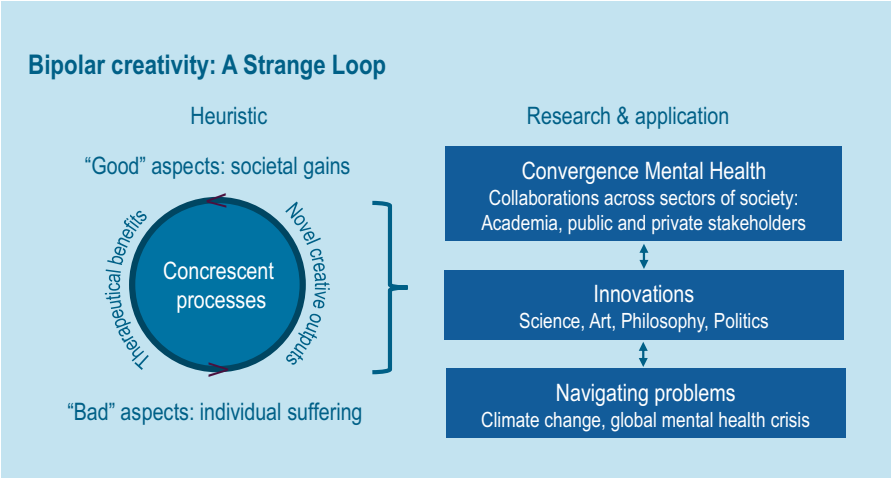


Fig. 2.1 This diagram presents bipolar creativity as a “strange loop” model. It highlights the heuristic value of studying both the positive and negative aspects of bipolar creativity. The intricate dynamics of this process (concrescence) are shown. The model encourages wide-ranging, interdisciplinary research to help navigate complex social-ecological issues through innovative approaches across various fields of study

2.4 Bipolar Creativity: A Strange Loop

Hofstadter [11, 12] defined strange loops as “paradoxical level-crossing feedback loops.” That is, a strange loop conceives a cyclic structure that runs through different levels (e.g., individuals, populations, societies) in a hierarchical system. A strange loop can involve self-reference that may arise when, by moving downwards or upwards through the system, it finds itself back at the starting point of its cyclic-ity. Such loops are ubiquitous and evident, for instance, in M.C. Escher’s lithograph “Drawing Hands,” human perceptions of the “I,” the liar’s paradox, and Kurt Gödel’s incompleteness theorem in mathematical formal systems.

Inherent in strange loops are unexpected ways in which a system can “boomer-ang” on itself, leading to a violation of conventional assumptions about how the system operates. For example, conventional scholarly doctrine in mathematical formal systems operating with natural numbers was that all theorems are provable. This held until Gödel’s discovery that some theorems, despite being true, are unde-cidable and unprovable, which has shattered the fundamentals of mathematics. By analogy, in bipolar creativity, the strange loop becomes evident when the absurd statement “bipolar disorder can be good for societies” fires back on the conventional logic that “the condition is bad for clinical populations (suffering, dysfunction) and societies (healthcare costs, productivity, and economic loss).”

The following text will provide practical examples to illustrate the bipolar cre-ativity strange loop. These unique examples demonstrate how art, science, and

creativity can become interlaced to drive the strange loop. They highlight the potential and limitations of bipolar creativity research that motivates Convergence Mental Health research. The examples are preliminary but show how the bipolar creativity strange loop can inform applied areas such as the clinic and outreach, and more generally other areas of human inquiry.

2.4.1 Art, Creativity, and Therapy

The arts have consistently been a crucial tool for individuals with bipolar disorder, enabling them to navigate their emotions and thoughts during episodes and between these. Essentially, the arts provide a platform for creative expression of their ideas. The “strange loop” relationship considers that bipolar creativity is influenced by both genetic and environmental factors. A genetic predisposition, in combination with life circumstances, can ignite creativity in individuals with bipolar disorder, leading to the creation of performing and visual arts. This creative output, or “the Good,” is a societal manifestation that arises from these individuals managing their negative emotions, or “the Bad,” during episodes (Fig. 2.1). In essence, the arts become a fiery display of their coping mechanism. The transformation of bipolar creativity into tangible art forms represents here only a bottom-up aspect of the strange loop, which does not reflect its cyclic behavior. Incorporating the clinical perspective adds a top-down dimension, to closing this cycle.

The suggestion is that bipolar creativity does not just result in an emanation of art as a societal benefit, but the entire process of creating art extends to be of therapeutic significance (Fig. 2.1). Art creation aids individuals with bipolar disorder in managing their symptoms. It offers a means to express emotions, assert their identity, find purpose, and achieve a sense of accomplishment, ultimately enhancing their quality of life [44–46]. This underscores the importance of art therapy and its potential use in clinical settings. The strange loop cycle is closed by the “Good” (artistic expressions) helping the “Bad” (coping with bipolar). A reiterative creative dialogue between the curse and blessing of bipolar creativity ensues that drives development in the arts and from which novel insight and potential for research may arise.

An example is a recent study that documents the creative associations a bipolar individual has made between heavy metal music and the symptoms of bipolar disorder [47]. Specifically, metal music, with its diverse subgenres, exhibits unique characteristics in song composition, rhythm, instrumentation, and vocal arrangement. These unique characteristics can be likened to the symptoms of bipolar disorder, particularly the recurring episodes of (hypo)mania and depression. These associations become allegorical of the “Bad” in the strange loop. The paper provides song examples that illustrate these analogies. The “Good” aspect emerges from the potential these analogies have. That is, they suggest that connections between distinct fields in the arts and sciences, particularly music and psychiatry, can be established, forming the basis for scientific clinical research. In addition to

forming a subjective connection between seemingly unrelated fields of knowledge, this paper suggests that the music analogy of bipolar symptoms could serve a heuristic function in clinical practices and public education about bipolar disorder and broader mental health issues. This underscores the importance of a unified Convergence Mental Health approach, where collaboration among stakeholders from academia and the private and public sectors can enhance our comprehension of the strange loop.

The inclusiveness of art-science collaborations building on the strange loop becomes especially evident in the wake of rapid scientific advances and technological and digital development that may revolutionize traditional views of bipolar creativity. Art creations can nowadays be communicated through interactive platforms and diverse channels, such as journalism, popular science communication, social media, films, museums, art galleries, conferences, blogs, and other media outlets. Creative expressions are increasingly inspired at the intersection of computer-based art and mental health. Artists often use technology to create artistic representations of their inner worlds, using digital art, including photography, graphic design, and digital painting, as a way to express their emotions, experiences, and struggles related to mental health. Some non-exhaustive examples are the #100 Days of Bipolar project [48] or the Perspective Project [49], which convey the emotional rollercoaster of bipolar disorder and mental health problems more generally, including representation based on computer-assisted generation of art. Artificial intelligence-driven platforms, such as NightCafé, demonstrate the potential of modern technology to generate and share bipolar artwork (NightCafé [50]) and indicate the potential to create entire galleries [51].

While the broad potential for collaboratively studying the strange loop of bipolar creativity is evident, it is also necessary to consider potential challenges. Specifically, visual or performing arts involve subjective portrayals, which can be risky as societal issues may seem remote and unrelated to personal experiences. The general public may struggle to interpret ambiguity, leading to potential misunderstandings and decontextualization of the issue at hand. This is evident with climate change [52]. In mental health, misconceptions and disconnections can arise from various factors [53, 54]: society's inability to recognize different forms of mental distress or specific disorders; public assumptions about the origins and treatments of mental disorders differing from those of professionals; the blurred line between recognized disorders and normal human behavior; the easy access to misleading mental health information; and differences in mental health literacy due to education, gender, culture, and urban-rural divides. These issues can be worsened by social, economic, and demographic factors, such as public deficiencies in science literacy and understanding of graphics and numeracy [55, 56].

To address these issues, I propose an alternative approach in the following example that combines creativity with the arts, especially music, and sciences. By illustrating the strange loop behavior of bipolar creativity, a "quasi-objective" art-science approach (i.e., data sonification) could potentially enhance the understanding and acceptance of evidence-based mental health care in societies. This could improve self-help strategies, provide suitable community support for individuals with

bipolar disorder and other prevalent mental conditions, and potentially inform and drive policy changes necessary to effectively tackle the escalating global mental health crisis [7].

2.4.2 Data Sonification: A Quasi-Objective Art-Science Approach

Combinations of science and art, whether in visual or performing representations, are a further example of the utility of a Convergence Mental Health approach to study the bipolar creativity strange loop. Combining the arts and sciences demonstrates interdisciplinary research potential emanating from the intersection of different realms of human inquiry that are not evident when studying each realm (art, science) alone. Bipolar creativity demonstrates this potential by combining many factors, such as technological and digital tools and especially mental health state monitoring in novel ways. An example is data sonification that creatively translates “cold” scientific or monitoring data into a human experience. Data sonification can be considered a relatively objective approach wherein the sentiments experienced through different stages of bipolar disorder can be represented with high fidelity, depending on how users choose to translate data into sound. That is, researcher choices for implementing the approach can be designed for specific aims to optimize learning; for instance, based on the stimulation of mood and psychological arousal through the selection of instruments and the adjustment of mode and tempo [57].

Data sonification “participating” in bipolar creativity has an advantage over subjective associative research and traditional art creation—as outlined in the previous example—whose expressions may sometimes risk not being fully comprehended, resulting in a disconnection of people with an issue at hand. Because of simultaneously appealing to people’s logic and emotions [58], data sonification has been used in many social and environmental contexts to increase understanding of and possible engagement with environmental and social challenges (e.g., [59, 60]). There is evidence that stimulating both learning domains, for instance, through active community participation in the creative process, can be more effective than expert communications of climate-related issues to a lay public [61]. Data sonification may have similar potential in psychiatric research, clinical applications, and mental health outreach. Convergence Mental Health offers again potential for future research.

A recent study demonstrates a data sonification approach that can be contextualized within the strange loop heuristic. A creative user with bipolar disorder converted iMoodJournal monitoring data into music [8, 10]. Inherent in the strange loop is the monitoring of the user’s struggles with depression which allowed for reconstructing his anamnesis and depicting it in a time-integrated way in the form of a visual graph. This can be regarded as the individual-level component of the strange loop representing the user’s trials and tribulations with bipolar disorder, i.e.,

the condition's "curse" side. The translation into music comprises the level-crossing aspect to the societal level. If widely applied at the mental health system level, data representing monitored mood states through music may contribute to enhancing the management of bipolar disorder in entire populations. Listening to one's own prolonged struggles compressed into a song lasting a few minutes can likely provide better insight into the self.

Although this study is preliminary and based on a single case, it suggests a potential innovative clinical approach to facilitate coping with patients' mental health conditions. Specifically, potentially improved therapy outcomes could likely lead to innovations in the clinic and reduced health care costs. Angeler et al. [8, 10] suggested that future research can build on this case study, speculating that further development may lead to dynamic, adaptive, and self-innovating health care service and delivery approaches emerging from an iterative learning process that may be creativity driven. Here, the cyclical, processual nature of the strange loop model suggests a form of Hegelian dialectic of opposites wherein the "Good" and "Bad" mutually inform each other (Fig. 2.1), potentially giving rise to unexpected innovations. This "creative dialogue" may ultimately benefit entire societies and contribute to fostering the "blessing" side of bipolar creativity.

In summary, the visual and performing arts have long served as a metaphor for human experience. Knowledge gaps in public awareness may similarly be overcome when learning is based on the combination of auditory and imaged modes of presentation. These combined representations may, therefore, also be useful for communicating issues about mental health. Using data sonification complemented with visual arts or music support may reiteratively refine a combinatory approach to contribute to a better understanding of the bipolar creativity strange loop.

2.5 Conclusion

Bipolar disorder is persistent, with significant societal and individual costs. Yet, societies have been brought on new trajectories due to the creativity of individuals with mental health conditions. Therefore, it is worth integrating bipolar creativity into efforts to improve mental health systems and navigate the challenges of an accelerating Anthropocene. The shared and unique aspects of bipolar creativity could stimulate Convergence Mental Health. This offers numerous opportunities to progress transdisciplinary research, shape comprehensive science, enhance mental health systems, and influence broader social-ecological systems [30, 62, 63]. Involving the public, professionals, politicians, scientists, stakeholders, and those with lived experience in dialogues will be crucial.

The strange loop model simplifies the complexity of implementing creativity-based transdisciplinary research. However, some drawbacks of adopting heuristics must be emphasized. Accepting strange loops more literally as descriptors of reality, realists may argue that the intricate feedback mechanisms and self-referential structures inherent in strange loops imply a fundamental determinism in biological

processes. A deterministic view, however, may overlook the broader perspective by emphasizing the predominant role of genetic factors in shaping complex phenomena, like bipolar creativity, often relegating immaterial processes to a secondary or epiphenomenal status. It is perhaps preferable to adopt an anti-realist stance and not necessarily take the strange loop at face value as a description of reality. That is, a strange loop may be seen as a pragmatic construct to envision complex phenomena while emphasizing the unpredictability and emergent properties within complex systems. The strange loop serves as a heuristic that helps organize and predict observable phenomena without making claims about the ultimate nature of the bipolar creativity strange loop. In viewing the bipolar creativity loop in this way, a certain level of skepticism or agnosticism regarding the ontological status of the model is maintained.

We should be careful when making definitive claims about bipolar creativity based solely on scientific models and theories. This is because oversimplifying or making presumptuous assumptions in Convergence Mental Health research could obstruct our understanding of bipolar creativity, which is a coevolving concept between individuals with bipolar disorder and society. This could also impede effective clinical management, aimed at reducing individual suffering and fostering societal benefits.

Philosophical and ethical considerations underscore the importance of maintaining a skeptical perspective. However, there remains a fundamental optimism that emerges from this discussion. The conceptualization of the bipolar creativity strange loop may offer an inclusive approach that holds potential benefits for mental health systems and broader social-ecological systems over time. The case studies presented herein can serve as a foundation upon which future Convergence Mental Health research can expand. With the rapid advancement of technologies such as artificial intelligence, there is the potential, if used responsibly, to transform agnosticism into credible research outcomes and alleviate skepticism surrounding this area of inquiry.

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Chapter 3

Epidemiology



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3.1 Incidence and Prevalence

The first epidemiological study utilizing DSM-III standards [1] approximated the lifetime occurrence of bipolar disorder (BD) at 1% within the broader population [2]. However, according to a 2023 analysis based on World Mental Health surveys in 29 countries [3], the lifetime prevalence of BD was 2.5% (2.4–2.7) among men

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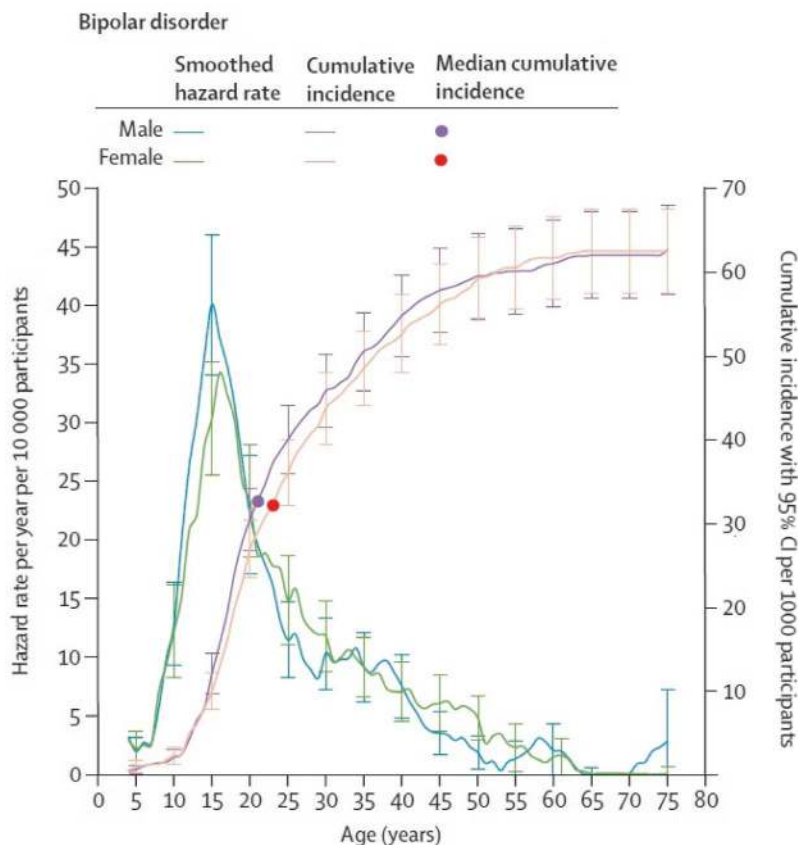


Fig. 3.1 Bipolar disorder. This figure was published in *Lancet Psychiatry*, Volume 10, Issue 9, McGrath JJ, Al-Hamzawi A, Alonso J, et al., “Age of onset and cumulative risk of mental disorders: a cross-national analysis of population surveys from 29 countries,” Pages 668–681, Copyright Elsevier (2023)

and 2.3% (2.1–2.4) among women. Figure 3.1 presents the smoothed hazard rate and cumulative incidence of BD by age and sex according to that study. In other studies, estimates suggest that lifetime prevalence rates of BD range from 1% to 5% in the general population [4–7]. Bipolar disorder type II (BDII) lifetime prevalence is believed to range from 0.5% to 3.0% [8–12]. Moreover, it is known that the prevalence has increased over the last few decades. From 1990 to 2019, the Global Burden of Disease study observed a rise in the incidence, prevalence, and years lived with disability due to BD [13]. The global incidence increased by 48% from 1990 to 2017, ranging from 3.06 million to 4.53 million during this period [14]. In 2019, it was estimated that 40 million people experienced BD [14]. The disease also places a significant societal burden in terms of illness severity, death rates, decreased productivity, and financial expenses [15].

Table 3.1 Statistical models suggest that three age-of-onset groups can be distinguished [26]

	Mean ± Standard deviation	% of the sample
Youngest subgroup	17.24 ± 3.20 years	41.7%
Middle subgroup	23.93 ± 5.12 years	24.7%
Oldest subgroup	32.20 ± 11.96 years	33.6%

3.2 Age of Onset

It is known that BD usually emerges during late adolescence or young adulthood [16]. The peak age at which the first symptoms manifest is typically between 15 and 19 years old, while studies indicate that around 70% of patients exhibit symptoms before reaching the age of 25 [17, 18]. The median age at onset among 2839 patients diagnosed with BD, as documented by the Stanley Center Bipolar Disorder Registry, was 17.5 years (with a mean age of 19.8 years) [19]. Moreover, a recent meta-analysis revealed that the average age of BD onset is approximately 19.5 years, while the median age is 33 years [20]. The onset of BD is frequently manifested by depressive episodes, as evidenced by both retrospective and prospective studies [21, 22]. While the exact proportion of individuals experiencing a depressive index episode varies across studies, it consistently exceeds 50%, ranging from 50% to 80% [23]. Considering that the effectiveness of BD treatment is higher in the initial phases, early identification and appropriate treatment are crucial [24]. However, a patient can wait for up to 9 years before being diagnosed with BD after their first depressive episode [25] (Table 3.1).

Individuals experiencing an early age of onset are often linked to heightened depression severity, increased rates of comorbidity with anxiety and substance use, as well as a more prolonged delay in initiating treatment [27].

3.3 Gender

In contrast to Major Depressive Disorder (MDD), where strong and consistent evidence reveals gender differences, studies on BD have yielded conflicting results [28]. Until recently, most research suggested that the prevalence of BD, particularly type I, did not significantly differ between men and women, with some evidence of a slightly higher prevalence of hypomania and BDII in women [29]. However, a review published in 2021 found that in recent years, there is a higher preponderance of female patients in samples of BD studies, with an increase in BD diagnosis in females [30].

The clinical features, phenomena, and evolution of BD differ between men and women [31]. Manic episodes are more common in men, commonly as their first mood episode, while depressive episodes occur more frequently in women [32].

However, women exhibit a higher propensity for experiencing mixed mania and manic switches during antidepressant treatment [33]. Suominen et al. [34] reported that the median time to recurrence after remission was 3.1 months longer among men than among women and that women had a higher hazard of recurrence (HR 2). The type of psychiatric comorbidity also differs. Men are more likely to present substance use disorders, commonly alcohol and cannabis abuse/dependence, and conduct disorders, while women usually present comorbid eating disorders and post-traumatic stress disorder [28, 32]. No major sex differences have been found in the polarity of onset symptoms, severity of illness, suicidal behavior, and response to treatment [28, 30].

The evidence regarding the age of onset is still controversial. Older studies identified that women experience episodes at later ages compared to men [35, 36]. In a study involving 69 euthymic outpatients diagnosed with BD, women encountered the onset of depressive episodes (27.2 ± 1.3 years versus 22.4 ± 1.2 years) and manic episodes (25.9 ± 1.0 years versus 21.8 ± 1.0 years) at significantly later ages than men [35]. Another recent study involving 360 outpatients with BD similarly concluded that women typically experience the onset of BD approximately 3.2 years later than men [36]. However, more recent studies do not corroborate this finding, ruling out gender differences in age of disease onset [28, 30].

3.4 Marital Status

Because of its early onset of symptoms, BD impacts interpersonal relationships, sometimes negatively influencing personality development, posing challenges in establishing and maintaining connections with others [29]. When it comes to marital status, some epidemiological studies have found that individuals with BD are less likely to be married, and are two–three times more likely to divorce when compared to the general population [37, 38]. Most clinical-based studies reported that approximately one-third of bipolar patients were never married, and over 20% were divorced or separated [37].

Furthermore, marital status can serve as a protective factor against relapse and poor prognosis. A retrospective study evaluated that married women with BD tend to experience fewer depressive episodes (mean of 7.1 versus 9.1, respectively; p -value = 0.03) and lower cumulative severity of depression compared to their unmarried counterparts (mean of 13 versus 17.3 on depressive scores, respectively; p -value = 0.02) [39].

3.5 Socio-Economic Aspects

Several studies have investigated the prevalence and incidence of BD according to sociodemographic variables, generally presenting inconsistent findings [40, 41]. Most recent epidemiological data show an equal distribution of the disorder among all social classes and educational levels [29]. However, regarding the consequences of the disorder, a recent cohort study showed that, when compared to healthy controls, BD patients had 0.75 lower odds of achieving the highest educational level (95% CI: 0.73–0.77), 0.16 lower odds of being employed (95% CI: 0.159–0.168), and 0.33 lower odds of belonging to the highest income category (95% CI: 0.32–0.35) in the baseline [42]. These trends remained similar during the 23-year follow-up [42].

3.6 Cultural Aspects

For decades, there have been studies evaluating the prevalence and incidence of BD across races and cultures. Until now, there has been no strong association between race/ethnicity and BD, except for lower rates of many psychiatric disorders in Asian countries [29]. Earlier studies have already shown that African American individuals with BD have significantly higher rates of receiving an initial clinical diagnosis other than BD, in comparison to white individuals [43, 44]. A 2004 study found that African Americans were four times as likely to have a schizophrenia diagnosis when compared to otherwise similar white Americans [45]. This could be influenced by different symptom manifestations, as some studies have found that African Americans are more likely to experience psychotic symptoms, greater manic and depressive sleep-related disturbances, and more dysphoric or mixed syndromes [46]. However, the morbidity and mortality of people with serious mental illness are magnified by racial disparities in access to or provision of healthcare [47].

3.7 Comorbidity

In psychiatry, classical BD, characterized by episodes of euphoric mania alternating with depression, stands as one of the most distinct clinical syndromes. However, the boundaries defining BD remain a topic of debate, influencing prevalence rates and our comprehension of risk factors. Key boundary issues include its overlap with psychotic features, schizoaffective disorder, and schizophrenia, as well as its intersection with unipolar depressive disorder, apparent personality disorders (especially Cluster B), and comorbid substance abuse.

About 22% of individuals diagnosed with BD present an additional somatic condition, while 39% suffer from a secondary psychiatric disorder (of which two-thirds

are linked to substance abuse) [48]. The *Epidemiologic Catchment Area* (ECA) study revealed that bipolar patients are more likely to receive a diagnosis of substance abuse or dependence compared to individuals with any other Axis I disorder [10]. Bipolar patients who abuse substances tend to exhibit elevated rates of suicide attempts, panic attacks, and rapid cycling [49]. Another important comorbidity that sometimes is also a differential diagnosis is between BD and borderline personality disorder (BPD). It is known that BD and BPD co-occur in about 10%–20% of patients with either disorder [50]. This is frequently related to a lower response to treatment and a worse prognosis [50–52]. Goodwin and Hoven [53] discovered that the simultaneous occurrence of BD and panic attacks correlates with an earlier onset and a more severe manifestation of panic disorder. Moreover, the prevalence rates of both depressive and bipolar spectrum disorders among individuals with epilepsy seem to surpass those in the general population [54]. Recent data derived from community samples indicate rates significantly higher than those observed in patients both with and without other chronic diseases [54].

The co-occurrence of general medical conditions is common and prevalent in BD, resulting in premature mortality, with women and men experiencing an average reduction in lifespan of 9 and 8.5 years, respectively, compared to the general population [55]. Nearly all patients with BD, accounting for 96.3%, exhibit at least one medical condition spanning cardiovascular, metabolic, endocrine, respiratory, and musculoskeletal systems [55]. In a meta-analysis conducted in 2023, researchers identified 23 papers documenting 19 studies examining five primary physical health comorbidities, employing diverse study methodologies across seven nations [56]. Results highlighted that the average prevalence of cardiovascular disease among older adults with BD was 32.6% [56].

3.8 Suicidality and Mortality

Suicidal behavior is the most severe outcome of BD, with a lifetime prevalence of suicide attempts reaching up to 30% [57]. Patients with BD are approximately 20–30 times more likely to die by suicide compared to the general population [18]. The rates of suicide attempts and completed suicides are similar in bipolar disorder type I (BDI) and BDII, with approximately one-third of patients experiencing suicide attempts during the course of illness [58, 59] and one in 25 individuals with BDII completed suicide [17]. Findings from the Stanley Foundation Bipolar Network indicate various factors associated with an elevated risk of suicidal behavior among individuals with BD, including genetic and familial factors, childhood and recent environmental stressors, diminished social and medical support, psychiatric comorbidities, and a more severe trajectory of illness [60]. Most studies on bipolar patients suggest that women demonstrate a higher propensity for suicide attempts (OR = 1.54), whereas men are more likely to complete suicide (OR = 1.83) [58].

Despite suicide being a significant cause of mortality among individuals with BD, it has also been shown that those patients also face an increased risk of premature death due to various medical conditions [61]. Natural deaths among BD patients are over 1.5 times greater than in the general population, primarily due to nearly double the risk of death from circulatory diseases (such as heart attacks, strokes, etc.), and a threefold risk of death from respiratory diseases (including chronic obstructive pulmonary disease, asthma, etc.) [62]. Unnatural deaths are approximately seven times more prevalent among individuals with BD, with a heightened risk of suicide by approximately 14 times and other forms of violent deaths (such as accidents, homicide, etc.) nearly four times as likely [62]. It is also known that cardiovascular diseases are the most common cause of premature mortality in BD patients [18].

Moreover, mortality studies indicate that BD is associated with reduced life expectancy [18]. A Danish study evaluated nationwide registers of all inpatient and outpatient contacts to psychiatric hospitals from 1970 to 2012 [63]. It found that the remaining life expectancy was decreased by 8.7–12.0 years for males and 8.3–10.6 years for females in typical patients aged 25–45 years [63]. A recent meta-analysis produced similar results, showing that BD patients experienced reduced life expectancy relative to the general population, with approximately 13 years of potential life loss [64]. The analysis also revealed that life expectancy was significantly lower in male patients compared to females. In this scenario, men lost slightly more years of potential life (11.7 years) than women (10.5 years) with BD [64].

The reduction in life expectancy in BD patients compared to the general population seems to reflect a combination of various factors as follows [63, 64]:

- Higher occurrence of risk factors (including lifestyle factors) for many chronic diseases, such as cardiovascular diseases, and some types of cancer.
- Side effects of some psychotropic medications.
- Higher rates of suicide, accidental death, and violent death.
- Poor access to physical healthcare and decreased attention to physical disorders.

3.9 Risk Factors

Identifying early symptoms of BD poses a challenge for researchers. The likelihood of experiencing a depressive episode in BD patients is three times higher than that of a manic episode, and the symptoms of unipolar depression are not significantly different from those of bipolar depression [65]. Consequently, when the correct BD diagnosis is made, it is often at an advanced stage of the disorder. While some work has been done to develop instruments for screening early symptoms of BD among high-risk populations, these instruments often fail to incorporate protective factors and biological markers [66].

To date, the literature has identified several risk factors for BD focused on clinical factors. These include early episodes of depression, psychotic symptoms, a high number of hospitalizations, suicide attempts, subsyndromal depressive and hypomanic symptoms, attention deficit hyperactivity disorder (ADHD) diagnosis, early adverse events, anxiety symptoms, mood dysregulation, substance use or dependence, somatic problems, personality traits, alterations in circadian rhythm, and genetic predisposition [67–73]. Researchers have compiled this information for the development of screening measures, and have reported a conversion rate of 14.3% within 12 months of follow-up among adolescents and young adults [74], and a 25% conversion rate among children and adolescents who did not meet Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for BD [75]. More aspects related to each risk factor will be further explored in another chapter.

Another significant and challenging topic in the field of risk factors for BD is early adverse events. This is particularly noteworthy due to their high prevalence among individuals with mood disorders in general [76]. When utilizing this information as a risk factor for BD and aiming to enhance diagnosis, it is crucial to differentiate the risk between unipolar depression and bipolar depression. Therefore, a better understanding of the topic is necessary, including whether certain adverse events are directly linked to BD or if they could trigger its development when combined with other factors.

Expanding the temporal dimension, potential risk factors for BD may emerge even before an individual's birth. A meta-analysis has identified additional prenatal and perinatal risk factors for BD. Oxygen deprivation during delivery amplified the chances of BD by 46%, maternal stress during pregnancy escalated it by 12 times, complications during delivery heightened the risk by 41%, and birth weight below 2500 g resulted in a 28% increase [77].

3.10 Protective Factors

In brief, the literature lacks articles on protective factors for BD. Therefore, it is crucial to recognize the risk factors and consider that addressing them could potentially be protective against the development of the disorder. Moreover, for high-risk populations, some studies suggest that interpersonal and social rhythm therapy (IPSRT) may help delay symptoms onset by regulating circadian rhythm [78]. Similarly, mindfulness-based cognitive therapy (MBCT) also demonstrates promising results, aiding in regulating sleep patterns, reducing anxious symptoms, and improving emotional regulation [79]. However, both interventions have a limited number of studies and encounter challenges in keeping participants engaged, especially when they do not exhibit symptoms. This results in low motivation for treatment, consequently leading to low retention rates in studies.

3.11 Course of Illness and Prognosis

The trajectory of BD is notably diverse, potentially progressing with associated brain alterations [80]. BD patients remain symptomatic for approximately half of their lifespan, with approximately two-thirds of that time characterized by depressive symptoms. Estimates further suggest that the quality of life for these patients is inferior to that of individuals without the disorder, even during asymptomatic periods [17, 81].

The hypothesis of neuroprogression states that a subset of BD patients may experience a worsening of their condition over time [80]. A meta-analysis showed that the prevalence of dementia is higher in BD patients compared to those with MDD, identifying an increase of 2.96 (95% CI: 2.09–4.18, $p < 0.001$) in the risk of developing this condition in BD patients. Additionally, in this same meta-analysis, it was possible to observe a significant relationship between the number of episodes and the higher risk of conversion to dementia, as well as the important role of lithium treatment in decreasing this risk [82].

A higher number of affective episodes appears to be associated with an increasing risk of recurrence of episodes, increasing duration of episodes, increasing symptomatic severity of episodes, decreasing threshold for developing episodes, and risk of developing dementia [83]. Some studies also show that successive episodes can be a risk factor for treatment resistance induction [80]. The longitudinal course and clinical progression of BD are further explored in another chapter.

3.12 Clinical Considerations

- Lifetime prevalence of BD is estimated to range from 1% to 5% in the general population; the condition typically emerges during late adolescence or young adulthood, with a peak age at first symptoms between 15 and 19 years old.
- Early age of onset is linked to heightened depression severity, increased comorbidity rates, and delayed treatment initiation.
- Women have a higher risk of recurrence and are more likely to experience mixed mania and manic switches during antidepressant treatment.
- Individuals with BD are less likely to be married and have higher divorce rates; also, being married can serve as a protective factor against relapse and poor prognosis.
- BD patients tend to have lower educational levels, higher unemployment rates, and lower income compared to healthy controls.
- There is no strong association between race/ethnicity and BD, except for lower rates in some Asian countries.
- BD patients commonly present with additional somatic and psychiatric conditions, including substance abuse disorders and mood spectrum disorders.

- BD patients have a significantly higher risk of suicide attempts and completed suicides compared to the general population.
- Premature mortality due to medical conditions, particularly cardiovascular diseases, is elevated in BD patients.
- Several clinical factors increase the risk of developing BD, including early episodes of depression, psychotic symptoms, substance use, and genetic predisposition.
- BD trajectory is diverse, with depressive symptoms prevailing for approximately two-thirds of the time.
- Neuroprogression hypothesis suggests worsening of BD over time, with a subset of patients at risk of developing dementia.

3.13 Future Perspectives

It is important to identify key epidemiological targets for studies needed to improve the understanding and outcomes of BD. While recent analyses have provided updated prevalence rates for BD, further research is needed to understand the variations across different populations, regions, and time periods. Longitudinal studies could provide insights into trends and changes in BD prevalence and incidence rates over time.

Understanding the factors influencing the onset of symptoms could inform early intervention strategies and improve outcomes. Identifying and understanding risk factors for BD is crucial for early detection and prevention efforts. Future research should focus on elucidating the interplay between genetic, environmental, and psychosocial factors in the development and progression of BD, as well as the potential role of biomarkers and novel predictive models. Moreover, it is known that protective factors for BD have received less attention in the literature. Their exploration is essential for developing assertive approaches to disease management. Future studies should investigate potential protective factors, including psychosocial interventions, lifestyle modifications, and resilience factors, to mitigate the impact of BD and improve long-term outcomes.

Further research is also needed to understand how interpersonal relationships affect the course and outcome of BD. Long-term studies could help us understand how marital status, social support, and disease progression interact, revealing protective factors and potential interventions. Additionally, investigating socioeconomic and cultural factors can help identify ways to reduce disparities and improve outcomes. We also need more research to understand how BD relates to other psychiatric and medical conditions, including their impact on disease course, treatment response, and outcomes.

Another important aspect concerns the course of the disease and prognosis. Knowing that BD is a condition with high risks for harm over time, developing management strategies to delay the disease's evolution process becomes imperative. Therefore, research on neuroprogression hypotheses and their implications provide

valuable insights into preventive strategies and treatment approaches. By addressing these research gaps, the scientific community can advance our understanding of bipolar disorder and enhance clinical practice, ultimately improving the lives of individuals affected by this complex condition.

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Chapter 4

Genetics of Bipolar Disorder



Evangelia Eirini Tsermpini and Martin Alda

4.1 Introduction

Bipolar disorder (BD) has been long recognized as a familial condition. However, the progression from the early clinical observations to more systematic investigations of its genetic basis has been slow and complicated by the arguably heterogeneous nature of the illness. Only in recent years, due to advances in molecular genetic techniques, have we started to better understand the genetic architecture of BD and its clinical features.

4.2 Family Studies

The first notion of the genetic underpinning of BD originated in observations that close relatives of affected individuals had higher rates of the same as well as other, presumably related, psychiatric conditions. These observations led to numerous family studies, with an increasingly rigorous methodology, aimed at reducing biases of the earlier investigation, such as unsystematic case selection, unblinded assessments of study participants, or the lack of proper comparison groups. The combined data from 25 studies and more than 2000 families showed that the age-adjusted risk of BD in first-degree relatives (FDRs) of bipolar probands was $8.8 \pm 4.8\%$ compared to $0.4 \pm 0.5\%$ in FDRs of unaffected probands (relative risk of 22.6); in studies that did not correct for variable age at onset, the rates were $9.1 \pm 6.0\%$ and $0.9 \pm 0.9\%$ (relative risk of 10.1), respectively (unpublished review). The familial risk involves not only BD but also unipolar depression (UD) ($8.2 \pm 5.9\%$ compared

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to $4.7 \pm 2.5\%$ in control families in age-adjusted studies, and $19.7 \pm 15.7\%$ versus $7.4 \pm 3.1\%$ in age-unadjusted studies) as well as some other psychiatric disorders [1]. For instance, in a large healthcare registry study from Sweden, the relatives had higher rates of not only BD and major depressive disorder (MDD) but also schizophrenia (SZ) [2]. However, another study that quantified the degree of family history using family genetic risk scores for MDD, BD, and SZ found that the familial loading was disorder-specific, associated with an early age at onset, and with increased rates of recurrence [3].

Several family studies investigated the familial specificity of various subtypes of severe mood disorders. Concerning differences between BDI and BD II disorder, FDRs of BD I probands have similar morbidity risk for bipolar type I and II, whereas FDRs of bipolar II probands have a higher risk of bipolar II than bipolar I disorder [4–6].

Schizoaffective disorder (SZA) has been variably defined since the initial description by Kasanin [7]. A 1982 study based on Research Diagnostic Criteria (RDC) reported the highest rates of mood disorders among the relatives of patients with SZ and progressively lower prevalence in families of probands with BD I, II, and MDD, respectively [4]; thus, SZA would have the strongest genetic risk among mood disorders. Some other RDC-based studies proposed that SZA was heterogeneous, where some forms with predominantly affective [8] or manic episodes [6] were considered genetically closer to mood disorders, while those with more schizophrenia-like symptoms or schizoaffective-depressive subtype were viewed as related to SZ [6, 8]. In DSM classifications, SZA is positioned as an intermediate between mood and psychotic disorders. This was supported by Kendler et al., who found both the risks for affective disorders and SZ increased in relatives of schizoaffective probands [9].

Specific types of family investigations are the so-called high-risk studies that examine the risk of psychiatric illness among the offspring of patients. Such data, among others, can provide helpful information for clinical counseling. A recent summary of such studies argued for a transdiagnostic risk of severe mental illness. For BD specifically, the offspring of parents with BD have 55% lifetime probability of developing any psychiatric disorder, representing 2.1 times higher risk than the general population [10].

The clinical presentation of bipolar disorder is highly variable and heterogeneous. Some of its clinical features appear to be familial. Several studies examined, for instance, the familial nature of the clinical course, psychiatric comorbidities, substance abuse, lithium response, and suicidal behavior. In a meta-analysis of these studies, Scott et al. found significant familial effects for the BD subtype (bipolar I versus bipolar II), age of onset, psychosis, alcohol use disorder, and panic disorder. Several additional traits have been investigated in only one study, and of these, lithium response, polarity at onset, obsessive-compulsive disorder, mood incongruent, and puerperal psychosis were reported familial [11]. These findings contribute to a more refined phenotypic characterization that may be useful in future molecular genetic studies (see below). The partial specificity of familial risk of BD II seems consistent with the recent findings from genome-wide association studies (GWAS) (see below).

Although family studies supported the role of genetic background and transmission of affective disorders, the evidence of familial aggregation does not necessarily imply genetic etiology. Family members share not only their genetic makeup, but also their lifestyle, diet, infections, and exposure to environmental influences, in general. More conclusive support for the role of genes in the etiology of BD thus comes from studies of twins and from comparisons of adopted and non-adopted children.

4.3 Twin Studies

Twin studies are based on the notion that monozygotic twins (MZ) share 100% of their genomes, while dizygotic twins (DZ) share 50% on average. Thus, assuming the comparable contribution of environmental factors, the difference between the concordance of identical and fraternal pairs is due to genetic differences only. All the twin studies in mood disorders have recorded higher concordance rates in MZ than in DZ, suggesting the influence of genetic factors (but also the role of environmental factors as the concordance of MZ is less than complete). In a combined analysis of twin studies published between 1928 and 1999, the aggregate twin concordance was 49% for monozygotic and 11.6% for dizygotic pairs [12].

Twin studies have several limitations. As twin births are not that common, most studies had to contend with small twin samples. Most also suffered from the absence of structured diagnostic assessments and a lack of blinding. Several twin studies combined BD and UD into a single phenotype. In spite of these limitations, they provided supporting evidence that susceptibility genes contribute to BD familiarity by suggesting that familial aggregation is mainly attributable to genetic factors, while environmental factors play a less prominent role.

4.4 Adoption Studies

Additional evidence for the role of genetic underpinning of BD has come from adoption studies, which examined the risk of the illness in biological (typically children adopted away) and adoptive relatives of probands. Further, adoption studies can potentially assess the role of environmental factors if individuals at low genetic risk are adopted into families with mental illness. However, the adoption studies suffer from their own shortcomings. Even more so than twin studies, the samples are limited, there are issues related to the confidentiality of adoption records, and not infrequently, there is a mismatch between the educational, socio-economic, and even ethnic backgrounds of adoptive and biological families. Furthermore, adoption agencies typically seek adoptive families with high social stability with no history of mental illness.

Adoption studies found that biological parents of people with BD are more likely to have BD in comparison to adoptive parents. The rates of bipolar, unipolar, schizoaffective, and cyclothymic disorders were two times greater in biological parents in comparison with the adoptive parents, and biological relatives of affected adoptees were more likely to have committed suicide, had higher rates of MDD and alcoholism in comparison with the adoptive relatives. Studies on childhood adoption indicated that stressful prenatal and postnatal environmental factors, as well as adoption early in life, are associated with the emergence of psychiatric disorders in adulthood and higher levels of depression, anxiety, and personality disorders [13]. Aiming to address potential genetic confounding and gene–environment interactions, Lehto et al. found that the polygenic scores (PGS) for depressive symptoms, SZ, and neuroticism were all associated with an increase in the odds of being adopted, with PGS for SZ having the largest effect. Meanwhile linkage disequilibrium score regression indicated positive genetic correlations between MDD, SZ, smoking, and childhood adoption and negative correlations with educational attainment. However, BD status in this study was based on self-report, and the authors did not differentiate BD I and II subtypes [14].

4.5 Molecular Genetic Findings

Establishing a genetic basis for an illness is the first step in identifying specific genetic mechanisms, that might ultimately improve the diagnostic classification, and inform clinical management. Historically, the search for individual susceptibility genes has been influenced by several factors: (1) the increasing number of genetic markers and the hugely reduced cost and increased speed of genotyping; (2) the decreasing family size in most countries; and (3) the growing numbers of people enrolled in various population databanks and commercially operated genetic services. The history of molecular genetic research tracks closely the development of molecular genetic methods. Early studies had to rely on few available markers mapped to specific loci, for example, blood groups or HLA types. Gradually, the number of markers increased from hundreds (restriction fragment length polymorphisms) to thousands (microsatellites) to millions of SNPs, and eventually whole genome (WGS) sequencing.

4.6 Linkage Studies

Spurred by the success of genetic investigations of Mendelian traits such as cystic fibrosis or Huntington's disease, psychiatric genetics turned to linkage studies in the 1980s. Linkage analysis investigates the cosegregation of the putative susceptibility gene with genetic markers in families with multiple individuals affected by the same or related diseases. Initially, genetic linkage studies in BD focused on

large extended families, investigating a few candidate regions based on a priori hypotheses (e.g., the hypothesis of a susceptibility gene on X-chromosome) and the availability of suitable markers. As the first promising reports often failed to replicate [15, 16], the design of linkage studies moved towards larger numbers of small (nuclear) families and used markers covering more or less the whole genome (whole genome scan). Heterogeneity and possible involvement of multiple genes (oligogenic or polygenic inheritance) have been among the factors cited as responsible for inconsistent findings. To circumvent these problems, researchers focused on families with presumably more homogeneous forms of the illness. This approach was motivated by successes in specific forms of otherwise complex conditions—for instance, the *BRCA1* gene in early onset breast cancer or Apo $\epsilon 4$ association (first discovered by linkage analysis) in late-onset Alzheimer's disease. In psychiatric research, more homogeneous samples were sought among populations with unique ethnic backgrounds (Old Order Amish [17], French Canadians [18], Costa Ricans [19], Faroe Islands [20]), early onset [21], or families of probands responsive to lithium [22].

Overall, BD linkage studies have produced a plethora of suggestive findings practically on all chromosomes but have not provided conclusive evidence of specific major gene(s). Nevertheless, some of the early findings, such as those on chromosome 11 or chromosome X, are congruent with later genome-wide association studies (GWAS) results. In particular, one of the most significant signals of the first GWAS published by the Psychiatric Genomics Consortium (PGC) BD group was an intronic variant in *ODZ4*, a member of a family of cell surface proteins found at chromosome 11q14. The subsequent PGC2 BD also pointed to the importance of region 11q by identifying six SNPs mapped in genes located in this chromosome, whereas the latest PGC BD report highlighted the significance of the gamma-aminobutyric acid (GABA) system on chromosome X. A meta-analysis of previous genome-wide linkage scan datasets also highlighted the importance of a region on chromosome 6 in the proximity of the melanin-concentrating receptor 2 gene (*MCHR2*). This gene is involved in intracellular calcium release, phosphoinositol, and kynurenine pathways, which have been implicated in lithium effects and have also emerged in subsequent GWAS and next-generation sequencing studies. Some of the linkage findings were not entirely specific to BD; for instance, the *DISC1* gene, located on chromosome 1, previously found associated with SZ possibly contributes to psychotic symptoms in BD patients.

Finding and assessing multiply affected families, as well as intrafamilial heterogeneity and likely involvement of multiple genes, are just a few of the factors for which linkage analysis is now being replaced by genetic association studies. The inconsistent linkage results in BD are seen as evidence that no single gene explains most of the genetic susceptibility for the illness. In other words, single-gene forms of BD are hypothetically possible but unlikely to account for more than a fraction of cases.

4.7 Candidate Gene Association Studies

Genetic association studies are another approach that has gained popularity and is now the most common method for studies of complex traits. They compare allelic frequencies of genetic variants between affected and unaffected individuals—either in the general population (case–control design) or within families (family-based association studies). The method is appealing for its simplicity and easier collection of clinical or population samples in comparison with linkage (Fig. 4.1).

Common variants with small effect sizes have strong evidence in BD and can be detected through genome-wide association studies. On the contrary, very rare variants with large effect sizes have limited evidence in BD and can be detected through linkage analysis and next-generation sequencing methods. BD: bipolar disorder, NGS: next-generation sequencing, GWAS: genome-wide association studies.

The first association studies were based on a candidate-gene approach, focusing on specific genes hypothesized to play a role in disease susceptibility or involvement in the mechanism of action of pharmacological treatments or other clinical aspects of the illness. Their shortcomings, especially the limited numbers of available genetic markers and reliance on the knowledge existing at the time, were later offset by the development of genome-wide association methods (GWAS, see the next section).

The early candidate gene studies focused on genetic variants in neurotransmission—enzymes involved in the synthesis and metabolism of neurotransmitters, dopamine and serotonin in particular, and their receptors. Similar to linkage results, these studies produced inconsistent and rarely replicated findings. The first positive reports may have been the victims of the “winner’s curse,” that is preferential publication of a result inflated by chance [23]. It was not long before it became obvious that the number of potential genes is much larger than initially thought; this would

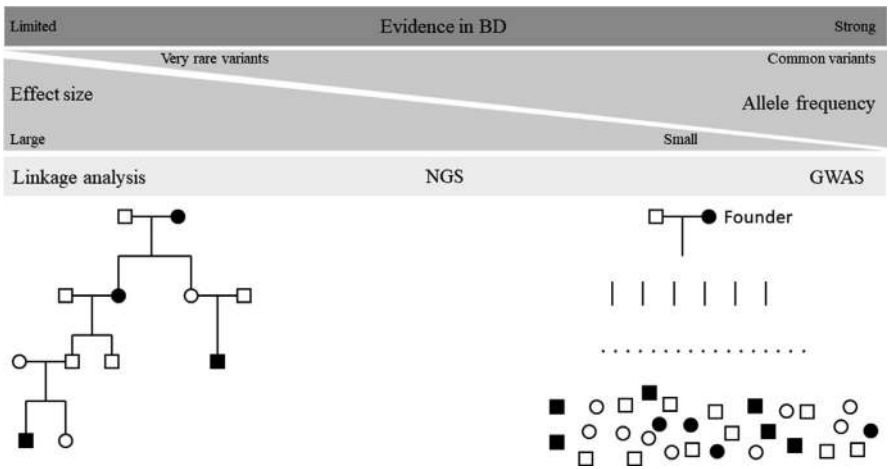


Fig. 4.1 Contribution of genetic variants in bipolar disorder

also mean that much larger samples would be required to account for multiple hypotheses tested. Nevertheless, candidate gene studies remain relevant for testing specific hypotheses, especially with respect to specific traits of BD, such as age of onset, cognitive deficits, comorbid anxiety disorders, BD diagnostic classification (i.e., BD I vs. BD II), and therapeutic outcomes, which can impact compliance and prognosis. It remains to be seen which of these associations will be confirmed in GWAS or next-generation sequencing (NGS) studies. For instance, only recently, PGC4 BD reported for the first time the enrichment of dopamine-related biological processes [24].

4.8 Genome-Wide Association Studies

In the last decade and a half, the cornerstone of genetic research in complex traits has been genome-wide association studies (GWAS), which take advantage of rapid and inexpensive genotyping of single nucleotide variants (SNPs). In principle, GWAS compare distributions of genetic variants covering the entire genome in a case-control design. Common variants not directly genotyped are imputed using reference genome panels, facilitating comparisons and meta-analyses of GWAS data. The large number of statistical comparisons leads to a significant penalty for multiple tests. Typically, the number of genotyped + imputed SNPs in a single study ranges between 6.5 and ten million [25–27]; the accepted genome-wide significance threshold is 5×10^{-8} (0.05 corrected for 10^6 independent tests) as a large proportion of SNPs are in linkage disequilibrium and thus are not considered independent. Findings that pass this threshold are more likely to be replicated. Thus, substantial samples are required for sufficient statistical power. These days, most GWAS are carried out in collaborations with international consortia, especially the PGC, and/or based on samples from various national biobanks (UK, Estonia, and Finland). This approach has successfully generated samples counting tens of thousands of cases and often hundreds of thousands of controls [24, 25, 28]. The expanding samples have led to an increasing number of positive findings, as shown in Fig. 4.2 and Table 4.1.

The proportion of phenotypic variance accounted for by the established GWAS associations, the so-called SNP heritability, is substantially lower than the heritability estimated from family and twin studies. In the most recent GWAS of BD, the h^2_{SNP} was 0.22. As it is likely that further significant associations will be detected, but these will, at the same time, have smaller effect sizes, the number of common genetic variants to come close to the twin-based heritability figures is estimated at 8000 [25]. This will also require even larger sample sizes than are currently available, possibly at a cost of further “dilution” of the phenotypic characterization, as seen with the self-report data from some of the biobanks. This may further increase the heterogeneity, reduce statistical power, and generate findings not specific to BD. [29]. On the other hand, focusing on specific sub-phenotypes, such as early

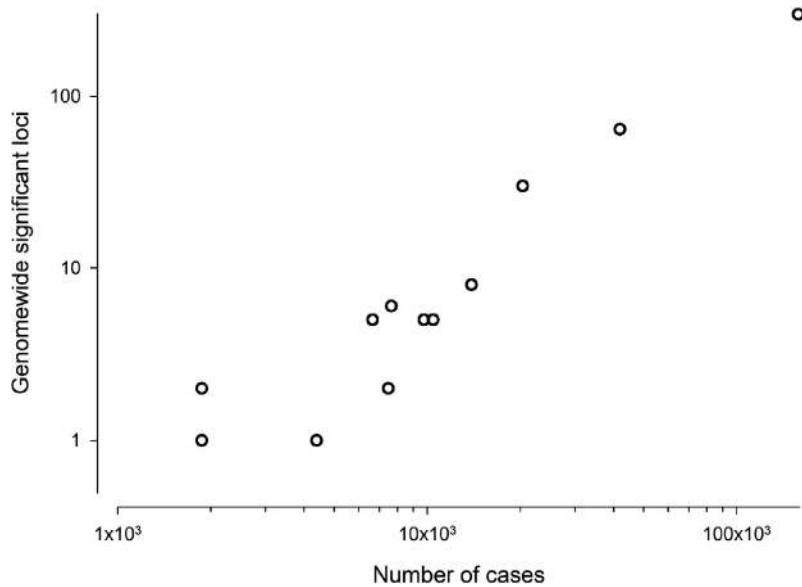


Fig. 4.2 Number of genome-wide significant loci in bipolar disorder as a function of sample size

Table 4.1 Genome-wide association studies of bipolar disorder among Caucasian populations

Author/Group (year)	Discovery cohort		Replication cohort		Genome-wide significant loci	Reference
	BD patients	Controls	BD patients	Controls		
Wellcome Trust Case Control Consortium (2007)	1868	2938	–	–	1	[30]
Ferreira et al. (2008)	4387	6209	–	–	1	[31]
Baum et al. (2008)	461	562	772	876	1	[32]
Cichon et al. (2011)	682	1300	7759	34,062	1	[33]
Jiang et al. (2011)	1868	2938	–	–	2	[34]
PGC1 BD (2011)	7481	9250	4496	42,422	2	[35]
Bergen et al. (2012)	836	2093	–	–	0	[36]
Chen et al. (2013)	6658	8187	1115	2728	5	[37]
Muhleisen et al. (2014)	9747	14,278	–	–	5	[38]
Hou et al. (2016)	7647	27,303	2137	3168	6	[39]
Charney et al. (2017)	13,902	19,279	–	–	8	[40]
Ikeda et al. (2018)	10,445	71,137	–	–	5	[41]
PGC2 BD (2019)	20,352	31,358	9412	137,760	30	[28]
PGC3 BD (2021)	41,917	371,549	–	–	64	[25]
PGC4 BD (2023)	158,036	2,796,499			298	[24]

NA not available, PGC BD Psychiatric Genomics Consortium Bipolar Disorder Working group

onset or familial cases, can improve the statistical power (but may make the recruitment more difficult).

GWAS need to address several methodological issues. Controlling for population stratification is important, especially in large cohorts. To decrease type I errors, cases and controls should be matched carefully for ethnicity, and GWAS data with substantial genetic background differences should be excluded. Missing genotypes are usually inferred by imputation using reference panels, but for non-Caucasian populations, the availability and accuracy of reference panels are limited. Ideally, the reference panel and the GWAS cohorts should be genotyped using the same platforms, but this rarely can be achieved. Thus, one must ensure that variants are mapped to the same genome build (e.g., Genome Reference Consortium Human Build 37 [GRCh37] or GRCh38) with alleles labeled on the same DNA strand. Imputed values are estimates and, thus, are associated with random errors, which can lead to bias and loss of information. Sometimes, imputation can result in an exclusion of a proportion of the original sample, causing a loss of power.

The first GWAS of BD were part of an investigation of seven major diseases and found an association of BD with a single locus, the *PALB2* gene, known for its role in tumor suppression. However, the finding has not been replicated [30]. Since 2007, several GWAS of BD have found an increasing number of positive associations as the sample size of these studies continues to increase [Table 4.1].

The first GWAS by the Psychiatric Genomics Consortium (PGC1) BD confirmed the previously reported association with calcium voltage-gated channel subunit $\alpha 1C$ (*CACNA1C*), supporting the view that ion channels and calcium signaling may be involved in BD pathophysiology [35]. The combined data of the GWAS meta-analysis and follow-up samples analysis of PGC2 BD identified 20 novel loci containing genes that encode ion channels, neurotransmitters, and synapses. PGC2 BD also found a strong genetic correlation between BD I and SZ and BD II and MDD [28], which was confirmed by subsequent GWAS [25, 42]. Of the identified loci, 34 have been previously associated with SZ and MDD, and 33 were novel. Twenty-eight out of the 30 associations from PGC2 were replicated in PGC3. SNPs in and close to the major histocompatibility complex (MHC) locus reached genome-wide significance, and GWAS signals were enriched in genes of the synaptic signaling pathway and brain-expressed genes.

The PGC3 also reported the results of expression quantitative trait loci (eQTL) analysis, used to help identify causal variants. Among these, *HTR6* and *MCHRI* represent potential drug targets. The study also showed that smoking initiation might be a risk factor for BD [25]. Finally, the most recent GWAS by PGC pointed to genes related to dopamine- and calcium-related pathways and GABAergic interneuron development [24].

The phenomenon of pleiotropy, that is, genetic variants contributing to more than one trait, has also emerged at a genome-wide level. It should not be surprising as diagnostic classification in psychiatry does not align completely with biological boundaries. Pleiotropy can also be due to additional factors, including gene–gene interactions and environmental effects. For example, genes involved in calcium channels (*CACNA1C*), synaptic plasticity (*ANKK3*), and inflammatory and infectious

responses (*ITIH3-ITIH4*) have reached genome-wide significance for both BD and SZ [43], suggesting a genetic overlap of the two disorders. On the other hand, SNPs located in genes that participate in cell surface signaling (*ODZ4*), transcription factors, regulators of neural stem cells (*TCF4*), and other loci attained genome-wide significance for either BD or SZ but not for both. Combining cases of BD and SZ has helped further identify genome-wide significant regions. These include the major histocompatibility complex (*MHC*) and genes that enable ATP and GTP activity (*TRANK1*, *IFI44L*), cell cycle control and tumor suppression (*MAD1L1*), as well as *PIK3C2A*, involved in cell proliferation, survival, and migration. Ruderfer et al. concluded that it is very likely that the shared loci between BD and SZ have significant differential effects, which can potentially help us better understand the biological differences between the disorders [44]. PGC BD and SZ combined data also pinpointed 114 shared genome-wide significant loci involved in synaptic and neuronal pathways. Comparing SCZ to BD cases, there has been an enrichment of potassium ion response genes, suggesting that potassium metabolism might be the mechanism that distinguishes the two disorders [45].

The majority of GWAS focus on European cohorts. Studies that included East Asian populations suggested that BD might be characterized by both common and population-specific susceptibility genes. Common genes that reached genome-wide significance include those involved in ion channels (*CACNB2* and *KCTD12*), neuronal development (*ANKK3*), and cell surface signaling (*ODZ4*). On the other hand, regions that regulate brain development (SNPs near *SP8* and *ST8SIA2*) and plasma lipid levels (*FAD1/2/3*) are significantly associated with Han Chinese and Japanese populations, specifically [41, 46].

The GWAS to date are consistent with the view of the polygenic nature of BD. So far, only a proportion of the genetic variability has been clarified, and the exact role of genes underlying the pathophysiology of BD waits to be established. The specific role of the genetic variants needs to be further validated in functional studies. An example of such a follow-up approach is the study by Chen et al., who performed a functional genomic analysis that identified 16 functional SNPs that disrupted the binding of 7 transcription factors and thus could play a role in the regulatory mechanisms of BD risk variants [47].

4.9 Next-Generation Sequencing

Whole genome (WGS) and whole exome sequencing (WES) can capture rare single nucleotide variants and short insertions/deletions, possibly accounting for some of the missing heritability not explained by GWAS. Some of the rare variants can, in fact, have large effects. Several sequencing studies have highlighted the role of calcium signaling and potassium channels, which have previously emerged from GWAS, and the extracellular signal-regulated kinase (ERK)/ mitogen activated protein kinase (MAPK) and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)-regulated signaling pathways, which are the target of mood

stabilizers and are essential for neuronal and synaptic plasticity, cognition, and response to chronic stress. However, there is still the need to sequence many additional bipolar samples to explain previous association findings. Using combined gene-level results of BD and SZ, Palmer et al. (2022) reported the involvement of *AKAP11*, providing evidence that rare variation overlaps in these two disorders [48].

Some family-based sequencing studies, including those in a large Old Order Amish pedigree, failed to identify rare pathogenic variants, attributing the negative results to within-family genetic heterogeneity. On the other hand, WES of multigenerational families identified 14 rare and likely deleterious variants associated with BD shared among the affected family members but absent in the unaffected relatives. Among those were genes previously identified by GWAS, involved in calcium ion channel (*EPS15*), and GTPase activation (*ARHGAP32*, *MYO9A*, *PPP1R12B*, and *TBC1D10C*), known lithium targets. Two rare variants in the serotonin transporter gene (*SLC22A1*), a receptor that received much attention in the candidate gene era, were also detected in one affected individual [49].

4.10 Rare Variants

Kataoka et al. [50] and Goes et al. [51] sequenced proband-parent trios and found significant enrichment of genes highly intolerant to protein-altering variants in the general population and loss of function, and damaging missense de novo mutations (DNMs) in constrained genes and genes involved in postsynaptic density. Gene ontology enrichment analysis of genes hit by deleterious germline DNMs in BD identified, among others, clusters related to synapses and calcium ions. To identify rare variants associated with BD, still much larger number of samples will be required. Several collaborations currently underway (e.g., Bipolar Sequencing Consortium) aim to combine WGS and WES data to further investigate the role of rare variants. The availability of rapid and inexpensive WGS is expected to increase, which may in the future inform the diagnostic classification and possibly clinical management.

4.11 Copy Number Variants

Most studies found no significant overall increase in copy number variant (CNV) burden, except an increase in de novo CNVs in BD patients with early onset of their illness [48]. Georgieva et al. showed that the role of de novo CNVs is smaller in BD compared with SZ and that de novo mutations could be more often found in patients with a positive family history [52].

Large rare CNVs have been associated with SZ, as well as BD and recurrent depression combined, but not BD separately. Very large CNVs, especially deletions of >1 Mb, contribute less to BD than SZ. Still, the exact contribution of rare CNVs and rare coding variants is unclear.

4.12 Polygenic Scores, Cross-Disorder Analyses, and Psychiatric Phenotypes in GWAS

GWAS make it possible to combine their results into polygenic scores (PGS) calculated as the sum of the risk-associated variants weighted by their respective effect size (relative risk). The scores are calculated for all independently significant loci up to a certain threshold—type I error—typically set to maximize the phenotypic variance explained by the PGS. The PGS can be then used as an index of additive polygenic liability. They also provide one of the possible methods to investigate the mutual relationship between genetic predispositions to two or more conditions. For instance, the first study of PGS in psychiatry published in 2009 by the International Schizophrenia Consortium showed that the combined effect of common variants that were not individually significant in the initial GWAS also contributed to BD risk. Such studies have consistently shown a genetic correlation between SZ and BD, a moderate correlation between SZ and MDD, BD and MDD, and attention deficit hyperactivity disorder (ADHD) and MDD, and a low correlation between SZ and autism spectrum disorders (ASD). Specific SNPs have been found to be significantly associated with multiple psychiatric disorders, namely four regions on chromosomes 3p21 and 10q24 and two SNPs in *CACNA1C* and *CACNB2* genes, all associated with SZ, BD MDD, ADHD, and ASD [53]. Pathway analysis further established the role of calcium channel signaling genes and the common genetic overlap of these five disorders [54]. Using genomic structural equation modeling (gSEM), Richards et al. derived components of liability shared between SZ, BD, and MDD, as well as components that differentiate them. Mania, psychosis, and depression were components of genetic liability that differentiate BD, MDD, and SZ, respectively. Higher shared liability was associated with mania, independently of psychosis, but not with psychosis independently of mania [55]. Combining polygenic signatures with clinical symptom dimensions can give the clinician additional helpful information. Ruderfer et al. demonstrated that BP PGS was correlated with mania in SZ patients, with the strongest association being at the end of the mania distribution. These findings indicate that there is possibly a sub-group of bipolar patients characterized by high genetic loading for BD and high mania scores. Allardyce et al. reported strong associations between PGS for MDD and SZ with depression and psychosis dimensions in bipolar patients, respectively. Interestingly, they found a weak association between PGS for BD and the mania dimension [56]. PGS for SZ have also been associated with the age of onset and psychotic symptoms in BD [45] and non-response to lithium [57]. High PGS for BD have been associated with an early age of onset of depression and more depressive episodes, especially in patients with a family history of depression [54]. PGS can also be used to identify groups at risk in early life. For instance, Zwicker et al. found that the PGS for ADHD in youth that have parents with BD, MDD, and SZ spectrum disorders were associated with exposure to adversity defined by childhood maltreatment, bullying, and socio-economic disadvantage [58].

Genetic correlation analyses also highlighted differences between BD subtypes; they showed an increased SZ PGS and lower depression PGS in BD type I, while in BD type II, the PGS for depression was higher. Suicidal ideation was associated with higher PGS for BD, indicating that polygenic load of BD might predetermine a more severe form of the disorder [59]. Allardyce et al. found that PGS in those patients with the diagnosis of schizoaffective disorder, or BD I, were higher than controls, but this was not the case for BD II patients. In addition, there was an exposure-response gradient across clinical phenotypes, with the strongest PGS association for SZ, followed by SZA BD, BD I, and II. Schizophrenia PGS could discriminate between patients with BD and schizoaffective bipolar disorder but not between BD with and without psychosis [57]. On the other hand, Aminoff et al. reported that BD PGS was higher in patients with psychotic symptoms than in patients with non-psychotic symptoms [54]. Notably, among bipolar cases, prominent mood incongruent psychotic features had the strongest association, followed by mood-congruent psychosis and BD without a history of psychosis [57]. In spite of the proliferation of investigations based on PGS, their clinical use remains limited mainly due to the fact that to date, they generally explain only a fraction of total phenotypic variance. This may change in the future with larger GWAS samples used to derive scores with better explanatory power.

4.13 Family History in Clinical Practice

Genetic information contributes to clinical management in psychiatry. It can help in differential diagnosis, treatment selection in some instances as well as estimating genetic risk in the offspring of people with BD. For some families, the notion of BD having a genetic underpinning could be helpful in dealing with the stigma of mental illness. While ongoing efforts are underway to develop laboratory markers, to date, family history remains an important part of the assessment. To maximize its usefulness, family history should be obtained using a structured approach reviewing each family member in turn, rather than asking summary questions such as “Did anybody in the family have...?” Interviewing additional family members can also improve the validity of the information. It has been shown repeatedly that family history obtained in a routine fashion can be quite inaccurate [60], while a structured, systematic approach yields a more accurate picture [61]. Assessing family history is also an opportunity to understand better the dynamics in the family and the attitudes of family members towards psychiatric illness.

The effect size of PGS in psychiatry largely overlaps with the effects of family history, but their predictive power is smaller. PGS can be more helpful when there are not enough details of family history; notably, PGS of neuroticism and subjective well-being could be better risk predictors, probably due to their role as transdiagnostic factors. Given that the first signs of psychopathology begin early in life, PGS of such transdiagnostic indicators can help stratify the degree of risk for mood and psychotic disorders.

4.14 Pharmacogenetics

Effects of medications, including response to treatment and side effects, are partly dependent on the genetic background of the patient. In psychiatry, the most studied pharmacogenetic mechanisms are those related to drug metabolism, the cytochrome P450 system in particular. This has some relevance for the treatment of BD with antidepressants and certain antipsychotics, as well as their combinations. Currently, genetic testing could be indicated in patients who do not respond to high doses of such medications in the absence of any side effects (ultra-rapid metabolizers) or conversely in those who experience adverse effects on low medication doses (slow metabolizers). The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics working group provide recommendations for using CYP2D6 and CYP2C19 genotype results to help inform prescribing for antidepressants and antipsychotics that can be applied in the psychiatric clinical practice [62, 63]. The available evidence from pharmacogenetic studies that focus on lithium remains limited. The GWAS from the International Consortium on Lithium Genetics, in more than 2500 cases, detected genome-wide significant associations between four linked SNPs on chromosome 21 and lithium response, confirmed in an independent, prospective cohort, in which the carriers of the identified alleles had a significantly lower relapse rate. The number of pharmacogenetic studies of anticonvulsants used in BD is also limited. However, clinically useful are the associations of Stevens–Johnson syndrome risk with specific HLA variants, both for carbamazepine and lamotrigine [48].

4.15 Risk Prediction

A family history of BD and/or completed suicide is considered the strongest risk factor for BD. The illness characteristically develops in stages with anxiety in childhood, followed by nonspecific mood symptoms and more typical depressive or manic episodes in late adolescence or early adulthood [64]. Prediction of the risk of BD is clinically relevant as the majority of first mood episodes are those of depression, yet young people at risk of BD may respond poorly to antidepressants or even experience worsening of their depression and increased suicidality. Careful clinical assessment, including details of the clinical course, comorbid psychopathology, substance abuse, history of suicide, and family history, can help us identify the underlying predisposition to BD. Beyond the clinical presentation, there are no diagnostic tests to aid in differential diagnosis of early onset depression. However, PGS methods are being investigated in high-risk studies; they are already beneficial in the clinical practice of other complex diseases. For instance, risk prediction tools in cardiology are well-established worldwide and can be used clinically. These tools can combine PGS with risk factors such as age, sex, smoking habits, family history of heart disease, total and high-density lipoprotein cholesterol, and

electrocardiogram results, to calculate the individual's total risk score. Early examples of this approach in BD can be found in the PGC group for high-risk studies that reported the combined contributions of family history and PGS for several phenotypes, neuroticism in particular, as contributory to the risk of mood disorders [65].

4.16 Conclusions

The high heritability of BD stands in contrast to the slow progress of the search for specific genetic mechanisms—likely due to multiple factors, including its complex genetic architecture and phenotypic and genetic heterogeneity. For now, family history remains the best tool at our disposal to improve personalized clinical management. However, we hope that, combined with multi-omics approaches such as epigenomics, transcriptomics, or proteomics, genetic findings will allow more accurate classification of BD and pave the way to early diagnosis, personalized treatment selection, and more accurate prognosis, as well as developing new treatments.

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Chapter 5

Prodromal Symptoms and Risk Markers of Bipolar Disorder



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5.1 Introduction

Large population-based studies suggest that the prevalence of bipolar disorder in the general population ranges from 1.5% to 2.2% [1–3]. Bipolar disorder is also associated with impaired occupational and interpersonal functioning, and quality of life, as well as increased psychiatric comorbidity, use of health care services, and life years lost due to illness [4]. Suicidal behavior is also more common in patients with

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bipolar disorder, with a lifetime prevalence of suicide attempts being reported in up to 33.9% of patients (95% CI: 31.3%–36.6%) [5]. Furthermore, bipolar disorder appears to have a neuroprogressive course in at least a subset of patients [6]. Thus, a deeper understanding of this disorder is important for risk identification, preventive interventions, early diagnosis, and effective treatment management [7].

Possible risk markers for bipolar disorder throughout an individual's life have long been a target of investigation for experts, as a way to improve early diagnosis and implement early interventions that could prevent further development or worsening of the disorder. Bipolar disorder is known to be a highly heritable disease, meaning that a positive family history has been widely correlated with a higher likelihood of developing the disorder. Prenatal and perinatal events [8], as well as childhood trauma [9] and substance use [10], have also been associated with increased risk of bipolar disorder. However, establishing consistent causal relationships between these risk markers and bipolar disorder can be difficult, requiring large samples and careful analyses of potential bias or confounding factors [7].

An understanding of the bipolar disorder as a neuroprogressive illness has focused attention on what is now called “latent bipolar disorder,” which is the period that precedes the diagnosis [6]. This change in view of its clinical progression brings awareness to the fact that there are prodromal symptoms that may appear years before the onset of the illness. This has important clinical implications, as it could further improve early diagnosis and guide effective and safer therapeutic interventions [4, 11].

The present chapter aims to highlight the latest evidence on risk markers and prodromal symptoms of bipolar disorder. Current evidence on treatment approaches and staging models are also assessed, summarizing a comprehensive picture of modern knowledge about the longitudinal course of the illness.

5.2 Family History and Prenatal/Perinatal Risk Markers

5.2.1 Family History

A positive family history of bipolar disorder is well-established in the literature as a risk factor for the development of this disorder. In fact, a diagnosed relative has long been a reason for suspicion in the clinical setting, even if the patient has not yet presented with mood elevations but only depressive episodes [12]. Twin and family studies have estimated the heritability of bipolar disorder to be between 60% and 85% [12–14], making it one of the most heritable of all psychiatric disorders, surpassing schizophrenia and autism spectrum disorder [15].

A recent genome-wide association study [16] identified 64 genomic loci associated with the disorder, some of which were already correlated with other psychiatric disorders, mainly schizophrenia and major depressive disorder, and other traits such as smoking, problematic alcohol use, and sleep quality. However, the concordance

between monozygotic twins was well below 100%, suggesting that bipolar disorder cannot be explained by genetic inheritance alone.

There is a consensus that the genetic predisposition to bipolar disorder is complex, involving multiple loci and genes with varying effect sizes and frequencies across populations, and interacting with environmental factors. Technological advances in genetics may eventually lead to a better understanding of the genetic overlaps and differences between bipolar disorder and other mental disorders, as well as the different phenotypes of this disorder. This could have important clinical implications as the development of polygenic risk calculators could aid in early diagnosis and therapeutic development [12, 16].

On the other hand, a positive family history of bipolar disorder could serve as a risk factor for bipolar disorder in ways other than genetic inheritance. Studies of individuals at high risk for developing the disorder typically compare individuals diagnosed with bipolar disorder to a control group of individuals at low risk, but also to high-risk individuals who did not develop the disorder. In this way, environmental risks attributed to being raised by a relative diagnosed with bipolar disorder are also assessed [17]. A systematic review published in 2020 [17] found that families with parents diagnosed with bipolar disorder had higher rates of bipolar disorder and mood disorders, in general in their offspring, compared with parents without a psychiatric diagnosis. Interestingly, there was no significant difference in rates of bipolar disorder in offspring when parents diagnosed with bipolar disorder were compared with parents diagnosed with any major psychiatric disorder. Family environment was also assessed, and results consistently showed that parents with bipolar disorder reported lower family cohesion, while families with bipolar disorder-diagnosed offspring reported higher conflict, both of which may act as environmental risk factors for psychiatric disorders in general, and higher emotional dysregulation in patients with bipolar disorder.

5.2.2 Prenatal/Perinatal Risk Markers

In the history of psychiatry, a long-standing debate about the pathophysiology of schizophrenia—whether its nature is neurodegenerative or neurodevelopmental—culminated in the neurodevelopmental risk factor model. This hypothesis includes genetic predisposition, early neural insults, childhood and adult adversity, and environmental exposures throughout life as important risk factors for the development of this disorder [18]. Schizophrenia and bipolar disorder share a number of similarities in their pathophysiology and genetic predisposition, suggesting that the neurodevelopmental risk factor model may be an important tool for understanding bipolar disorder as well, which has been supported by recent evidence [19]. Thus, prenatal and perinatal risk factors have fostered an increasing interest in the field [7] not only as a means to better understand these two mental disorders but also as a possible target for preventive measures [20].

In this context, several prenatal and perinatal variables have been considered as potential risk factors for the development of bipolar disorder in various primary studies, but lack of statistical power led to inconsistent results across studies and replication proved difficult [8]. For instance, older paternal age was associated with a higher risk of developing bipolar disorder [21], but a later study [22] was unable to replicate this finding. To overcome this challenge, Shintani et al. [8] combined primary studies in a systematic review and meta-analysis. Twenty-seven studies were included and 18 factors were analyzed. Four factors were identified as statistically significant risk factors for bipolar disorder: peripartum asphyxia, low birth weight (less than 2500 g), maternal stress during pregnancy, and obstetric complications. It is worth noting that both peripartum asphyxia and low birth weight (less than 2500 g) had their effect sizes compromised by the leave-one-out procedure, which may indicate that their effect sizes are attributable to a few studies. Maternal stress during pregnancy was the strongest factor, with an odds ratio of 12, significantly higher than the others, which ranged from 1.28 to 1.46. These findings contribute to the neurodevelopmental risk factor model hypothesis, as the same four risk factors for bipolar disorder were also found to be risk factors for psychosis in a similar study [20]. While this deepens our knowledge of the etiopathogenesis of bipolar disorder, it calls for further investigation, as bipolar disorder and schizophrenia are still very different mental disorders, with specific clinical presentations and management, requiring individualized risk prediction tools for early diagnosis [4].

Another systematic review and meta-analysis [23] evaluated prenatal tobacco exposure as a possible risk marker for the development of mood disorders in offspring. Ten studies were included and a small but positive association was found for both depressive and bipolar disorders (RR = 1.44; 95% CI: 1.21–1.71 and RR = 1.44; 95% CI: 1.15–1.80, respectively). In addition, the studies that assessed different levels of exposure showed a dose-related effect of prenatal tobacco use. High exposure was associated with a higher risk of offspring mood disorders (RR = 1.54; 95% CI: 1.46–1.62) compared to moderate exposure (RR = 1.36; 95% CI: 1.30–1.42). However, the heterogeneity and confounding factors of the studies must be taken into account. The studies that adjusted for maternal psychiatric history or maternal age, education, social class, and parental income showed slightly lower but still positive and significant risk ratios. A recent birth cohort study [24] further supports the association between bipolar disorder and maternal tobacco exposure during pregnancy, as an increased risk of this disorder was associated with both maternal smoking (OR = 1.419; 95% CI 1.091–1.841) and maternal passive tobacco exposure (OR = 1.425; 95% CI 1.086–1.875) even after controlling for confounders.

5.3 Early Trauma

Early trauma has been associated not only with increased risk for many psychiatric disorders but also with worse clinical outcomes, such as suicide attempts and earlier age of onset of the disorder [9]. In bipolar disorder, early trauma plays an important role in the pathophysiology, as it is significantly more prevalent in these patients than in the general population being present in over 50% of diagnosed patients [9, 25]. In addition to higher prevalence rates, multiple trauma episodes and subtypes, as well as the severity of the trauma, were higher in individuals diagnosed with bipolar disorder [26–28]. A comparative study found that the presence of at least two types of traumas was 3.48 times (95% CI: 2.08–5.82) more common in patients with bipolar disorder than in controls [28].

As shown by Jansen et al. [9], sexual abuse may play a specific role in bipolar disorder. Multivariate analysis revealed the highest prevalence ratio (PR) in patients with bipolar disorder compared to controls (PR = 9.16; 95% CI: 1.03–81.60) and major depressive disorder (PR = 0.77; 95% CI: 0.03–18.15). Early trauma seems to act as a mediating factor between a family history of mood disorders and a higher risk of developing a mood disorder. This reinforces the concept that familial risk is both direct (genetic) and indirect (early adversity) in increasing the risk of developing a mood disorder [9]. Thus, early identification and intervention in high-risk families may serve as an important strategy to mitigate the development and severity of bipolar disorder.

There is a plethora of clinical and functional factors that have been correlated with childhood trauma in patients with bipolar disorder, and evidence shows that there appears to be a “dose-related” effect, as the number of traumatic events has been associated with a worse prognosis for this disorder in several domains [27]. In the natural history of bipolar disorder, early trauma appears to be associated with a younger age of onset, delayed diagnosis, and increased number of hospitalizations. In terms of symptomatology, the number and severity of depressive episodes, the intensity of manic symptoms, and the frequency of psychotic symptoms were all higher in patients with bipolar disorder with a history of early trauma. Cycling was also affected, as faster cycles and a higher prevalence of rapid cycling were also correlated with trauma. Suicide attempts were 1.6 (95% CI: 1.07–2.39; $p = 0.023$) and 1.8 (95% CI: 1.14–2.86; $p = 0.012$) times more frequent, respectively, in patients with bipolar disorder with a history of emotional and sexual abuse in childhood, while rapid cycling was 2.04 (95% CI: 1.21–3.42; $p = 0.007$) times more frequent in patients with bipolar disorder with a history of sexual abuse [29]. Finally, drug dependence and suicide risk were also increased by childhood trauma [26]. Some studies suggest that early trauma may also have an impact on worsening treatment response, but more research is needed because current evidence lacks statistical power and has a high risk of bias, so this effect was not confirmed in a recent meta-analysis [30].

In conclusion, early trauma should always be considered and assessed in the clinical setting, whether to determine the risk of developing a mood disorder or to

predict and prevent more severe progression of bipolar disorder. Because it is such a detrimental factor not only in the setting of bipolar disorder but for mental health in general, early trauma should be a priority target for intervention, once it is a modifiable factor.

5.4 Substance Use

The association between substance use disorder and bipolar disorder leads to greater impairment in both functionality and quality of life [31]. In addition, substance use is associated with the risk of developing bipolar disorder [10, 32].

A nationwide population-based study aimed to identify risk factors for bipolar disorder in patients with rheumatoid arthritis and, using matched regression models, found that alcohol use disorder was an independent risk factor (HR = 5.29) [33]. A prospective five-year follow-up study examined the incidence of bipolar disorder in 301 patients with a single episode of depression and showed that conversion to bipolar disorder increased in patients with alcohol or drug abuse (HR = 2.4; 95% CI: 1.1–5.1) [34]. Strakowski and Delbello [35] observed that patients with substance use disorders had late-onset bipolar disorder, suggesting that substance exposure (alcohol or drugs) may have triggered the development of bipolar disorder in patients who would not otherwise have bipolar disorder. They also demonstrated a demographic pattern in which the mean age of substance use disorder onset is lower than that of bipolar disorder, strengthening the hypothesis of substance use as a predictor of bipolar disorder.

There is also a substantial body of research examining cannabis use as a risk factor for bipolar disorder. A two-wave analysis of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) showed that 9.1% of the 391 participants who reported regular cannabis use at wave 1 developed bipolar disorder at wave 2 (OR = 1.38, 95% CI: 1.11–1.72) [36], whereas only 3% of participants without regular cannabis use developed bipolar disorder at wave 2. A longitudinal study using data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) among the Dutch population aged 18–64 years showed that cannabis use was a predictor of bipolar disorder within a three-year follow-up period. Furthermore, an increased frequency of cannabis use, particularly 1–4 times per week, was associated with an increased risk of bipolar disorder (OR = 8.93, 95% CI: 2.77–28.82) [37]. Another prospective study examined the relationship between cannabis use during adolescence and hypomania in adulthood in a sample of 3370 individuals aged 17 years and confirmed the hypothesis of an association between cannabis use and hypomania [38]. Furthermore, the same study showed an increased incidence with the usage of 2–3 times per week, as previously demonstrated. A prospective study investigated whether cannabis use increases the risk of developing manic symptoms in a sample of 4815 adults with a mean age of 41.2 years and showed that cannabis use was a risk factor over a three-year follow-up period, with an even higher risk for individuals who used 3–4 times per week [39]. In a recent

paper published in early 2024, Jorge et al. aimed to assess whether early lifetime cannabis use is associated with subsequent bipolar disorder in young adults aged 18–22 years of age using a birth cohort sample of 3781 individuals. Lifetime cannabis use predicted the onset of bipolar disorder at age 22 (OR = 1.82, 95% CI: 1.10–2.93), and the effect remained after controlling for socioeconomic status, sex, skin color, and parental physical abuse (OR = 2.00, 95% CI: 1.20–3.25). However, this association was attenuated to non-significance after further adjustment for all available covariates, including lifetime cocaine use (OR = 1.79, 95% CI: 0.95–3.19) [40].

In examining cocaine use as a risk factor for bipolar disorder, a prospective cohort study of 585 outpatients aged 18–60 years examined cocaine use as a predictor of conversion from major depressive disorder to bipolar disorder and found that cocaine use tripled the risk of bipolar disorder [41]. Richardson and Garavan [42] demonstrated in a non-clinical sample that higher doses of cannabis, 3,4-methylenedioxymethamphetamine (MDMA), cocaine, and amphetamine correlated with more severe symptoms of hypomania.

Therefore, substance use is a risk factor for bipolar disorder, especially cannabis use, which is more extensively documented in the literature. There is also an association between the frequency of cannabis use and the risk of bipolar disorder. It is important to note that substance use is not only a predictive factor but it also exacerbates the symptoms of bipolar disorder.

5.5 Prodromal Symptoms

A set of prodromal symptoms precedes the diagnosis of bipolar disorder, and recognition of this phenotypic manifestation can improve early diagnosis and intervention.

In 2019, an International Society of Bipolar Disorders Task Force report was published to clarify the clinical features that precede the onset of bipolar disorder. It began by analyzing prospective studies and categorizing the prodromal phase into homotypic and heterotypic risk factors. The homotypic factors consist of mood lability, subsyndromal depression, subsyndromal hypomanic symptoms (particularly when accompanied by subclinical psychosis), symptoms of elation or irritability (especially when occurring together), cyclothymic temperament, and major depressive disorder with subsyndromal hypomanic symptoms or psychotic symptoms. These factors appeared to be significant predictors of later bipolar disorder. However, hypomanic symptoms were found to be sensitive but not specific indicators, with rates of progression being more predictive than family history, especially when recurrent or persistent and when combined with other predictors or precursors. Heterotypic risk factors include anxiety syndromes, sleep disturbances, substance abuse, behavior disorders, ADHD, and early violence. These have been associated with bipolar disorder but can precede a range of psychopathologies, making them nonspecific. Furthermore, when we look at the retrospective studies, there seems to be a significant prevalence of prodromes that occur about 10 months

before the first episode. Both retrospective and prospective data highlight attenuated hypomanic features. Converging evidence suggests that mood lability and mood swings are core features. Also, depressive symptoms are more often prodromal to depressive episodes or a mixed state [11].

A meta-analysis published in 2016 aimed to understand the differences in symptom prevalence between prior initial mood episodes and prior recurrent mood episodes. The most common symptoms before the first episode were too much energy, reduced ability to think, indecisiveness, pressured speech, talkativeness, elated mood, academic or work difficulties, insomnia, depressed mood, and being over-productive. In meta-regression, older age seemed to be associated with less mood lability, and lower frequencies of anxiety seemed to be more common in the USA. Looking at the prevalence of subthreshold symptoms before a recurrent mood episode, only too much energy occurred in more than half of the people. When analyzing the difference in the period before a recurrent manic or depressive episode, for the most part, the reported symptoms were mostly consistent with a subthreshold presentation of the subsequent mood episode. The only significant subgroup analysis is that women had more irritability. Another interesting point raised by this study is the duration of the prodromal period. The prodrome before an initial mood episode lasted 27.1 ± 23.1 (range 4.6–130) months and the one preceding a recurrent manic episode was 1.0 ± 0.9 (range 0.5–1.3) months. This shows that there seems to be an important period to evaluate a possible future diagnosis and to discuss intervention [43].

Moreover, a population-based birth cohort study (1993 Pelotas Birth Cohort study) evaluated premorbid IQ and school failure frequency risk markers measured at age 18 for the formal diagnosis of bipolar disorder at age 22 years. Results showed that a lower IQ (below 70) at age 18 years increased the risk of a diagnosis of bipolar disorder at age 22 years (adjusted odds ratio [aOR] = 1.75; 95% CI: 1.00–3.09; $p < 0.05$) and that individuals with bipolar disorder were more likely to have a higher number of school failures compared to those who did not have a mood disorder (aOR = 1.23; 95% CI: 1.11–1.41; $p < 0.001$). This eludes the need to pay attention to these measures as suggestions of early disease (premorbid factor) [44].

Using the same birth cohort, Rabelo-da-Ponte et al. performed a predictive analysis on a 22-year community to identify early bipolar disorder using machine learning techniques. At the 18-year follow-up, the algorithm was able to predict who would develop bipolar disorder at age 22 with an Area Under the Curve (AUC) of 82% (sensitivity: 72%; specificity: 77%), considering the most important variables as suicide risk, Generalized Anxiety Disorder (GAD), parental physical abuse, and financial problems. All these variables showed a weak correlation with each other, so the result cannot be explained by collinearity. The positive predictive value of the model was low, leading to a high number of false positives, probably because some participants had not yet developed bipolar disorder by the age of 22. Nevertheless, it opens the possibility for future identification of early onset [45].

Because the onset of bipolar disorder usually begins with a depressive episode [46], differential diagnosis with major depressive disorder can be challenging. The population-based birth cohort study that analyzed premorbid IQ and school failure frequency as risk markers for bipolar disorder also measured the association between

higher IQ (above 120) and major depressive disorder, finding an aOR of 2.16 (95% CI: 1.24–3.75; $p < 0.001$) [44]. Besides that, a meta-analysis conducted in 2017 collected studies that followed patients with major depressive disorder for at least 6 months and found that nearly a quarter (22.5%) of adults and adolescents with major depressive disorder followed for an average of 12–18 years developed bipolar disorder, with the greatest risk of transition in the first 5 years. It was found that transition was indicated by a family history of bipolar disorder with an OR of 2.89 (95% CI: 2.01–4.14; $N = 7$), an earlier age of onset of depression ($g = -0.33$; $SE = 0.05$; $N = 6$), and the presence of psychotic symptoms (OR = 4.76; 95% CI: 1.79–12.66; $N = 5$) [47].

In conclusion, it is clear that there are no pathognomonic symptoms of bipolar prodrome, since they are nonspecific, i.e., they can be present in different disorders, and some are prevalent in functional contexts. Therefore, they are more important when they are associated and when highly predictive factors, such as family history, are present. Also common to these reviews is the recognition that some of the reported findings are heterogeneous and, in particular, may have a retrospective recall bias. Even so, these studies shed light on the early stages of bipolar disorder and open the discussion that it may be possible to intervene in the course of the illness through early therapeutic detection and approaches.

5.6 Treatment Approach

The role of early intervention in patients at risk of developing bipolar disorder is critical to mitigate disease progression and morbidity [48]. The staging model of bipolar disorder presented by Berk et al. and Kapczinski et al. suggests a latent phase in which individuals experience subthreshold anxiety, depressive and hypomanic symptoms [49, 50]. As difficult as it may be to establish criteria for the latent phase of bipolar disorder, recognizing its importance is essential to preventing treatment delay and its consequences.

A study published in 2015 found, in line with previous evidence, that the longer the delay in obtaining the correct diagnosis and thus initiating treatment, the more unfavorable the course of the illness may be, along with an increased likelihood of episode recurrence. Analyses have shown not only differences in the prevalence of further stages of bipolar disorder in patients with longer delays in treatment but also more mood episodes compared to those with shorter delays [48]. Another study evaluated the development of comorbid general medical conditions in 309 patients over the age of 18 who met DSM-IV criteria for bipolar disorder types I and II. Their medical records were analyzed to determine an association between the prevalence of a general medical condition and treatment delay for bipolar disorder. This study found that the most common general medical conditions were metabolic (23%) and vascular (21%), with metabolic syndrome and hypertension being the most common. The study also found that female gender and duration of untreated illness were significant predictors of a general medical condition in these patients [51].

For early intervention, it is well-known that as long as the heterogeneity of symptoms may delay or hinder diagnosis, non-pharmacological interventions play a central role in the management of these cases, as they offer a safe risk-benefit approach [52]. Evidence for these approaches is limited, but growing.

A 2009 review of the literature argues that psychoeducation and cognitive therapy interventions may be useful therapeutic options when targeted to patients in the early stages [53]. Another study evaluated the effectiveness of a Cognitive Behavioral Therapy (CBT)-based approach—with additional elements of mindfulness-based cognitive therapy and psychoeducation—compared to unstructured group meetings in patients with subthreshold bipolar symptoms and at risk (positive family history, reduction in psychosocial functioning) for severe mental illnesses. Among 128 randomized patients, both groups developed improvements in both mania and depression scores, independent of the approach received [54]. Regarding other psychotherapeutic approaches, a 2011 study examined whether a version of family-focused therapy adapted for this population could reduce the risk of syndromal conversion in children aged 9–17 years at risk for bipolar disorder. Despite the small sample size ($n = 13$), the results showed improvements in social functioning and depressive and hypomanic symptoms [55]. Another randomized controlled trial from the same study group, with a larger sample ($n = 40$) of high-risk children, showed that family-focused therapy improved recovery from mood symptoms and patients remained in remission for more weeks [56].

Moreover, because of the complexity of treating undiagnosed individuals, especially young ones given the pattern of the prodromal stage, pharmacological alternatives offer an increased barrier keeping in mind that patients may not convert to bipolar disorder at all. One RCT evaluated lithium administration in a sample of prepubertal major depressive disorder patients with a potential conversion to bipolar disorder based on a strong family history of bipolar disorder. Lithium was found to be no more effective than a placebo in treating depressive symptoms in this sample, calling into question its risk-benefit ratio in this context [57]. Regarding the use of valproate sodium, a 2003 study treated 24 children aged 6–18 years with mild affective symptoms and at least one biological parent diagnosed with bipolar disorder. The authors found that valproate sodium was well tolerated, with no discontinuations due to adverse effects, and showed a significant reduction in manic and depressive symptoms [58]. On the other hand, a 2007 randomized controlled trial with a similar sample suggested that valproate sodium was indeed well tolerated, but did not produce significant treatment effects on manic and depressive symptom ratings compared with placebo [59].

A strong association between metabolic disorders and bipolar disorder is well-established, indicating a higher risk of developing type 2 diabetes mellitus, obesity, and cardiovascular disease [60–62]. Additionally, a deeper implication lies in the worst prognosis and treatment difficulties of these patients [61, 63]. Therefore, a physical activity approach is warranted not only to address treatment adherence and success but also to improve manic and depressive symptoms. An RCT conducted in 2013 by Kilbourne et al. compared a program based on health behavior change and self-management through diet, exercise, and symptom-coping strategies, guided by

a specialist compared with usual care. They found that enrolled patients had lower blood pressure and fewer manic symptoms [64]. Another study conducted by Sylvia et al. as a pilot for a new integrated psychosocial treatment based on diet, exercise, and psychoeducation found that patients improved their quality of life through weight loss and reduced depressive symptoms [65]. As a result, there is evidence that adjunctive multimodal lifestyle interventions may be a promising choice, mainly for patients with metabolic comorbidities who benefit the most [66].

5.7 Clinical Considerations

5.7.1 *Family History*

- Bipolar disorder is one of the most heritable psychiatric disorders, which means that a positive family history should raise suspicion for this diagnosis.
- The heritability of bipolar disorder is mediated by a highly complex polygenic interaction with the environment, and there is a genetic overlap between bipolar disorder and other psychiatric disorders, such as schizophrenia and major depressive disorder.
- Familial risk includes both direct genetic risk and indirect risk mediated by exposure to early adversity.

5.7.2 *Prenatal and Perinatal Risk*

- The literature on prenatal and perinatal risks for the development of bipolar disorder has examined a large number of variables that may be associated with an increased incidence of this disorder, but the lack of statistical power in primary studies has led to inconsistent and nonreplicable results.
- Peripartum asphyxia, low birth weight, maternal stress during pregnancy, and obstetric complications were identified as risk factors for bipolar disorder in a recent systematic review with meta-analysis, with maternal stress being the strongest of all (OR = 12; 95% CI: 3.30–43.59). These four factors were also found to be risk factors for schizophrenia, indicating a lack of specificity.
- Tobacco exposure has also been identified as a possible risk factor for bipolar disorder. A systematic review with meta-analysis suggested a dose-related effect on the risk of mood disorders in general.

5.7.3 Early Trauma

- Early trauma is up to three times more common in people diagnosed with bipolar disorder than in the general population, and the presence of multiple trauma episodes and the severity of trauma are also higher in this population.
- Although emotional neglect, physical neglect, emotional abuse, and physical abuse are also higher in patients with major depressive disorder, sexual abuse seems to play a specific role in bipolar disorder, as it is the only type of trauma that is significantly increased in this disorder and not in major depressive disorder.
- Childhood trauma appears to have a dose-related effect in worsening the prognosis of bipolar disorder in several domains, including earlier onset, increased hospitalizations, worse symptomatology, and higher suicide risk.
- Assessment of childhood trauma in a clinical setting is important for determining the risk of developing mood disorders and for predicting or preventing a more severe longitudinal course of bipolar disorder. Given its significant impact on mental health, it should be a priority target for intervention.

5.7.4 Substance Use

- Substance use is a predictive factor for bipolar disorder and also a stressor that can worsen the course of the illness with cannabis use being particularly well-documented in the literature.
- Substance exposure may trigger the development of bipolar disorder in patients who would not otherwise have developed the disorder, with the onset of substance use disorder typically preceding the onset of bipolar disorder.
- Frequent cannabis use (1–4 times per week) significantly increases the risk of bipolar disorder.
- Cocaine use increases the risk of conversion of major depressive disorder to bipolar disorder.

5.7.5 Prodromal Symptoms

- Mood lability, hypomanic symptoms, and academic or work difficulties seem to be the most indicative prodromes.
- Heterotypic risk factors include anxiety syndromes, sleep disturbances, substance abuse, behavioral disorders, ADHD, and early violence.
- Symptoms preceding recurrent episodes are usually a subthreshold presentation of the subsequent mood episode.

- A significant proportion of major depressive disorders convert to bipolar disorder with increased risk over the next 5 years, highlighting the importance of recognizing risk factors and prodromal symptoms of bipolar disorder.

5.7.6 Treatment Approach

- Delayed treatment is associated with a more unfavorable course of the disease, which is why early detection is so important.
- Untreated disease may predict a greater chance of developing metabolic and vascular disorders.
- A non-pharmacological approach, including psychoeducation, cognitive behavioral therapy, and family-focused therapy, has shown promising results in the literature.
- Pharmacologic treatment of the prodromal stages remains controversial. The efficacy of well-known drugs such as lithium and valproate in these stages is not conclusive.
- Due to the close relationship between metabolic disorders and bipolar disorder, lifestyle intervention based on multiple multimodal approaches is well-justified and may also improve mood symptoms.

5.8 Future Perspectives

It is clear that genetic components play an important role in the course of bipolar disorder and that there are identifiable risk factors from the prenatal period to adulthood. In the early stages, a review has shown that some early symptoms can help guide diagnosis and, with the right interventions, possibly prevent progression to the next stages. Even so, there is still much to be understood and clarified through future research.

Recent advances in technology and genetics have allowed researchers to deepen our understanding of the heritability of several psychiatric disorders. However, because of the complex relationship between several genes involved in psychopathology and the genetic overlap between different disorders, such as schizophrenia and major depressive disorder, we have not yet been able to develop effective ways to apply this knowledge in the clinical setting. To date, genetic risk markers for bipolar disorder have proven to be nonspecific. Further investigation and larger sample studies are needed to develop a specific and reliable polygenic risk calculator that could aid in early diagnosis and possibly reveal novel genetic therapeutic targets. Genetic risk markers for more severe clinical presentations of bipolar disorder may also be a promising area of investigation that could help guide therapeutic management.

Current knowledge of prenatal and perinatal risk markers for bipolar disorder confirms that what happens to a child and mother during pregnancy and childbirth can affect the likelihood that the child will develop bipolar disorder later in life. However, few risk markers have been shown to be statistically significant in increasing the risk of bipolar disorder, and primary studies have mostly been inconsistent and lacked statistical power to establish strong associations. In addition, these markers were not specific to bipolar disorder, as they have also been shown to increase the risk for schizophrenia. Therefore, more research is needed to evaluate more specific risk markers that may help distinguish between bipolar disorder and schizophrenia.

Moreover, the detrimental effects of early trauma are already well-established in the scientific literature. Further investigation is needed to determine the most effective ways to mitigate the effects of early trauma on bipolar disorder. Recent evidence suggests that resilience may play an important protective role in the development of mood disorders, which could be enhanced by psychotherapy as a possible early intervention for high-risk family members [67]. Although adjunctive psychotherapy is included in global treatment guidelines for bipolar disorder, there is still a lack of evidence on how childhood trauma affects the efficacy of purely psychological interventions, and further research is needed [30].

Substance use has also been studied as an important factor in the course of bipolar disorder. However, due to the large number of substances to be studied and the different analytical methods used, there is still a need to reduce the heterogeneity in the literature and to analyze polysubstance use.

Thus, the developmental pathway to the full manifestation of bipolar disorder is multifactorial, involving distal factors (from the prenatal and perinatal periods, combined with important genetic features). In addition, risk may be influenced by environmental factors during childhood, and finally, more proximal factors may act as triggers for the onset of the illness (Fig. 5.1).

When it comes to understanding the prodromal phase of bipolar disorder, most original studies have the limitation of recall bias because they are mostly retrospective. More prospective studies are needed to clarify which symptoms are more prevalent and which indicators are stronger. Besides, looking at the future development of the field, predictive models may play an important role in the use of artificial intelligence for early detection of the disease. From this perspective, early treatment of latent bipolar disorder is challenging. In this regard, studies on pharmacological options to address this issue are extremely relevant but still scarce. Moreover, the role of physical activity as part of an intervention in the prodromal stages of bipolar disorder is still unclear. However, it seems to be an optimal area for further research.

Finally, staging models are a growing trend in progressive psychiatric disorders. They are expected to become part of clinical practice as more evidence is published about the natural history of bipolar disorder.

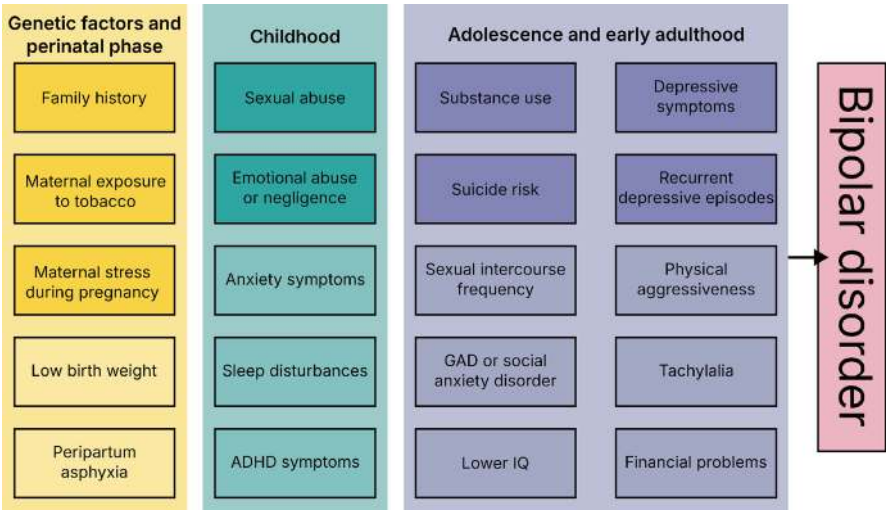


Fig. 5.1 Developmental risk markers for full-blown bipolar disorder. Lighter shades indicate lower levels of evidence in the scientific literature

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Chapter 6

Diagnosis, Clinical Features, Differential Diagnosis, and Psychiatric Comorbidities



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6.1 Introduction

The human mood is inherently dynamic. Typically, individuals experience a stable mood state known as euthymia, punctuated by context-dependent fluctuations that can manifest as heightened (e.g., feeling happy, motivated, or energetic) or diminished (e.g., feeling sad, tired, or unmotivated) moods. Bipolar disorder (BD) is characterized by episodic mood disturbances that swing to extremes, encompassing states of intense elevation (mania or hypomania), profound depression, or a

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combination of both [1]. This disorder spans a spectrum that includes bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified bipolar disorders. Globally, the lifetime prevalence of bipolar I disorder is approximately 0.6%, bipolar II disorder is around 0.4%, and subthreshold bipolar disorder affects about 1.4% of the population. Taken together, the entire spectrum of bipolar disorders has a worldwide prevalence of approximately 2.4% [2].

6.2 Diagnosis

Chapter 1 of the current text delineated the historical evolution of bipolar disorder. In the 1950s, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) categorized manic depression as a psychotic disorder. By the following decade, in DSM-II, it was reclassified within the affective disorders category. The term "bipolar disorder" made its debut in DSM-III, introducing the concept of mood episodes as a pivotal criterion for diagnosis [3]. Subsequent editions saw further advancements: DSM-IV incorporated mixed episodes and refined the hypomania category, while DSM-5 and its revised version, DSM-5-TR, established the current diagnostic criteria for bipolar disorder [4, 5].

6.2.1 Current Classification Systems

Since the publication of DSM-5, bipolar disorder has undergone significant revisions. Firstly, bipolar disorder and related conditions now occupy a distinct chapter within the diagnostic manual. Secondly, the diagnostic criteria now encompass mood swings and changes in activity or energy levels. A notable change includes the revision of mixed mood episodes: previously, full criteria for both mania and depression simultaneously were required, whereas now, the presence of at least three manic symptoms during a major depressive episode is sufficient [5]. Additionally, DSM-5 introduces a dimensional approach for research purposes, facilitating the assessment of psychopathology along a continuum spanning depressive to manic symptoms [6]. Notably, DSM-5-TR situates bipolar and related disorders between the schizophrenia spectrum and depressive disorders chapters, highlighting its distinct clinical and diagnostic profile.

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While DSM criteria are predominantly utilized in the United States, most countries utilize the *International Classification of Diseases* (ICD) criteria for diagnosing mental health disorders. Over time, the ICD system has evolved alongside the DSM, and despite inherent differences, the current eleventh edition (ICD-11) and DSM-5-TR demonstrate substantial alignment in diagnosing bipolar disorders [7]. One significant point of divergence between the two systems pertains to the classification and criteria for mixed mood episodes, which will be further elucidated in subsequent sections.

6.2.2 *Mania and Hypomania*

Mania is characterized by a distinct period of euphoric, expansive, or irritable mood which represents a marked departure from the individual's usual mood state [5, 7]. Affective lability, involving rapid shifts between different mood states, is commonly observed during manic episodes. Both DSM-5-TR and ICD-11 stipulate that this extreme mood state persists for at least 1 week, occurring most of the day, nearly every day, unless abbreviated by treatment or hospitalization. Concurrently, there must be increased energy or activity (or a subjective sense of increased energy) that significantly exceeds the individual's typical level. Additional criteria required for diagnosing a manic episode include specific symptoms outlined by both classification systems [5, 7].

While psychotic symptoms like delusions and hallucinations often accompany manic episodes, they are not essential for diagnosis. ICD-11 specifies the need for “several” of a set of seven symptoms, whereas DSM-5-TR requires three or more (or four if the mood is only irritable) from a similar list of seven symptoms, concurrently present with the mood disturbance [5, 7].

Patients experiencing a manic episode frequently exhibit inflated self-esteem or grandiosity, with beliefs in their ability to accomplish extraordinary feats. In cases of psychosis, these beliefs can manifest as grandiose delusions [7]. Another common symptom is a reduced need for sleep, where individuals may feel rested after only a few hours and report being able to function normally on minimal sleep, which differs from insomnia where sleep is desired but difficult to achieve [5, 7].

Manic patients often display rapid speech (tachylalia) or a pressured need to keep talking (pressured speech). They may experience a flight of ideas, where thoughts race rapidly, leading to disjointed conversation or difficulty maintaining coherence [5, 7]. Additionally, other symptoms commonly observed during manic episodes include distractibility, increased goal-directed activity (socially, sexually, or at work), and psychomotor agitation or impulsivity. Mental health professionals should closely monitor these symptoms as patients may engage in risky behaviors due to impulsively pursuing pleasurable activities or making hasty decisions without proper consideration [5, 7]. Table 6.1 provides a summary and comparison of DSM-5-TR and ICD-11 criteria for manic episodes.

Table 6.1 DSM-5-TR and ICD-11 criteria for manic episode

DSM-5-TR—manic episode		ICD-11—manic episode
A.	A distinct period of mood changes lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary), characterized by both:	Both of the following features occur concurrently and persist for most of the day, nearly every day, during at least 1 week, unless shortened by a treatment intervention:
–	Abnormally and persistently elevated, expansive, or irritable mood	– An extreme mood state characterized by euphoria, irritability, or expansiveness that represents a significant change from the individual's typical mood
–	Abnormally and persistently increased activity or energy	– Increased activity or a subjective experience of increased energy is present and represents a significant change from the individual's typical level
B.	During the period of mood disturbance and increased energy/activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:	Several of the following symptoms represent a significant change from the individual's usual behavior or subjective state:
1.	Inflated self-esteem or grandiosity	– Increased self-esteem or grandiosity
2.	Decreased need for sleep	– Decreased need for sleep
3.	More talkative than usual or pressure to keep talking	– Increased talkativeness or pressured speech
4.	Flight of ideas or subjective experience that thoughts are racing	– Flight of ideas or experience of rapid or racing thoughts
5.	Distractibility as reported or observed	– Distractibility
6.	Increase in goal-directed activity (socially, sexually, at work) or psychomotor agitation	– An increase in sexual drive, sociability, or goal-directed activity
7.	Excessive involvement in activities that have a high potential for painful consequences	– Impulsive, reckless behavior
C.	The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features	The mood disturbance results in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning, requires intensive treatment (e.g., hospitalization) to prevent harm to self or others, or is accompanied by delusions or hallucinations
D.	The episode is not attributable to the physiological effects of a substance or another medical condition	The symptoms are not a manifestation of another medical condition and are not due to the effects of a substance or medication on the central nervous system, including withdrawal effects
–	Not applicable	The clinical presentation does not fulfill the diagnostic requirements for a mixed episode

DSM-5-TR: *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision;
 ICD-11: *International Classification of Diseases* 11th Revision

Hypomania exhibits symptoms akin to mania, rendering them qualitatively analogous to mood episodes. However, hypomania is delineated by a milder intensity and briefer duration of mood disturbance compared to full-blown mania. According to DSM-5-TR and ICD-11 criteria, a hypomanic episode does not cause significant impairment in personal, social, familial, occupational, or other functional domains. Moreover, it does not necessitate hospitalization and is devoid of psychotic features such as delusions or hallucinations. The presence of psychotic symptoms categorizes the episode as mania per definition [5, 7]. Table 6.2 succinctly outlines the DSM-5-TR and ICD-11 criteria governing hypomanic episodes.

Table 6.2 DSM-5-TR and ICD-11 criteria for hypomanic episode

DSM-5-TR—hypomanic episode		ICD-11—hypomanic episode
A.	A distinct period of mood changes lasting at least four consecutive days and present most of the day, nearly every day, characterized by both:	Both of the following symptoms occur concurrently and persist for most of the day, nearly every day, for at least several days:
–	Abnormally and persistently elevated, expansive, or irritable mood	– Persistent elevation of mood or increased irritability is observable or reported, and represents a significant change from the individual’s usual range of moods
–	Abnormally and persistently increased activity or energy	– Increased activity or a subjective experience of increased energy is present and represents a significant change from the individual’s typical level
B.	During the period of mood disturbance and increased energy/activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have present to a significant degree:	Several of the following symptoms represent a significant change from the individual’s usual behavior or subjective state:
1.	Inflated self-esteem or grandiosity	– Increased self-esteem or grandiosity
2.	Decreased need for sleep	– Decreased need for sleep
3.	More talkative than usual or pressure to keep talking	– Increased talkativeness or pressured speech
4.	Flight of ideas or subjective experience that thoughts are racing	– Flight of ideas or experience of rapid or racing thoughts
5.	Distractibility as reported or observed	– Distractibility
6.	Increase in goal-directed activity (socially, sexually, at work) or psychomotor agitation	– An increase in sexual drive, sociability, or goal-directed activity
7.	Excessive involvement in activities that have a high potential for painful consequences	– Impulsive, reckless behavior
C.	The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.	Not applicable

(continued)

Table 6.2 (continued)

DSM-5-TR—hypomanic episode		ICD-11—hypomanic episode
D.	The disturbance in mood and the change in functioning are observable by others	Not applicable
E.	The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic	The mood disturbance is not sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, and is not accompanied by delusions or hallucinations
F.	The episode is not attributable to the physiological effects of a substance or another medical condition	The symptoms are not a manifestation of another medical condition and are not due to the effects of a substance or medication on the central nervous system, including withdrawal effects
–	Not applicable	The clinical presentation does not fulfill the diagnostic requirements for a mixed episode

DSM-5-TR: *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision; ICD-11: *International Classification of Diseases* 11th Revision

6.2.3 Bipolar Depression

Depression is defined as a period characterized by a pervasive low mood or anhedonia that persists most of the day, nearly every day, for a minimum of 2 weeks. This state represents a notable deviation from the individual’s usual functioning and is accompanied by additional cognitive, behavioral, or neurovegetative symptoms [5, 7]. According to DSM-5-TR criteria, a major depressive episode requires the presence of five or more symptoms from a specified list of nine, with at least one symptom being either a depressed mood or loss of interest or pleasure [5]. In line with ICD-11 criteria, a depressive episode necessitates at least five symptoms from a list of 10, including at least one from the affective cluster (depressive mood or anhedonia). The remaining symptoms are categorized into neurovegetative and cognitive-behavioral clusters [7].

The hallmark feature of depression is a depressed mood, which entails subjective feelings of sadness, emptiness, or hopelessness. It can also manifest as observable affective changes, such as tearfulness or a defeated appearance. Importantly, in children and adolescents, depression may present as irritability [5, 7]. However, a depressive episode does not necessarily require a depressed mood if it includes another affective cluster symptom: markedly diminished interest or pleasure in activities (anhedonia). This decrease in interest typically affects almost all activities, including those previously enjoyed by the individual, such as sexual desire. It persists throughout most of the day, nearly every day, and can be subjectively experienced or observed externally by others [5, 7].

The neurovegetative symptoms associated with depression encompass changes in appetite or weight, disrupted sleep patterns, alterations in psychomotor activity, and feelings of fatigue or loss of energy. Significant changes in appetite, whether

diminished or increased, occur nearly every day and may result in noticeable weight loss or gain, typically defined as a 5% change in body weight within a month. In children, these changes can manifest as a failure to achieve expected weight gain [5, 7]. Sleep disturbances are also prevalent in depression, with symptoms including insomnia (difficulty falling asleep, frequent awakenings during the night, early morning awakening) or hypersomnia (excessive daytime sleepiness), occurring nearly every day [5, 7].

Changes in psychomotor activity represent another characteristic aspect of the neurovegetative symptoms observed in depression. These changes can manifest as either psychomotor agitation or psychomotor retardation, occurring nearly every day. It is essential to emphasize that these changes must be objectively observable by others, rather than just subjective reports of feeling restless or slowed down. In cases where psychomotor agitation is present, it is important to assess for potential mixed features accompanying the depressive episode [5, 7]. Fatigue or loss of energy is also a significant neurovegetative symptom of depression. Individuals affected by depression often report a pervasive sense of weariness or exhaustion, even following minimal physical or mental exertion [5, 7].

The cognitive-behavioral cluster of symptoms in depression encompasses feelings of worthlessness or excessive/inappropriate guilt, which can even include delusional beliefs. These feelings must be present nearly every day and should not be considered merely self-reproach or guilt related to being depressed or ill [5, 7]. In addition to feelings of worthlessness and guilt, other cognitive symptoms within this cluster include a diminished ability to concentrate or maintain attention, indecisiveness, and reduced cognitive processing speed, often described as a slowed flow of thought (bradypsychism) [5, 7].

Recurrent thoughts of death, distinct from a fear of dying, along with recurrent suicidal ideation (with or without a specific plan) or a suicide attempt, are critical symptoms that can manifest during a depressive episode. These symptoms must always be thoroughly assessed in clinical practice to ensure the safety and well-being of the individual [5, 7]. In addition, feeling hopeless about the future is a significant and commonly observed symptom of depression. Notably, this criterion is specifically included in the ICD-11 diagnostic guidelines [7].

A major depressive episode can manifest with varying degrees of severity and may include additional symptoms such as anxiety, psychotic features, melancholic features, atypical features, and catatonia. It can also present with peripartum onset, occurring during pregnancy or the postpartum period, and may follow a seasonal pattern, known as seasonal affective disorder. Depression significantly impacts multiple facets of life, including personal distress, occupational functioning, and interpersonal relationships [5, 7]. Table 6.3 provides a summary of the DSM-5-TR criteria for major depressive episodes and ICD-11 criteria for depressive episodes.

Table 6.3 DSM-5-TR and ICD-11 criteria for depressive episode

	DSM-5-TR—major depressive episode	ICD-11—depressive episode
A.	Five (or more) of the following symptoms have been present most of the day, nearly every day during a period lasting at least 2 weeks, representing a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure	The concurrent presence of at least five of the following characteristic symptoms occurring most of the day, nearly every day during a period lasting at least 2 weeks, represents a change from previous functioning. At least one symptom from the affective cluster must be present
		<i>Affective cluster</i>
1.	Depressed mood as indicated by either subjective report or observation made by others <i>note: In children and adolescents, it can be irritable mood</i>	– Depressed mood as reported by the individual or as observed <i>note: In children and adolescents, it can be irritable mood</i>
2.	Markedly diminished interest or pleasure in all, or almost all, activities	– Markedly diminished interest or pleasure in activities (including sexual desire)
		<i>Neurovegetative cluster</i>
3.	Significant weight loss or gain or decrease or increase in appetite <i>note: In children, consider failure to make expected weight gain</i>	– Significant change in appetite (diminished or increased) or significant weight change (gain or loss)
4.	Insomnia or hypersomnia	– Significantly disrupted sleep (insomnia) or excessive sleep (hypersomnia)
5.	Psychomotor agitation or retardation (observable by others)	– Psychomotor agitation or retardation (observable by others)
6.	Fatigue or loss of energy	– Reduced energy, fatigue, or marked tiredness
		<i>Cognitive-behavioral cluster:</i>
7.	Feelings of worthlessness or excessive or inappropriate guilt (may be delusional)	– Beliefs of low self-worth or excessive and inappropriate guilt (may be delusional)
8.	Diminished ability to think or concentrate, or indecisiveness	– Reduced ability to concentrate and sustain attention to tasks or marked indecisiveness
9.	Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	– Recurrent thoughts of death, recurrent suicidal ideation (with or without a specific plan), or evidence of attempted suicide
–	<i>Not applicable</i>	– Hopelessness about the future
B.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning	The mood disturbance results in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. If functioning is maintained, it is only through significant additional effort
C.	The episode is not attributable to the physiological effects of a substance or another medical condition	The symptoms are not a manifestation of another medical condition and are not due to the effects of a substance or medication, including withdrawal effects

(continued)

Table 6.3 (continued)

	DSM-5-TR—major depressive episode	ICD-11—depressive episode
–	<i>Not applicable</i>	The clinical presentation does not fulfill the diagnostic requirements for a mixed episode
	<i>Note: Responses to a significant loss may include symptoms that may resemble a depressive episode. The presence of a major depressive episode, in addition to the normal response to a significant loss, should also be carefully considered. This decision requires the exercise of clinical judgment based on the individual’s history and cultural norms for the expression of distress in the context of loss</i>	The symptoms are not better accounted for by bereavement

DSM-5-TR: *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision;
ICD-11: *International Classification of Diseases* 11th Revision

6.2.4 Mixed Features or Mixed Episodes

It is crucial to acknowledge that mood episodes, such as depression and mania, can co-occur in what are termed mixed states. In these states, individuals may simultaneously experience symptoms of both depression and mania or hypomania. During a manic episode with mixed features, typical depressive symptoms may include a dysphoric mood (feeling sad or down), feelings of worthlessness and hopelessness, and thoughts of suicide or suicidal behaviors. Conversely, in a major depressive episode with mixed features, manic symptoms that can manifest include irritability, racing thoughts, increased talkativeness, and restlessness or psychomotor agitation. These mixed states present a diagnostic and treatment challenge in mood disorders, as they exhibit a unique combination of symptoms that often necessitate customized management approaches [5, 7].

According to DSM-5-TR criteria, mood episodes with mixed features specifiers are diagnosed when an individual meets the full criteria for a manic, hypomanic, or major depressive episode, while also experiencing at least three symptoms from the opposite mood state for the majority of the episode’s duration [5]. Under DSM-5-TR guidelines, bipolar I disorder can exhibit mixed features in any type of mood episode (manic, hypomanic, or depressive), while bipolar II disorder may display mixed features during hypomanic or major depressive episodes [5]. In contrast, as previously mentioned, ICD-11 categorizes a mixed episode as a distinct mood episode similar to mania, exclusively applicable to bipolar I disorder. In ICD-11, a mixed episode is defined by the simultaneous presence of prominent manic and depressive symptoms, either co-occurring or alternating very rapidly. These symptoms must be present for most of the day, nearly every day, over a minimum duration of 2 weeks unless shortened by effective treatment [7].

It is important to recognize the presence of mixed states during diagnostic evaluations due to the overlap of symptoms and mood poles, which can pose additional challenges in clinical settings. Mixed features are observed in a significant

proportion of individuals with bipolar disorder, ranging from 19.6% to 35.2% when using DSM-5 specifier criteria [8, 9]. Similar findings are reported when focusing on specific aspects of depressive, manic, or hypomanic episodes [10]. Mixed features in bipolar disorder are associated with more severe illness, rapid cycling of mood episodes, heightened risk of suicide, and poorer psychosocial functioning [10]. Therefore, identifying and addressing mixed states are critical in providing comprehensive care and improving outcomes for individuals with bipolar disorder.

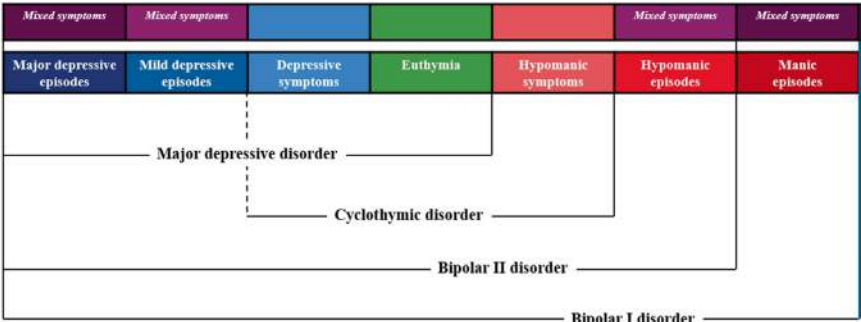
6.2.5 Diagnostic Criteria for Bipolar Disorders

Bipolar I disorder requires at least one manic episode in the individual's lifetime, even though hypomanic and depressive episodes may also exist (and often exist) during the course of the illness. The manic episode may or may not have psychotic features. The presence of a manic episode is a requirement for bipolar I disorder for both DMS-5-TR and ICD-11 l classificatory systems [5, 7]. However, as aforementioned, ICD-11 considers mixed episode as a distinct mood episode equivalent to mania; thus, for ICD-11, the presence of either a manic or a mixed episode is needed for bipolar I disorder diagnosis [7]. In contrast, the requirements for bipolar II disorder diagnosis are almost the same in both classificatory systems: it must have at least one hypomanic episode and one major depressive episode during the lifetime. In addition, major depressive episodes may present with psychotic features, but never during hypomania. Any history of mania excludes a bipolar II disorder diagnosis. Again, the differences between the manuals are that DSM-5-TR allows mixed features during hypomanic and depressive episodes while ICD-11 does not [5, 7].

Cyclothymic disorder is characterized by persistent and chronic mood fluctuations between periods of hypomanic and depressive symptoms. In adults, these mood changes must persist for at least 2 years, while in children and adolescents, the duration is 12 months according to DSM-5-TR criteria [5]. Hypomanic symptoms in cyclothymic disorder may include euphoria, elation, increased energy, or psychomotor agitation, among others. Depressive symptoms can encompass sadness, fatigue, insomnia, and psychomotor retardation. According to DSM-5-TR criteria, these symptoms must not meet the full criteria for a hypomanic episode or major depressive episode in terms of number, severity, pervasiveness, or duration. The diagnosis of cyclothymic disorder is made only if the criteria for a major depressive, manic, or hypomanic episode have never been met [5]. In contrast, ICD-11 allows for hypomanic periods that may or may not meet the full criteria for a hypomanic episode but does not permit the presence of a full depressive episode for the diagnosis of cyclothymic disorder [7].

In DSM-5-TR, the residual category "Other specified bipolar and related disorders" encompasses conditions that do not meet the full criteria for bipolar I disorder, bipolar II disorder, or cyclothymic disorder. This category includes various presentations such as: (1) cases where there are short-duration hypomanic episodes accompanied by a major depressive episode; (2) hypomanic episodes with insufficient symptoms to meet the criteria for a major depressive episode; (3) hypomanic

a DSM-5-TR



b ICD-11

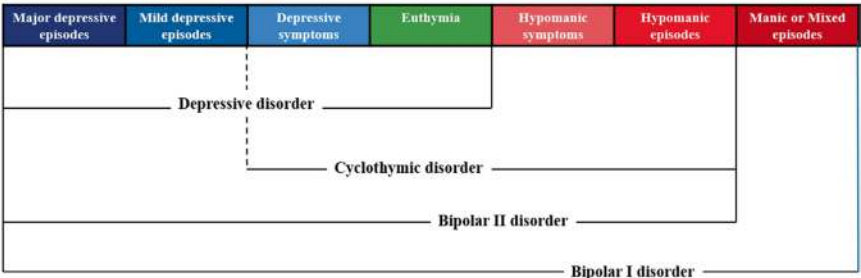


Fig. 6.1 Diagnosis according to DSM-5-TR and ICD-11 criteria for bipolar disorders. DSM-5-TR: *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision; ICD-11: *International Classification of Diseases* 11th Revision. Figure adapted from [11]

episodes occurring without a major depressive episode. These presentations represent significant mood disturbances characteristic of bipolar disorders but do not fit neatly into the specific criteria for classic bipolar spectrum disorders [5]. Similarly, ICD-11 includes a residual category called “Other specified bipolar or related disorders,” which serves a similar purpose. It is designed to classify conditions that do not precisely meet the criteria for bipolar I disorder, bipolar II disorder, or other specified mood disorders outlined in the classification system [7]. This category allows for the diagnosis and classification of conditions with diverse presentations within the spectrum of bipolar and related disorders that do not align with the defined categories (Fig. 6.1).

6.2.6 The Diagnosis Process

Diagnosing bipolar disorder remains a significant challenge in psychiatric practice despite ongoing efforts. While mania and hypomania are hallmark features of the disorder, depressive episodes typically manifest first and often drive individuals to

seek treatment [12]. Several factors contribute to the difficulty in diagnosing bipolar disorder, including limited access to healthcare services and the overlap of symptoms with other psychiatric conditions. These challenges frequently result in initial misdiagnosis or missed diagnosis altogether. The delay from the onset of symptoms to an accurate diagnosis can range from 5 to 8 years, with even longer delays observed in cases of bipolar II disorder [13, 14].

A thorough diagnostic evaluation for bipolar disorder should commence with a comprehensive psychiatric and medical history, coupled with a detailed assessment of current and past symptoms. This includes evaluating both depressive and euphoric features, episodes of heightened energy, engagement in risk-taking behaviors, presence of psychotic symptoms, thoughts of suicide, history of hospitalizations, and instances of seeking emergency healthcare. Furthermore, gathering information about the patient's lifestyle habits, substance use patterns, medical conditions, current medications (both psychiatric and general), and family history of psychiatric disorders is crucial. Family history of psychiatric diseases, in particular, warrants thorough exploration. Finally, obtaining input from family members or other collateral informants can provide valuable insights into the patient's condition. Individuals with bipolar disorder may have limited awareness of their symptoms, making external observations and perspectives especially valuable during the diagnostic process. A meticulous and comprehensive approach ensures that all pertinent information is carefully considered, thereby facilitating an accurate diagnosis and appropriate treatment planning.

General laboratory studies are essential in the diagnostic process of bipolar disorder to rule out potential medical conditions that may mimic psychiatric symptoms, such as hypothyroidism or hyperthyroidism. These studies are also crucial for guiding treatment decisions, especially in cases with underlying liver or kidney dysfunction. For example, neuroimaging studies may be utilized when clinically indicated, although their role in diagnosing bipolar disorders remains supportive rather than definitive. Despite advancements in biomarkers and brain imaging research, the primary diagnosis of bipolar disorders still relies on clinical judgment based on the patient's reported experiences and observed behaviors. Clinicians must approach the diagnostic process cautiously, conducting a thorough investigation into the patient's mood history and continuously reassessing to ensure an accurate diagnosis. Attention should be paid not only to the symptoms present during mood episodes but also to the inter-episode features, including social relationships, level of functioning, personality traits, and the long-term trajectory of the illness. These factors provide critical insights that aid in distinguishing bipolar disorder from other psychiatric conditions. In summary, while laboratory and neuroimaging studies are valuable adjuncts in diagnostic evaluation, the foundation of diagnosing bipolar disorders lies in comprehensive clinical assessment and careful consideration of the patient's overall clinical presentation and history.

After collecting an adequate anamnesis and observing the patient's behaviors, the clinician must make the diagnosis following DSM-5-TR or ICD-11 criteria. It is an essential step because the correct terminology helps communicate with other health professionals and in conducting treatments and evaluating the prognosis (Fig. 6.2).

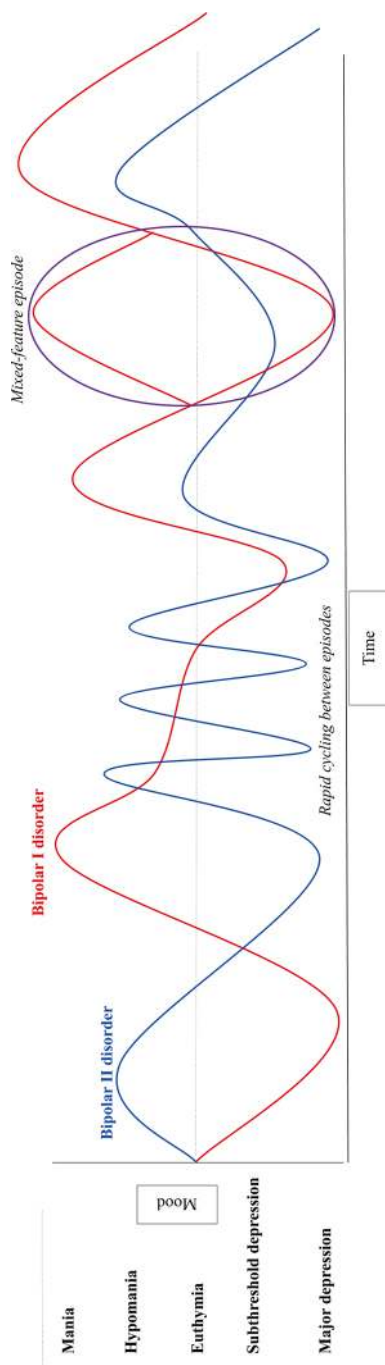


Fig. 6.2 Longitudinal trajectories of bipolar disorders. Figure illustrating the differences between bipolar I disorder and bipolar II disorder overtime and shows rapid cycling features and mixed episodes

6.3 Clinical Features

The natural history of bipolar disorder is quite variable so, each individual may have a unique illness trajectory and degree of severity. Some patients respond optimally to treatments, leading productive lives and maintaining healthy interpersonal relationships despite the burden of the disease. In contrast, others face challenges in achieving euthymia and experience significant impairments in social, occupational, cognitive, autonomy, and global health domains.

6.3.1 *The Longitudinal Course of Symptoms*

Formerly, Kraepelin has observed that manic states can vary in duration from weeks to several months and that severe forms of mania with excitement and psychotic features tend to be relatively longer manic episodes, whereas depressive states are longer than mania and can sometimes persist for years and tend to become more prominent in older ages [15, 16]. Currently, pharmacological treatments effectively control the episodes and reduce the severity, which was previously not possible. Even with the advent of treatment, symptoms and course of the disease are still chronic and challenging, with depressive poles seeming to remain predominant.

A 20-year follow-up study that evaluated the long-term symptoms status confirmed that bipolar I disorder and bipolar II disorder have chronic courses and that patients were symptomatic approximately half of all follow-up weeks (BD-I 46.6% and BD-II 55.8% of weeks) [17, 18]. This study highlighted that patients with bipolar II disorder spent more time with symptoms compared to those with bipolar I disorder, putting bipolar II disorder in a place of intense and chronic depressive features that are not simply the “lesser” of the bipolar disorders [17]. Bipolar II disorder patients spent 37 times more weeks with depressive symptoms (51.9% of weeks) than with hypomanic symptoms (1.4% of weeks). In comparison, bipolar I disorder patients also had three times as many weeks with depressive symptoms (30.6% of weeks) than with manic/hypomanic symptoms (9.8% of weeks) [17]. This study also observed that bipolar I disorder patients presented more weeks of cycling/mixed polarity, hypomanic, and subsyndromal hypomanic symptoms and that both bipolar disorders present mainly moderate and subsyndromal symptoms (minor depressive, hypomanic) rather than severe symptoms [18]. Figure 6.3 shows the percentage of weeks spent by individuals with bipolar I disorder and bipolar II disorder in each mood episode during a long-term follow-up.

Anxiety symptoms and comorbid anxiety disorders are prevalent among people with bipolar disorder [19]. Meta-analyses have indicated that the prevalence of any anxiety disorder among people with bipolar disorder ranges from 34.7% to 44.7% [19, 20]. The most commonly observed anxiety disorders include generalized anxiety disorder (GAD) with prevalences between 11.6% and 13.3%, social phobia affecting 9.7–13.5% of individuals, panic disorder with a prevalence of 18.1%, and

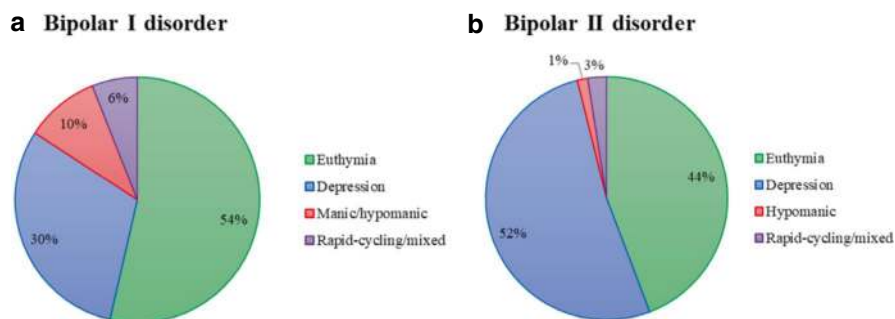


Fig. 6.3 Percentage of weeks spent in each mood episode during a long-term follow-up. Part A shows bipolar I disorder; Part B shows bipolar II disorder. Data adapted from [17, 18]

specific phobia at 9.7% [19, 20]. In pediatric populations, the rates of anxiety disorders are even higher, with any anxiety disorder affecting up to 44.7% of children and adolescents with bipolar disorder; specifically, generalized anxiety disorder (GAD) is prevalent in 27.4%, social phobia in 20.1%, and separation anxiety disorder in 26.1% of cases [21]. Investigating these comorbidities is crucial because anxiety disorders are predictors of poor outcomes in bipolar disorder, including lower remission rates of depressive symptoms and impaired functioning [22–24].

Psychotic symptoms, such as delusions and hallucinations, are prevalent in a significant proportion of individuals with bipolar disorder over their lifetime. Research indicates that approximately two-thirds of bipolar patients experience psychosis at some point, with nearly half exhibiting these symptoms during cross-sectional assessments [25]. Psychotic features can manifest in both manic and depressive episodes, though they are more commonly associated with mania or episodes with mixed characteristics [26]. Detecting psychotic symptoms in individuals with bipolar disorder can be challenging, as patients may attempt to conceal their experiences. Thorough and extended clinical histories are essential to uncover these symptoms effectively. It is important to note that bipolar patients with psychotic symptoms typically experience a poorer prognosis. They often face longer hospital stays, more frequent relapses, greater severity of illness, and increased morbidity compared to those without psychosis [27–30].

As discussed earlier, the course of mood disorders, particularly bipolar disorder, is highly variable among individuals. However, a greater number of mood episodes, particularly manic episodes, often correlate with a progressive course of the illness [31]. This pattern suggests that the risk of recurrence increases with each subsequent episode, establishing manic episodes as a clinical marker of progression in bipolar disorder [31]. Illness progression refers to the observed discrepancies in prognostics among individuals with bipolar disorder. Some patients exhibit a progressive course characterized by more frequent and severe episodes over time, potentially leading to functional impairment and poorer outcomes. Research indicates that this subset of patients may also experience structural and functional changes in the brain as a consequence of repeated mood episodes, a concept termed

neuroprogression [32, 33]. Neuroprogression hypothesizes that the cumulative impact of bipolar disorder on the brain contributes to worsening clinical symptoms and outcomes. It is important to note that while illness progression and neuroprogression provide valuable frameworks for understanding the course of bipolar disorder, they do not apply universally to all individuals. Variability in illness trajectories and severity underscores the heterogeneous nature of the disorder [34].

6.3.2 Rapid Cycling

Rapid cycling is defined as experiencing at least four mood episodes (manic, hypomanic, depressive, or mixed) within a span of 12 months. This phenomenon affects a substantial portion of individuals diagnosed with bipolar disorder, with year-prevalence rates ranging from 5% to 33.3%, and lifetime prevalence rates ranging between 25.8% and 43% [35]. Patients exhibiting rapid cycling features often face a worse prognosis characterized by a longer course of illness, an earlier age at onset, more alcohol and other substance abuse, and increased suicidality [35]. Several trigger factors have been proposed, including the use of antidepressants and hypothyroidism [35]. Besides rapid cycling being considered underrecognized, early detection is worthwhile because an appropriate treatment strategy may improve the long-term course [35].

6.3.3 Early Stages and Risk Factors

Despite the ongoing debate about staging in bipolar disorder, the literature consistently indicates that early intervention is more effective compared to later stages of the illness. Therefore, efforts should focus on early detection, as delays in diagnosis and treatment can exacerbate the disease's progression [36, 37]. However, early diagnosis remains challenging for several reasons. For instance, approximately half of patients experience depression as their initial episode [38], often leading to misdiagnosis of unipolar depression. Consequently, they may receive antidepressants without concomitant mood stabilizers or atypical antipsychotics, which can potentially worsen bipolar disorder by inducing manic, mixed, or rapid cycling symptoms.

Identifying populations at risk of bipolar disorder is crucial in the realm of youth mental health. It is noteworthy that when there is a family history of bipolar disorder, this information becomes particularly significant, warranting heightened suspicion for this potential diagnosis. Research indicates that individuals at higher risk of developing bipolar disorder often have at least one biological parent diagnosed with the condition [37, 39]. Estimates from twin studies, which assess disease concordance between monozygotic and dizygotic twins, suggest a heritability range of

60–90% [40, 41]. Family-based studies further demonstrate that the risk of bipolar disorder is substantially elevated: first-degree relatives of bipolar disorder probands have up to 7.9 times higher risk, second-degree relatives 3.3 times higher, and third-degree relatives 1.6 times higher compared to individuals without a family history of bipolar disorder [11, 42].

Children of parents with bipolar disorder constitute a high-risk group identifiable by shared psychopathological characteristics during childhood and adolescence. These include symptoms such as depressive and anxiety symptoms, mood instability, suicidality, and disrupted sleep [43]. Longitudinal studies focusing on individuals at familial risk indicate that the progression of bipolar disorder in this population typically follows a clinical sequence. During childhood, symptoms such as anxiety disorders and sleep disturbances are prevalent, with occasional findings of neurodevelopmental disorders [39]. In adolescence, the first signs of mood symptoms often emerge, frequently presenting as a major depressive episode [39]. Finally, in adulthood, the initial manifestation may involve manic or hypomanic episodes [39].

While genetic factors play a significant role in the development of bipolar disorder, there is growing evidence supporting the influence of environmental factors throughout various stages of life. Prenatal, early-life, and lifelong environmental aspects have been identified as important contributors to the clinical course of bipolar disorder [44]. For instance, a predictive model applied to a large birth cohort highlighted several critical variables associated with the development of bipolar disorder, including suicide risk, generalized anxiety disorder, parental physical abuse, financial difficulties, engagement in physical aggression, and a family history of psychiatric disorders [45]. Moreover, individuals at high risk for bipolar disorder often exhibit frequent substance use and depressive symptoms [45]. Another study focused on early-onset bipolar disorder identified psychosocial markers such as childhood abuse, recent cannabis use, recent bereavement, family history of suicide, schizotypal personality traits, and irritable temperament [46].

Prevention and identification of the first manic episode in bipolar disorder pose significant clinical challenges due to the nonspecific nature of prodromal symptoms [47]. Prodromes are preliminary symptoms that precede the onset of a full-blown episode and commonly include, as discussed, depressive symptoms, anxiety, sleep disturbances, and subthreshold hypomanic symptoms [39, 48]. Early signs of impending manic episodes may also include euphoric symptoms such as excessive energy, heightened communication, racing thoughts, inflated or irritable mood, reduced need for sleep, and excessive engagement in goal-directed activities [49]. Adding to the complexity, the majority of first manic episodes typically occur in late adolescence or early adulthood [50]. An earlier age of onset is associated with more severe illness outcomes, including higher rates of substance use, greater severity of depressive symptoms, increased anxiety comorbidity, and longer delays before receiving appropriate treatment [51]. These factors, compounded by delayed diagnosis and limited access to adequate healthcare, further impede early intervention efforts [52]. Therefore, improving recognition of prodromal symptoms and implementing timely interventions remain crucial in mitigating the severity and progression of bipolar disorder.

6.3.4 *Clinical Outcomes*

Individuals with longer durations of illness, multiple episodes, and varying degrees of psychosocial functional impairment are often categorized within the late stage of bipolar disorder [37, 53]. This subgroup frequently faces challenges with pharmacological treatments, experiencing incomplete responses, frequent recurrences, and residual symptoms, thus meeting the criteria for treatment-resistant bipolar disorder [37, 53]. Clinical features commonly observed in these individuals include mixed states, rapid cycling between mood episodes, prominent anxiety symptoms, and neurocognitive impairments, among other complexities [53].

Cognitive impairments are prevalent among individuals with bipolar disorder across all illness phases, including euthymia, though they are more pronounced during acute episodes [54–57]. Meta-analyses indicate that premorbid intelligence generally remains preserved, while attention, verbal learning and memory, and executive functions are typically the most affected domains [54, 57]. The variability in cognitive functioning is underscored by cluster analyses, which often reveal three distinct cognitive profiles: globally impaired, moderately impaired, or cognitively intact clusters [58, 59]. The cognitive trajectories of individuals with bipolar disorder also exhibit considerable heterogeneity. Some studies suggest that those with longer illness durations demonstrate worse cognitive performance [60], while longitudinal research has also reported specific impairments persisting at follow-up, alongside instances of cognitive stability or even improvement over time [61–64].

Patients with bipolar disorder frequently experience significant impairments in daily life activities, particularly in occupational outcomes [65, 66]. Unemployment rates in bipolar disorder, ranging from 40% to 60%, exceed those in the general population, and a similar percentage (40–50%) report a decline in job status and income [67]. These deficits are evident even in individuals newly diagnosed with bipolar disorder, including during periods of euthymia [68, 69]. Longitudinal studies underscore that while nearly all patients recover from mood symptoms within 2 years following the first manic episode, only about one-third achieve functional recovery [70]. Moreover, research indicates that 42% of individuals with bipolar disorder experience functional impairments even during periods of euthymia [71].

In addition to impairments in psychosocial and neurocognitive functioning, bipolar disorder is associated with significantly higher mortality rates compared to the general population [72, 73]. Natural deaths in individuals with bipolar disorder are reported to be 1.5–1.91 times higher, while deaths from unnatural causes are seven times higher [72, 73]. Particularly alarming is the rate of suicide among individuals with bipolar disorder, which ranges from 11 to 20 times higher than in the general population [72, 73]. Studies estimate that between one-third to half of individuals with bipolar disorder attempt suicide at least once, and approximately 15–20% die by suicide [74]. Several risk factors contribute to the heightened risk of suicide in bipolar disorder, including previous suicide attempts, predominant depressive episodes, rapid mood fluctuations, mixed moods, impulsivity, and comorbid substance use [75]. Current depressive and mixed episodes are particularly

critical risk periods for suicide attempts, with incidence rates increasing by 25-fold and 65-fold, respectively [76].

Given the severity of these impairments, many individuals with bipolar disorder rely on caregivers, which can contribute to additional distress [77]. Collectively, these challenges impose a substantial economic burden estimated between US\$195 and \$202 billion [78, 79].

As cited above, the literature points out that there are several risk factors associated with psychosocial functional impairment in bipolar disorder, such as subclinical depressive symptoms, comorbid anxiety symptoms, comorbid substance use, number of mood episodes, and neurocognitive functioning [60, 80–82]. Addressing these risk factors and implementing effective prevention strategies are crucial to reducing morbidity and mortality rates and improving outcomes for individuals with bipolar disorder. The aforementioned data strengthen the argument for the importance of early diagnosis and prompt initiation of treatment, aiming to lessen the illness's impact.

6.4 Differential Diagnosis

The differential diagnosis of bipolar disorder poses a considerable challenge due to the potential overlap in symptoms with various psychiatric and general medical conditions. Research from the National Depressive and Manic-Depressive Association indicates that 69% of individuals with bipolar disorder were initially misdiagnosed, receiving an average of 3.5 incorrect diagnoses before accurate identification [83]. In primary care settings, the misdiagnosis rate is reported to be even higher, with bipolar disorder being missed in 78% of patients [84]. The following sections will elaborate on crucial clinical features essential for achieving an accurate differential diagnosis.

6.4.1 *Depressive Disorders*

As previously mentioned, mania and hypomania are hallmark features of bipolar disorder, but patients typically seek treatment during depressive episodes [1]. Depressive episodes are the initial presentation in at least half of individuals with bipolar disorder [1, 38]. Moreover, the clinical manifestations of bipolar depression may closely resemble those of unipolar depression, which is more prevalent in the general population. Consequently, without adequate screening and clinical acumen, bipolar disorder is prone to misdiagnosis [85]. Research indicates that approximately 4% of individuals in the general population screen positive for bipolar disorder using tools like the Mood Disorder Questionnaire [86]. Furthermore, a systematic review with meta-analysis suggests that up to 15% of patients initially diagnosed with depression in primary care settings may actually have undiagnosed bipolar

disorder [86]. An incorrect diagnosis can lead to delays in initiating appropriate mood-stabilizing treatments, which are crucial in managing bipolar disorder and reducing the risk of suicidal behavior, improving social functioning, and minimizing hospitalizations [87]. Additionally, the use of antidepressants without concurrent mood stabilizers can precipitate manic, mixed, or rapid cycling episodes in certain individuals [88, 89].

Misdiagnosis of bipolar disorder as unipolar depression often occurs due to two main reasons. Firstly, depression frequently manifests as the initial polarity of the disorder. Secondly, the diagnostic criteria for major depressive episodes are identical in both bipolar and depressive disorders. While a definitive diagnosis of bipolar disorder requires the presence of previous manic or hypomanic episodes, certain clinical indicators can raise suspicion of bipolar depression during a depressive episode. For instance, a family history of bipolar disorder in first-degree relatives is a significant but not exclusive risk factor. Additionally, specific psychiatric history characteristics such as early onset of symptoms (before 25 years of age), a history of multiple prior episodes (≥ 5 episodes), psychiatric hospitalizations, prior psychotic depression, and a higher frequency of suicide attempts are associated with an increased likelihood of bipolar disorder [90]. These patients may also exhibit heightened irritability and mood elevation as adverse effects of antidepressant treatments and are more prone to treatment-resistant depression [90]. Furthermore, compared to unipolar depression, individuals with bipolar depression often present with distinct clinical features such as abrupt symptom onset, atypical depressive symptoms (e.g., hypersomnia, hyperphagia, leaden paralysis), mixed features (e.g., affective lability, irritability, racing thoughts, psychomotor agitation), psychomotor retardation, pathological guilt, and psychotic symptoms [90, 91]. These features collectively may assist clinicians in distinguishing bipolar depression from unipolar depression.

Table 6.4 provides a summary of differential diagnoses and clinical characteristics associated with bipolar disorder in the context of depression.

Table 6.4 Differential diagnoses and characteristics associated with bipolar disorder in the context of depression

	Suggestive of bipolarity	Suggestive of unipolarity
Symptomatology	• Atypical symptoms (increased appetite, hypersomnia) • Mixed features • Psychotic symptoms or catatonia • Abrupt onset and offset of symptoms • Psychomotor retardation	• Initial insomnia/reduced sleep • Appetite and/or weight loss • Normal or increased activity levels • Somatic complaints
Course of illness	• Early onset of first depression (<25 years) • Multiple prior episodes (≥ 5 episodes) • Treatment-resistant depression • Childhood sexual abuse	• Late onset of first depression (>25 years) • Long duration of current episode (>6 months)
Family history	Family history of bipolar disorder	Negative family history of bipolar disorder

6.4.2 *Schizophrenia and Other Psychotic Disorders*

Differentiating a psychotic episode in bipolar disorder from schizophrenia and other psychotic disorders can be challenging, particularly during the initial episode. When psychotic symptoms are present, individuals with bipolar I disorder are misdiagnosed and may be mistaken for schizophrenia or substance-induced psychotic disorder in approximately 31% of cases [92, 93]. A naturalistic study involving 214 patients with bipolar disorder and psychotic symptoms highlighted that the majority (61.5%) initially received a diagnosis other than bipolar disorder upon retrospective evaluation [27]. These patients often receive treatment with typical antipsychotics, which may reduce the duration of untreated psychosis but does not address the broader issue of untreated illness duration—a crucial metric in mood disorders. This delay in accurate diagnosis significantly impacts disease outcomes, as prolonged untreated illness duration correlates with increased hospitalizations, recurrent manic and depressive episodes, and decreased functional levels.

In patients with bipolar disorder, psychotic symptoms typically manifest more commonly as delusions rather than typical hallucinations, and their content often aligns with the mood episode, particularly at onset. For instance, delusions of grandeur may occur during manic episodes, while delusions of ruin can accompany depressive episodes [94]. However, severe manic episodes can occasionally present with psychosis that is incongruent with mood, such as delusions of persecution or threat [25]. The presence of manic symptoms preceding the onset of psychosis strongly suggests bipolar disorder [91]. Therefore, it is understandable that schizophrenia and other psychotic disorders are frequently misdiagnosed in individuals with bipolar disorder, ranking as the second most common misdiagnosis following major depressive disorder [93].

Schizophrenia, the primary differential diagnosis for psychotic bipolar disorder, is characterized by the absence of psychotic symptoms occurring concurrently with major mood episodes (i.e., mania or depression). If mood episodes do occur during the active phase of schizophrenia, they typically represent a minority of the total duration of the psychotic episode and residual periods of the illness [5]. Schizophrenia often features first-rank Schneiderian symptoms, such as auditory hallucinations that comment on the patient in the third person and thought sonorization, alongside negative symptoms like blunted affect [95]. While these symptoms are more commonly associated with schizophrenia, they are not exclusive to it. Grandiose delusions can also manifest in schizophrenia, although they do not accompany the expansive or euphoric mood observed in mania. Formal thought disorder, historically considered a hallmark symptom of schizophrenia, shares significant clinical and neurobiological overlap with bipolar disorder, as indicated by several recent studies. However, severe impairment in the theory of mind, characterized by pronounced deficits, is predominantly linked with schizophrenia [96, 97]. For accurate diagnosis, long-term observation of the illness is essential, as symptoms may overlap during crises. Nonetheless, these disorders follow distinct courses, with bipolar disorder generally resulting in less severe social, functional, and occupational impairments compared to schizophrenia.

6.4.3 *Borderline Personality Disorder*

An important differential diagnosis for bipolar disorder, particularly bipolar II disorder, is borderline personality disorder (BPD). These conditions are often challenging to distinguish due to overlapping symptomatology and a potential comorbidity rate of 10–20% [98, 99]. Therefore, careful and longitudinal clinical assessment is essential for an accurate diagnostic determination. In individuals with borderline personality disorder, periods of mood instability may resemble hypomania during brief evaluations, potentially leading to an erroneous diagnosis of bipolar disorder [100]. Conversely, persistent residual symptoms seen in individuals with bipolar disorder between manic or depressive episodes, such as chronic dysphoria or mixed symptoms, can also be misinterpreted as features of borderline personality disorder [98, 99].

Regarding similarities between BPD and bipolar disorder, affective instability and impulsivity are notable shared manifestations [101]. Affective instability is characterized by mood swings that are temporally unstable, intense, and slow to recover from dysphoria [102]. Both disorders exhibit affective instability but with distinct patterns: rapid shifts to anger or anxiety are more typical in BPD, whereas shifts from euthymia to depression or elation are characteristic of bipolar disorder [103]. Moreover, mood changes in BPD often occur in response to interpersonal stressors, whereas in bipolar disorder, mood shifts may be more spontaneous and sustained [102]. Impulsivity is another shared feature, although its expression differs between the two disorders. In BPD, impulsivity typically serves as a coping mechanism for managing negative emotions, whereas in bipolar disorder, impulsivity can be a trait but is more pronounced during mood episodes, particularly in manic or hypomanic states, compared to depressive episodes [104].

Differentiating between borderline personality disorder (BPD) and bipolar disorder is crucial in guiding appropriate clinical decisions. The primary treatment approach for bipolar disorder is typically pharmacological, which has demonstrated high efficacy. In contrast, borderline personality disorder is best addressed with psychotherapy, particularly dialectical behavior therapy (DBT) tailored for these patients [105]. An incorrect diagnosis of BPD in someone with bipolar disorder can lead to the omission of effective medication treatment, potentially worsening the course of the disorder. Conversely, misdiagnosing BD in a patient with BPD may result in polypharmacy, exposing them to long-term adverse effects with minimal therapeutic benefit and depriving them of the preferred psychotherapeutic approach [106]. This diagnostic challenge is compounded by psychiatrists' hesitancy to diagnose BPD, influenced by social stigmas and the limited availability of specific therapeutic interventions. Once a diagnosis is established, it tends to persist, potentially denying patients access to evidence-based treatments. Therefore, an accurate diagnosis should only be made following a thorough investigation and longitudinal follow-up to ensure appropriate management tailored to the specific needs of each patient.

6.4.4 *Post-traumatic Stress Disorder*

Post-traumatic stress disorder (PTSD) arises following direct exposure to a traumatic event, such as death, threatened death, serious injury, sexual violence, or other forms of violence [107]. It presents various clinical manifestations, including persistent intrusive recollections, avoidance of trauma-related stimuli, negative alterations in mood and cognition, and hyperarousal [107]. Bipolar disorder and PTSD frequently co-occur and share several overlapping symptoms, such as sleep disturbances, difficulty concentrating, increased risk-taking behavior, loss of interest in usual activities, heightened irritability, and persistent negative emotional states. Studies have indicated a wide prevalence range of PTSD among individuals with bipolar disorder, spanning from 4% to 40%, with higher rates observed among women and those with bipolar I compared to bipolar II disorder [108]. This increased prevalence may stem partly from the elevated risk of trauma exposure associated with engagement in risk-taking behaviors during manic and hypomanic episodes [108, 109]. Additionally, early-life trauma is recognized as a significant risk factor for developing both bipolar disorder and PTSD [107, 110, 111]. Childhood trauma has been linked to poorer clinical outcomes in bipolar disorder, including increased suicide risk, greater severity of depressive symptoms, and higher levels of functional impairment [112]. Differentiating between bipolar disorder and PTSD can be challenging but crucial. One key distinction lies in the timeline of symptom onset: PTSD symptoms emerge in response to a traumatic event and do not precede the event, whereas bipolar disorder symptoms occur independently of such external triggers [113].

6.4.5 *Attention Deficit Hyperactivity Disorder and Other Neurodevelopmental Disorders*

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder frequently co-occurring with bipolar disorder. A meta-analysis involving 71 studies and over 646,766 participants revealed that 17.11% of individuals diagnosed with bipolar disorder also had comorbid ADHD, whereas 7.95% of those with ADHD had comorbid bipolar disorder [114]. Additionally, this study indicated that bipolar disorder tends to manifest approximately 3.96 years earlier in individuals with comorbid ADHD. The relationship between these two disorders extends beyond their common co-occurrence; it involves how one diagnosis can influence or contribute to the development or progression of the other.

Studies focusing on the offspring of individuals with bipolar disorder indicate an elevated prevalence of non-mood psychopathologies, particularly attention deficit hyperactivity disorder (ADHD) [115]. Longitudinal research suggests that neurodevelopmental disorders like ADHD and learning disorders are part of the developmental trajectory leading to bipolar disorder in at-risk offspring [39]. Furthermore,

there is a robust familial association between bipolar disorder and ADHD, with offspring and first-degree relatives of individuals with bipolar disorder exhibiting increased risks (odds ratios of 2.33 and 2.71, respectively) [116]. Moreover, longitudinal studies indicate that a notable percentage of individuals diagnosed with ADHD during childhood or adolescence (ranging from 10.01% to 12.87%) are expected to develop bipolar disorder later in life [117].

Given the high prevalence of ADHD in individuals with bipolar disorder and the increased risk of developing bipolar disorder in those with ADHD, particularly when there is a positive family history of bipolar disorder, clinicians should carefully evaluate both conditions during clinical assessments. When evaluating patients with symptoms such as irritability, distractibility, impulsivity, and hyperactivity that appear episodic or worsen with psychostimulants or antidepressants, clinicians should assess for manic and mixed symptoms, especially if there is a family history of bipolar disorder. Conversely, in individuals with bipolar disorder who have exhibited distractibility, inattention, hyperactivity, and impulsivity since childhood, and whose symptoms cause impairment even during euthymic periods, ADHD should be considered and ruled out, especially if there is a positive family history. This comprehensive assessment of comorbidity and differential diagnosis between ADHD and bipolar disorder is particularly critical when evaluating children and adolescents who are offspring of parents with bipolar disorder, as ADHD is common and can co-occur with milder mood disorders such as cyclothymia or adjustment disorder.

6.4.6 *Autism Spectrum Disorder*

Although the link between bipolar disorder and autism spectrum disorder (ASD) is not as firmly established as that with ADHD, studies have demonstrated a higher prevalence of bipolar disorder among individuals with ASD compared to the general population [118, 119]. Research suggests that the prevalence of bipolar disorder in individuals diagnosed with ASD ranges widely from 3% to 27% [120], significantly exceeding the approximate 2% prevalence observed in the general population [121, 122]. Additionally, there is a notable occurrence of ASD in patients diagnosed with pediatric bipolar disorder [123].

Despite distinct diagnostic criteria, autism spectrum disorder (ASD) and bipolar disorder share overlapping symptoms that can complicate accurate diagnosis and treatment [119, 124, 125]. Common features such as mood dysregulation, impulsivity, and social skills deficits contribute to potential misdiagnosis between these conditions. Social cognition impairment is a significant aspect shared by bipolar disorder and ASD. Research indicates that individuals with bipolar disorder often exhibit difficulties in social cognition, which involves perceiving, thinking about, understanding, and interacting with others in social contexts [126, 127]. This impairment is observed not only in pediatric bipolar disorder but also in individuals at familial risk for the disorder [61]. In contrast, impaired social cognition is a

hallmark feature of ASD, along with repetitive and restricted behaviors and interests. Although social cognition deficits are common in various psychiatric disorders like schizophrenia, they are intrinsic to the core symptoms of ASD. Studies have shown that individuals with bipolar disorder and high autistic traits tend to experience a very early onset of bipolar disorder, higher rates of anxiety disorders, and longer in-hospital stays, but lower rates of substance use disorders compared to those with fewer autistic traits [120]. Additionally, both bipolar disorder and ASD can present with catatonic features, further complicating their differentiation and management [5].

Understanding the complexity of autism spectrum disorder (ASD) is crucial in the context of differential diagnosis, especially when distinguishing it from conditions like bipolar disorder. ASD can manifest in varying intellectual abilities, ranging from intellectual disability to high intelligence [128, 129]. Individuals with high intellectual abilities may exhibit unique intensities and over-excitabilities, which can sometimes lead to challenges such as perfectionism, rumination, and heightened worry [128, 130]. These traits can predispose individuals to anxiety and depression, complicating diagnostic considerations [131]. In clinical practice, ASD can present as both a differential diagnosis and a comorbidity, particularly when severe deficits in social cognition or resistance to conventional treatment are observed in individuals initially diagnosed with bipolar disorder. Conversely, periodic irritability or agitation seen in ASD may lead to considerations of bipolar disorder. Adults with bipolar disorder who present with treatment-resistant symptoms and multiple diagnoses should be evaluated for possible undiagnosed ASD [132]. Understanding the developmental history, including social communication skills and patterns of repetitive/restrictive behaviors and interests, is essential for accurately diagnosing ASD [132].

Table 6.5 provides an overview of similarities and differences between bipolar disorder, ADHD, and autism spectrum disorder.

6.4.7 Substance Use Disorders and Substance/Medication-Induced Symptoms

Substance use disorders represent prevalent comorbidities in individuals with bipolar disorder, with cannabis use ranging from 20% to 30% and alcohol use disorders affecting up to 42% of clinical populations [133–135]. These disorders significantly impact clinical outcomes, contributing to a higher frequency of manic episodes and an increased risk of suicidal behavior [135, 136]. Given these associations, it is crucial for healthcare providers to routinely assess for the presence of substance use disorders when evaluating patients with bipolar disorder.

Psychoactive substances have the potential to mimic mood symptoms or exacerbate existing mood episodes in bipolar disorder. For instance, substances like cocaine, amphetamines, and cannabis can induce manic symptoms in individuals without a prior diagnosis of bipolar disorder. Conversely, these substances can also

Table 6.5 Differential diagnoses and characteristics associated with bipolar disorder, ADHD, and autism

	Suggestive of bipolar disorder	Suggestive of ADHD	Suggestive of autism
Coinciding features	Impulsivity, irritability, mood swings, sleep disturbance, aggressive behavior, risk-taking behavior, restlessness, and agitation Executive dysfunction, focusing and functional difficulties Common comorbidities (e.g., anxiety, substance misuse) Genetic overlap		
Specific symptoms	• Episodic mood swings and changes in energy • It usually appears in adolescence/early adulthood • Functional and cognitive difficulties more prominent in mood episodes • Periods of euthymia with lesser symptoms	• Persistent distraction or hyperactivity • Appear by age seven • Daydreaming, boredom • Forgetfulness • Difficulty following directions • Situational mood changes	• Persistent deficits in social interaction and communication • Neurodevelopmental symptoms • Cognitive and behavioral rigidity • Narrow interest • Situational mood changes
Response to pharmacological intervention	• Favorable response to pharmacological intervention (mood stabilizers)	• Favorable response to pharmacological intervention (stimulants)	• Poor response to pharmacological interventions for the management of core symptoms

trigger new mood episodes in individuals who already have a diagnosed bipolar disorder. Therefore, when clinicians encounter new mood episodes that overlap with substance use, it is essential to investigate whether the substance is directly inducing the current symptoms or triggering a mood episode. According to the DSM-5-TR [5], substance-induced bipolar disorder is characterized by a prominent and persistent disturbance in mood that primarily manifests with manic symptoms. This mood disturbance typically develops during or shortly after substance intoxication or medication exposure, and it is biologically plausible for the substance to produce manic symptoms. Additionally, similar mood disturbances can occur during withdrawal from certain substances or medications. Importantly, this mood disturbance should not be better explained by any other primary bipolar spectrum disorder, such as bipolar I disorder or bipolar II disorder [5].

To differentiate between a primary bipolar disorder and a mood disturbance induced by medications or substances, the DSM-5-TR outlines several key considerations [5]: (1) temporal relationship (investigate whether the mood symptoms preceded the onset of substance or medication use); (2) persistence of symptoms (assess whether the mood disturbance persists for a significant period, approximately 1 month, after the cessation of acute substance intoxication or withdrawal); (3) evidence of independent disorder (look for additional evidence supporting the existence of an independent non-substance/medication-induced bipolar or related disorder); (4) exclusion of delirium (confirm that the mood disturbance is not solely

attributable to an episode of delirium). Substances such as alcohol and illicit drugs, as well as medications, can induce or exacerbate mood symptoms in individuals with bipolar disorder. For instance, antidepressants and psychostimulants are known to potentially worsen manic or mixed symptoms, or induce rapid cycling in susceptible individuals. Additionally, various medications can impact both manic/hypomanic and depressive symptoms in bipolar disorder.

Table 6.6 shows substances and medications that can be implicated in the induction of substances.

Table 6.6 Differential diagnosis of bipolar disorder with secondary mood disorders

Mood disorders secondary to substances or medications	
DSM-5-TR—nomenclature	ICD-11—nomenclature
– Substance/medication-induced bipolar and related disorders	– Substance-induced mood disorders with manic symptoms
– Substance/medication-induced depressive disorders	– Substance-induced mood disorders with depressive symptoms
– Substance/medication-induced bipolar and related disorders with mixed features	– Substance-induced mood disorder with mixed depressive and manic symptoms
– Substance/medication-induced depressive disorder with mixed features	
<i>Examples of substances and medications capable of inducing mood symptoms during exposure, intoxication, or withdrawal</i>	
Alcohol, antidepressants, anxiolytics, hypnotics/sedatives, steroids, L-dopa, opioids, cannabis, synthetic cannabinoids, cocaine, amphetamine, methamphetamine, methcathinone, synthetic cathinones, 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), ketamine, phencyclidine (PCP), hallucinogens, volatile inhalants, among other	
Mood disorders secondary to a general medical condition	
DSM-5-TR—Nomenclature	ICD-11—Nomenclature
– Bipolar and related disorder due to another medical condition	– Secondary mood syndrome, with manic symptom
– Depressive disorder due to another medical condition	– Secondary mood syndrome, with depressive symptom
– Bipolar and related disorder due to another medical condition with mixed features	– Secondary mood syndrome, with mixed symptom
– Depressive disorder due to another medical condition with mixed features	
<i>Examples of potentially explanatory medical conditions</i>	
Hypothyroidism, hyperthyroidism, Cushing’s disease, deficiency of vitamin B ₁₂ , systemic lupus erythematosus, multiple sclerosis, traumatic brain injury, epilepsy, cerebrovascular accident, brain tumors such as frontal lobe meningiomas, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, Parkinson’s disease, Huntington’s disease, frontotemporal dementia, among others	
DSM-5-TR: <i>Diagnostic and Statistical Manual of Mental Disorders</i> , Fifth Edition, Text Revision; ICD-11: <i>International Classification of Diseases</i> 11th Revision	

6.4.8 Medical Conditions

Several general medical conditions have the potential to mimic mood symptoms in individuals, even in those without a prior diagnosis of bipolar disorder. These conditions include neurological diseases such as multiple sclerosis (MS), stroke, and tumors, autoimmune illnesses like anti-N-methyl-D-aspartate encephalitis and systemic lupus erythematosus, as well as metabolic conditions such as Cushing's syndrome and hyperthyroidism. Additionally, certain infectious diseases can also present with mood disturbances. Furthermore, medical conditions that involve inflammatory or metabolic alterations may trigger new mood episodes in individuals who already have a diagnosis of bipolar disorder. When mood symptoms are induced by an underlying clinical disease, it is classified as "bipolar and related disorder due to another medical condition" according to the DSM-5-TR [5] or termed as secondary mood syndrome in ICD-11 [7]. Several pertinent topics will be discussed below, including infectious diseases, neurological diseases, and bipolar disorder secondary to neurocognitive disorders and other medical conditions.

6.4.8.1 Infectious Diseases

Various viruses have the capacity to invade the central nervous system, triggering inflammatory responses that manifest in conditions like meningitis or encephalitis. Case reports have documented instances where viral infections led to symptoms resembling bipolar disorder. For example, there are reports of patients exhibiting behavioral and manic-like symptoms following infections such as herpes simplex encephalitis and influenza-induced mania [137, 138].

COVID-19, caused by the SARS-CoV-2 virus, not only affects the respiratory system but also has the potential to invade and damage the central nervous system [139]. Alongside neurological manifestations, there is increasing evidence of psychiatric symptoms emerging during and after SARS-CoV-2 infection [140]. Specifically related to bipolar disorder symptoms, several case reports and studies have documented manic episodes triggered following COVID-19 infection, often appearing 1–3 weeks after the initial diagnosis [141–144]. A recent meta-analysis identified 23 cases where individuals experienced their first manic episode during COVID-19 infection, with predominant symptoms including elevated mood, euphoria, irritability (95.65%), rapid speech (91.30%), and reduced need for sleep (86.96%) [145].

Patients with human immunodeficiency virus (HIV) infection are predisposed to various psychiatric disorders, including bipolar disorder and its manic episodes [146]. In individuals with HIV/AIDS, mania can manifest as a component of preexisting bipolar disorder, as a result of direct neuronal effects of the infection itself, or secondary to treatments for HIV or other associated brain infections [147]. Although antiretroviral therapies have significantly improved clinical outcomes for HIV patients, certain medications like efavirenz have been linked to psychiatric side

effects such as mania, depression, suicidal thoughts, psychosis, and hallucinations [148]. Manic syndromes secondary to HIV often present later in the disease course, particularly after the onset of AIDS, and are characterized by typical manic symptoms accompanied by cognitive impairment, typically without a history of prior psychiatric disorders [149, 150]. These episodes are associated with a poorer prognosis, chronicity, and increased symptom severity [150].

Syphilis is primarily transmitted sexually and caused by the bacterium *Treponema pallidum*. In cases where the central nervous system is affected (neurosyphilis), patients may exhibit a wide array of symptoms, including reports of secondary mania documented in the literature [151, 152]. Although neurologic examination is generally normal, patients might present with dysarthria, hypotonia of the face and limbs, intention tremors, and abnormalities in reflexes. Treatment with intravenous crystalline penicillin is essential in these instances, often supplemented with mood stabilizers and/or antipsychotic medications.

These cases underscore the potential of infectious diseases to induce mood disturbances resembling those seen in bipolar disorder, illustrating the intricate relationship between infectious agents and neuropsychiatric symptoms.

6.4.8.2 Neurological Diseases

Neurological diseases can manifest with psychiatric symptoms, complicating differential diagnoses. Multiple sclerosis (MS), the most common chronic inflammatory disorder of the central nervous system, is characterized by demyelinating lesions primarily affecting the white matter in areas such as cerebral hemispheres, optic nerves, brainstem, cerebellum, and spinal cord. These lesions lead to a spectrum of symptoms, including psychiatric manifestations [153]. Psychiatric abnormalities in MS typically occur after diagnosis, but there are reports of patients presenting with initial symptoms that include both psychiatric and neurological features (2.3%), or solely psychiatric symptoms (0.2–2%), including manic symptoms [154–156]. Some individuals may already have a diagnosis of bipolar disorder before the onset of neurological symptoms. Importantly, the prevalence of bipolar disorder in MS is approximately twice that of the general population, estimated at 2.95% [153]. This association may partly be attributed to steroid treatment, but there is also evidence suggesting shared immune, genetic, and neurological factors between the two conditions [157, 158].

Brain tumors can present with a diverse range of psychiatric symptoms depending on the affected brain regions and their associated neural networks [159]. Systematic reviews and case reports have documented instances of manic symptoms in patients with brain tumors located in areas such as the olfactory groove, temporal lobe, posterior frontal lobe, and frontal lobe [160]. Although relatively rare, psychiatric symptoms can sometimes be the initial signs of a brain tumor. In such cases, neuroimaging should be considered for patients presenting with late-onset symptoms, no prior history of psychiatric disorders, new-onset psychosis,

recurrence of previously controlled psychiatric symptoms, atypical presentations, new-onset personality changes, or anorexia without body image disturbance [161].

Mood disturbances featuring manic symptoms can also manifest in neurocognitive disorders such as Alzheimer's disease, vascular dementia, and frontotemporal dementia (FTD) [162]. Among these, the behavioral variant of FTD is noteworthy for its characteristic symptoms of disinhibition, apathy, loss of empathy, and other behaviors that can resemble manic or hypomanic features [163].

When these mood symptoms become prominent, causing distress or functional impairments, they may be categorized as "bipolar and related disorders due to another medical condition" according to the diagnostic criteria [5].

6.4.8.3 Bipolar Disorder Due to Neurocognitive Disorders and Other Medical Conditions

According to DSM-5-TR, a bipolar and related disorder due to another medical condition is characterized by a prominent and persistent disturbance in mood marked by abnormally elevated, expansive, or irritable mood accompanied by increased activity or energy. This mood disturbance may include manic or mixed features or even resemble a full manic or hypomanic episode [5]. To establish this diagnosis, clinical investigation, including thorough history-taking, physical examination, laboratory tests, and neuroimaging when appropriate, must confirm that the mood alteration is a direct consequence of the underlying medical condition. It is crucial to differentiate this condition from other primary mental disorders that could potentially explain the mood disturbance [5].

According to DSM-5-TR, a diagnosis of bipolar and related disorder due to another medical condition is not applicable if the mood disturbance occurs exclusively during a delirium episode. However, it can be diagnosed if there is a neurocognitive disorder, such as dementia or mild neurocognitive disorder, where mood alterations are deemed to be a direct consequence of the biological basis of the neurocognitive disorder. For this diagnosis, mood symptoms must be a prominent and persistent part of the clinical presentation, causing significant distress or impairments in daily functioning [5].

Bipolar and related disorders due to another medical condition should not be diagnosed when the manic or hypomanic symptoms precede the medical condition. Other factors that should alert clinicians to possible mood symptoms secondary to general medical conditions are the sudden onset of manic/hypomanic symptoms coinciding with exacerbations of the medical condition and the age at onset of these mood disturbances [5, 7]. Bipolar disorders typically begin in late adolescence and early adulthood, with an overall average age of onset of 25 years, although it occurs less frequently in other age groups. Therefore, when an older person presents manic or hypomanic symptoms for the first time in their life without having a previous psychiatric history, a mood disorder secondary to neurocognitive disorders must be considered.

Table 6.6 shows potentially explanatory medical conditions for secondary mood symptoms.

6.5 Comorbidities in Bipolar Disorder

Besides substance use disorder, discussed in Chap. 11, psychiatric comorbidities are notably common in bipolar disorder. The prevalence of them differs between adults and youth with bipolar disorder. Studies report high rates of ADHD comorbidity in pediatric bipolar disorder, with an average rate of around 60%, significantly higher than the 17.1% observed in adults. Patients with this comorbidity exhibit higher severity of core ADHD symptoms, more externalizing disorders, addictive behavior, and increased hospitalizations [123]. Additionally, these patients experience a more severe and chronic course of the mood disorder, with fewer euthymic intervals, more episodes, greater instability, impulsivity, and more self-injurious behavior [164]. There is also an earlier onset of bipolar disorder in individuals with ADHD, with more than half showing an onset before 18 years of age [165].

ADHD shows a longitudinal co-occurrence with bipolar disorder, both at the individual and familial levels, suggesting an overlap between these conditions. A recent meta-analytic study showed that individuals with bipolar disorder (BD) have an increased risk of retrospective ADHD occurrence in childhood compared to the general population (OR = 8.94, 95% CI 5.68–14.06). Conversely, a personal history of ADHD significantly increases the risk of developing bipolar disorder (OR: 6.06, 95% CI = 3.86–9.51). Additionally, there is an increased risk for a first-degree relative to have one of these conditions, indicating a bidirectional relationship [166].

The use of stimulants for treating ADHD may increase the risk of manic switch and mood instability. Methylphenidate is the most studied medication in this context. Using methylphenidate without a mood stabilizer increases the risk of mania (HR: 6.7, 95% CI = 2.0–22.4). However, this risk appears to be very limited if the patient is using mood stabilizers and is euthymic when starting methylphenidate. Therefore, mood stabilization before treating ADHD is advisable. The evidence is more limited for other ADHD medications such as lisdexamfetamine and atomoxetine [167].

Another highly prevalent comorbidity in pediatric patients is disruptive behavior disorders. A recent systematic review showed a 47% prevalence of comorbidity between bipolar disorder and oppositional defiant disorder (ODD) in the pediatric population [123]. There is also a bidirectional association between bipolar disorder and disruptive behavior disorders, including ODD and conduct disorder. However, evidence is inconsistent regarding whether one condition influences the presentation of the other. The type of aggression in conduct disorder and bipolar disorder tends to differ: in bipolar disorder, aggression is usually impulsive, non-predatory, and disorganized, whereas in conduct disorder, it is predatory, purposeful, and organized [168].

In adults with bipolar disorder, the lifetime prevalence of anxiety disorders and obsessive-compulsive disorder (OCD) is high, at approximately 45% and 10.9%, respectively [169]. Among the anxiety disorders, the most commonly identified in individuals with bipolar disorder are generalized anxiety disorder (20%), social phobia (20%), panic disorder (19%), and post-traumatic stress disorder (17%) [169].

Research findings suggest that individuals with comorbid bipolar disorder and anxiety have a worse prognosis than those with bipolar disorder alone. These individuals experience increased severity of bipolar symptoms, more frequent and severe depressive episodes, higher utilization of mental health services, non-adherence to treatment, and decreased functioning and quality of life [82, 170]. There are limited clinical trials providing evidence for the treatment of this comorbidity [170]. First-line medications for most anxiety disorders, such as selective serotonin reuptake inhibitors (SSRIs), may interfere with the treatment of bipolar disorder. Antidepressants may be used with caution and under careful monitoring to avoid destabilizing mood symptoms.

Regarding OCD, the lifetime prevalence is 10.9%, which is 4.4 times higher than in the general population. OCD in individuals with bipolar disorder tends to follow a more chronic and persistent course [171]. SSRIs, which are considered the mainstay of OCD management, can destabilize bipolar disorder, making pharmacological treatment challenging. Thus, in both anxiety disorders and OCD, mood stabilization should be prioritized before considering the use of SSRIs or other antidepressants.

6.6 Conclusion

Identifying bipolar disorder may be a clinical challenge. This chapter presented valuable tools for recognizing this disease accurately, including understanding its clinical course, differential diagnoses, and the dynamic nature of its symptoms. Long-term observation is fundamental for an adequate diagnosis since affective symptoms can change over time. Given the chronic nature of bipolar disorder, correct and early detection allows patients to access appropriate treatment and so may reduce the social, occupational, functional, and economic burden.

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Chapter 7

Clinical Assessment Scales



Adriane R. Rosa, Flávia Lima, and Joana Bucker

7.1 Screening

Unfortunately, bipolar disorder often goes unrecognized, undiagnosed, and untreated, especially due to the heterogeneous nature of symptom presentation, which varies in terms of intensity, duration, and impact on the individual's functioning. Also, the presence of comorbidities can make bipolar disorder (BD) diagnosis and treatment difficult. The wide range of symptoms seen in these patients, including impulsive behavior, alcohol and substance abuse, fluctuations in energy level, and legal problems, are often attributed to problems other than bipolar disorder [1]. The consequences of delayed diagnosis or misdiagnosis are common concerns and can result in significant consequences for affected individuals. Carrying out an early diagnosis, and the consequent implementation of appropriate treatment as soon as possible, is a major challenge in managing this disorder.

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One method of increasing recognition and the ultimate treatment of an illness is to screen for it. The adoption of a brief and easy-to-use screening instrument can help better identify symptoms suggestive of bipolar disorder. There are some scales designed to help identify potential symptoms of bipolar disorder and assess the severity of mood-related symptoms. It is important to note that these screening tools are not diagnostic on their own, and a comprehensive evaluation by a mental health professional is necessary for a definitive diagnosis. Here are some commonly used screening scales for bipolar disorder.

7.1.1 Mood Disorder Questionnaire (MDQ)

The Mood Disorder Questionnaire (MDQ) is a self-report, single-page, paper-and-pencil inventory that can be quickly and easily scored by a physician, nurse, or any trained medical staff assistant. The Mood Disorder Questionnaire screens for a lifetime history of a manic or hypomanic syndrome by including 13 yes/no items derived from both the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-5) criteria and clinical experience. A yes/no question also asks whether several of any reported manic or hypomanic symptoms or behaviors were experienced during the same period of time. Finally, the level of functional impairment due to these symptoms (“no problem” to “serious problem”) is queried on a four-point scale [1].

The MDQ has satisfactory psychometric properties for the screening of BD in various different languages, such as French, Italian, Finnish, Spanish, and Chinese. Indeed, a general population study performed by Hirschfeld et al. [1] demonstrated that the MDQ had good specificity (0.97), albeit lacking good sensitivity for the detection of BD (0.28). Similar data was obtained from a study performed by Dodd et al. [2] involving Australian women recruited from the community. Thus, the MDQ might adequately rule out BD in the community. However, the use of the MDQ for screening studies involving general population samples might be compromised by the fact that many true cases of BD would be missed. There is evidence that BD is highly prevalent among primary care patients. The psychometric properties of the MDQ for the screening of BD in primary care are yet to be determined [3].

7.1.2 Hypomania Checklist (HCL-32)

The Hypomania Checklist (HCL-32) is a 32-item self-administered tool designed to identify hypomanic symptoms in depressed patients. It is a brief and easy instrument to apply and interpret. In the HCL-32, participants are asked to focus on “high periods” and indicate specific thoughts or emotions present during these states.

Furthermore, the questionnaire includes some severity and functional impact items related to the duration of the episodes and the positive and negative consequences in different areas, such as family, social, school, and leisure lives. Additionally, other people's reactions and comments on these episodes are also taken into account. The questions about hypomanic symptoms are retrospective, as the objective is to assist in the correct diagnosis of bipolar disorder (BD) in depressed patients, which will contribute to their treatment [4].

It is important to use these scales as part of a broader assessment process, and individuals who screen positive on these scales should seek further evaluation by a mental health professional. Additionally, these scales may be used in clinical and research settings to track symptom severity and treatment progress over time.

7.2 Diagnosis

The diagnosis of BD is conducted using established systems such as the International Classification of Diseases 11th Revision (ICD-11) [5] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) [6]. The use of these manuals is essential for the prescription for evidence-based treatments and the enhancement of communication among healthcare professionals. Nevertheless, despite the existence of these classification systems, assessing patients with BD remains a challenge for clinicians, especially due to the heterogeneous nature of symptom presentation, which varies in terms of intensity, duration, and impact on the individual's functioning.

Diverse diagnostic perspectives, encompassing both categorical and dimensional approaches, contribute to the increased complexity of achieving a precise BD diagnosis. Although manuals of mental disorders, such as the DSM-5-TR and ICD-11, predominantly employ a categorical system grounded in scientific literature, clinical practice and evidence-based studies also suggest a dimensional and continuous manifestation of mental disorders. This viewpoint reinforces the notion that symptoms can be shared across various psychopathological conditions.

Due to the intricate nature of BD diagnosis and the fact that its pathophysiology is not yet fully understood, many studies tried to find new biomarkers in order to develop novel etiological hypotheses for the condition. However, despite substantial investments in the quest for biological markers that can distinguish or characterize BD from other mental disorders, no specific biomarker or endophenotype has been identified yet. In light of this, some authors propose giving up the search for biomarkers of psychiatric disorders and a paradigm shift toward treatment response prediction [7].

Another important aspect to emphasize is that the diagnosis of BD is established through clinical assessment. Therefore, the use of other tools (such as scales and neuropsychological tests), is not intended to be a diagnostic method on its own but rather considered auxiliary tools. Therefore, conducting a detailed clinical interview

is of utmost importance to assist in the evaluation process. This underscores the significance of a differential diagnosis as well.

In the absence of a specific diagnostic scale for BD, structured or semi-structured interviews can prove valuable in assisting clinicians with the diagnosis, aligning with the criteria outlined in the ICD and DSM. One such tool is the Composite International Diagnostic Interview 2.1 (CIDI 2.1), a structured interview developed by the World Health Organization (WHO). It is designed to be administered by trained lay interviewers for the assessment of mental disorders, utilizing the definitions and criteria established in ICD-10 and DSM-5. Another noteworthy instrument is the Mini-International Neuropsychiatric Interview (MINI), a concise structured diagnostic interview aimed at major psychiatric disorders. The MINI is based on the criteria set forth in DSM-5 and ICD-10 and has been translated into more than 70 languages to facilitate its global use.

Finally, another significant aspect to consider is that a portion of individuals with mood disorders initially receive a diagnosis of depression but are later diagnosed with BD. The average delay in transitioning from one diagnosis to another is reported to be 8.74 years [8]. Therefore, achieving a precise and early diagnosis of the disorder is crucial for mitigating impairment and enhancing the quality of life for these patients.

7.3 Symptom Severity

There are different instruments to assess BD symptoms, depending on their purpose (screening, diagnosis, symptom severity, and/or associated domains). Given below are instruments for some of these objectives (see Table 7.1).

Table 7.1 Main scales used to assess symptoms in BD

Instrument	Objective	Number of items	Reference
Young mania rating scale (YMRS)	To evaluate the severity of manic symptoms	11	[9]
Hamilton depression rating scale (HAM-D)	To evaluate the severity of depressive episodes	21	[10]
Montgomery–Åsberg depression rating scale (MADRS)	To assess depressive symptoms	10	[11]
Beck depression inventory II (BDI-II)	To identify depressive episodes and assess symptom severity	21	[12]
Bipolar depression rating scale (BDRS)	To assess depressive symptoms and mixed states	20	[13]

7.3.1 *Young Mania Rating Scale (YMRS)*

One of the most commonly employed scales in both clinical and research settings is the Young Mania Rating Scale (YMRS). This scale serves to gauge the severity of manic symptoms, including elevated mood, speech patterns, and thought content, through a clinical interview. Administered by a trained clinician, the YMRS employs a Likert-style scoring system comprising a total of 11 items. A higher score on the scale corresponds to more pronounced symptom severity [9]. The administration of this scale typically requires 15–30 min and is applicable to both adults and adolescents exhibiting manic symptoms. The questions assess symptoms relating to the past 48 h. Despite its relative ease of administration, the YMRS does possess some limitations, notably a somewhat restricted focus on psychotic symptoms and variations in item scoring. Nevertheless, the YMRS has undergone translation and validation into numerous languages, including German, French, Portuguese, Spanish, Turkish, and Thai [14–19].

7.3.2 *Hamilton Depression Rating Scale (HAMD)*

The Hamilton Depression Scale (HAMD) [10] is regarded as the gold standard for assessing the severity of depressive episodes and is one of the most frequently utilized scales for evaluating depression. It was developed in 1960 to assess the effectiveness of the first generation of antidepressant medications. However, several issues with the scale have been identified, including an overemphasis on vegetative symptoms and an inadequate representation of atypical symptoms [20].

The scale comprises 21 variables and assesses various domains of depression, such as mood, changes in sleep patterns or appetite, and suicidal ideation. Each item is rated on a Likert scale ranging from 0 to 4, with a maximum possible score of 52. The questions inquire about symptoms experienced over the past 7 days. Notably, four items pertaining to diurnal variation, depersonalization/derealization, paranoid symptoms, and obsessive-compulsive symptoms are excluded from the total score. While these items assess important characteristics of depressive episodes, they do not contribute to the assessment of depression severity. The HAMD employs specific cutoff scores for classification: no depression (0–7 points), mild depression (8–17 points), moderate depression (17–23 points), and severe depression (above 24 points) [21]. Furthermore, the HAMD has been validated and translated into various languages, including Spanish, Portuguese, Tunisian dialect, and Lebanese, among others [22–25].

7.3.3 *Montgomery–Åsberg Depression Rating Scale (MADRS)*

The Montgomery–Åsberg Depression Rating Scale (MADRS) is a questionnaire consisting of ten items that assess depressive symptoms. A higher MADRS score indicates more severe depression, with each item rated on a scale from 0 to 6. The total score on this scale ranges from 0 to 60 [11]. All the items included in the MADRS are considered core symptoms of depressive illness. However, a few characteristic symptoms are omitted, such as motor retardation, primarily because it is relatively infrequent among patients [11]. The MADRS has been translated from English into several languages, including Brazilian Portuguese, German, Spanish, Persian, and Bangla [26–31].

7.3.4 *Beck Depression Inventory II (BDI-II)*

The Beck Depression Inventory II (BDI-II) is a self-report assessment tool comprising 21 items and is highly sensitive to changes in clinical patients. It is utilized for the identification of depressive episodes and the assessment of symptom severity, aligning with the criteria outlined in DSM-5 [32], and is intended for individuals aged 13 and older [12]. Patients rate the symptoms they have experienced over the preceding 2 weeks using a four-point Likert scale, which ranges from 0 to 3. The total score on the scale spans from 0 to 63, with severity categorized into four levels: subclinical (0–13), mild (14–19), moderate (20–28), and severe (29–63). The authors suggest that these cutoff points may be subject to adjustment based on sample characteristics and the specific purpose for which the BDI-II is being employed.

The BDI-II incorporates additional items aimed at identifying severity and depressive symptoms, replacing or modifying items from previous versions that assessed changes in sleep and appetite, body image, work-related challenges, weight loss, and somatic complaints. The BDI-II has undergone translation from English into several languages, including German, Croatian, Korean, Bangla, and Brazilian Portuguese [33–37].

7.3.5 *The Bipolar Depression Rating Scale (BDRS)*

The Bipolar Depression Rating Scale (BDRS), developed by Berk et al. [13] to assess depressive symptoms and mixed states in individuals with bipolar disorder (BD), represents a potential alternative tool. The BDRS consists of 20 items, which are rated on a four-point scale (0 = absence of symptoms, 1 = mild, 2 = moderate, and 3 = severe). This scale evaluates various phenomenological aspects of bipolar

depression, including features such as hyperphagia and hypersomnia. It was designed to be administered by psychiatrists or other trained professionals, considering both the objective assessment by the clinician and the patient's self-report.

A manual has been created to accompany the BDRS, featuring illustrative examples aimed at enhancing standardization and response reliability, thereby assisting clinicians in completing the scale. The BDRS has undergone validation and translation into multiple languages, including Portuguese, Turkish, Italian, Spanish, Chinese, and Korean [38–43].

7.4 Cognitive Measures

Cognitive dysfunction in BD is prevalent, persistent, and heterogeneous. Due to the negative impact on psychosocial functioning, quality of life, and disease prognosis, cognitive dysfunction has become a relevant issue in the management of BD. Typically, the most affected domains are memory, attention, and executive functions [44, 45]. The extent and severity of cognitive deficits vary among BD patients including (i) global impairment across several domains (23%), (ii) selective deficits in one or two domains (34%), or (iii) intact cognition (43%) [46].

The detection and treatment of cognitive dysfunction require the use of appropriate cognitive measures for better characterization and understanding of cognitive deficits in BD. The Targeting Cognition Task Force of the International Society of Bipolar Disorders (ISBD) not only suggests the screening and tracking of cognitive performance in remitted patients by means of objective measures (e.g., neuropsychological tests) but also recommends the evaluation of patients' subjectively experienced cognitive difficulties [47, 48]. Whereas objective cognitive measures allow us to assess the cognitive performance of an individual as compared to the normative population, subjective cognitive measures tend to assess the subject's cognitive function in comparison to their own premorbid levels [49, 50]. Furthermore, the patient's perception of their cognitive function is an important issue and should be considered.

Indeed, cognitive function is a complex construct, and a combination of instruments that allow us to assess different aspects may greatly contribute to the knowledge about the nature and extent of cognitive dysfunctions in BD. Therefore, an adequate assessment of cognition requires not only objective neuropsychological tests but also subjective cognitive measures. A comprehensive assessment, aiming to integrate clinical information and objective and subjective cognitive measures, is essential to determine the nature (subjective/objective) and severity (intact/selective/global) of cognitive dysfunction. The recommended tools by the ISBD that are commonly used for screening purposes or for monitoring cognition over time are listed below.

7.4.1 Subjective Cognitive Measure

The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) was carefully designed to assess cognitive difficulties associated with the main deficits experienced by patients with BD as reported in the literature. The COBRA is a 16-item self-report instrument measuring subjective cognitive difficulties experienced by BD patients in their everyday lives related to executive function, processing speed, memory, attention, and concentration. All items are rated using a four-point scale: 0 = never, 1 = sometimes, 2 = often, and 3 = always. The total score is obtained by adding up the scores of every item. The higher the score, the higher the number of subjective complaints [51].

The questionnaire exhibited satisfactory psychometric properties including high internal consistency [46, 49, 51–53], good discriminant validity with control groups, and good concurrent validity with other instruments used to assess cognitive complaints [46, 49, 51]. Notably, COBRA's psychometric properties were consistent across countries. Cutoff points to discriminate between BD and HC scores were similar between languages (i.e., >10 Portuguese (Brazil) and Spanish validation; >11 Chinese validation). In addition, most authors agreed in considering COBRA as a one-factor tool, indicating its better ability to detect global dysfunction rather than discriminate between deficits in different cognitive domains [46, 51, 53]. Nonetheless, the questionnaire showed only moderate sensitivity for the detection of objective cognitive impairment [49] and unclear concurrent validity with measures of objective cognition. Specifically, the COBRA had significant but weak correlations with measures of executive function and verbal and working memory [49, 51] but not global cognition [53] in BD patients. Overall, the evidence suggests that the COBRA is a feasible instrument for subjective cognitive assessment in BD. Currently, the COBRA is available in distinct languages and is free of charge on the ISBD website (www.isbd.org/cognitive-assessment).

7.4.2 Objective Cognitive Measure

The Screen for Cognitive Impairment in Psychiatry (SCIP) is an objective cognitive screening measure composed of five short tests, with an administration time of approximately 10–15 min and three parallel versions to enable repeating the measure [54]. This instrument assesses difficulties in working memory, verbal learning and memory, verbal fluency, and psychomotor speed, having shown high sensitivity and specificity in detecting cognitive impairments in BD [49]. It is one of the performance-based tools most commonly used to screen cognitive deficits in psychiatric disorders [55–57] and is available in many languages including English, Spanish, French, Italian, and German, among others [47]. Only a few studies have investigated the psychometric properties of this instrument in BD samples showing

good validity, reliability, and sensitivity [49, 55, 56, 58]. Interestingly, the SCIP total score was significantly associated with the global cognition composite scores measured by neuropsychological tests [49, 58]. Overall, preliminary data shows that the SCIP might be a feasible and valid instrument for use in BD for screening purposes or to monitor cognitive changes over time. The versions in Danish, English, French, and German are already validated with their respective normative data and cutoff points, while the versions in Chinese, Italian, Japanese, Persian, and Portuguese have been translated but still lack normative data. All of these versions of the SCIP can be obtained free of charge from the ISBD website (www.isbd.org/cognitive-assessment).

7.4.3 *MATRICES Consensus Cognitive Battery (MCCB)*

The ISBD proposed an adaptation of the MATRICS Consensus Cognitive Battery (MCCB), originally developed for schizophrenia, to assess cognition in BD. The ISBD endorsed the applicability of the majority of MCCB subtests, with recommendations made for the inclusion of additional executive function tests (core: Color–Word Stroop and the Trail Making Test—Part B (TMT-B); optional: the Wisconsin Card Sorting Task) and the substitution of verbal learning measures (i.e., the California Verbal Learning Test (CVLT) in place of the Hopkins Verbal Learning Test—Revised (HVLt-R)) that form the ISBD-Battery for the Assessment of Neurocognition (ISBD-BANC) [48].

The preliminary battery proposed by ISBD, with six cognitive domains derived from the scores of ten subtests, is presented in Table 7.2.

Table 7.2 Proposed cognitive battery for bipolar disorder

Cognitive domain	Neuropsychological test	Duration (min)
Speed of processing	Brief assessment of cognition in schizophrenia (BACS):	3
	Symbol coding	2
	Category fluency: Animal naming	2
	Trail making test—Part A	
Attention/vigilance	Continuous performance test—identical pairs (CPT-IP)	13
Working memory	Wechsler memory scale—III letter–number sequencing	6
	Wechsler memory scale—III spatial span	5
Verbal learning/ memory	Hopkins verbal learning test—Revised (substitute)	5
	California verbal learning test (substitute)	10
Visual learning	Brief Visuospatial memory test—Revised	5
Executive function	Stroop test	5
	Trail making test—Part B	5
	Wisconsin card sorting test (optional)	20

7.4.3.1 Functioning Measures

The International Classification of Functioning, Disability, and Health (ICF) defines disability as a health experience within a context, rather than a challenge confined solely to the individual. Based on the biopsychosocial model, the ICF posits that disability and functioning result from the interplay between health conditions and contextual factors. This model recognizes the multidimensional nature of disability, arising from the interaction between individual attributes and aspects of the person's physical, social, and attitudinal environments. It expands the understanding of disability, enabling examination of medical, individual, social, and environmental influences on functioning and disability [59].

In Table 7.3, we have listed distinct instruments utilized for the assessment of functional status in BD. Among them, the most frequently employed scales are the

Table 7.3 Instruments used to assess functioning in BD

Instrument	Objective	Reference
World Health Organization disability assessment scale (WHODAS)	To assess functioning or disability	World Health Organization
Global assessment of functioning (GAF)	To assess the severity of symptoms or functioning	[60]
Functioning assessment short test (FAST)	To assess the six domains of functioning	[61]
Social and occupational functioning assessment scale (SOFAS)	To assess exclusively the patient's level of social and occupational functioning without accounting for the severity of the individual's clinical symptoms	[62]
Multidimensional scale for independent functioning (MSIF)	To evaluate the patient's inherent responsibilities, the level of assistance provided by others to maintain the role, and the level of performance in which the patient can successfully fulfill roles in work, educational/vocational training, and residential environments	[63]
UCLA social attainment survey	To assess the social adjustments of patients based on same-sex peer relations, leadership in same-sex peer relations, opposite-sex peer relations, dating history, sexual experience, outside activities, and participation in organizations	[64]
Medical outcomes study short form (SF-36) psychosocial functioning and health rating questionnaire	To assess limitations in physical activities, social activities, bodily pain, general mental health, vitality, general health perception, and usual role limitations due to physical or emotional problems	[65]
Sheehan disability scale	To evaluate patient impairment levels in the areas of work/school activities, family relationships, and social functioning	[66]

Global Assessment of Functioning (GAF) and Functioning Assessment Short Test (FAST), which are further described in detail. Indeed, in a systematic review including 40 studies assessing functional impairments in BD, the GAF and FAST were used in 40% of them, while the remaining scales were utilized in only one study each [67].

7.4.3.2 Global Assessment of Functioning (GAF)

The Global Assessment of Functioning (GAF) was introduced by Endicott et al. [60] as a single rating scale for evaluating a person's "psychological, social and occupational functioning on a hypothetical continuum of mental health-illness" [60]. The primary aim of this measure was to communicate the extent of severity and impairment, and it highlighted the requirement for professional assistance and illustrated any progress or alterations over time. The GAF scale was initially endorsed by the American Psychiatric Association and was introduced in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R and DSM-5 versions) as a gold standard to assess functional status. More recently, the GAF was excluded from the DSM classification system, specifically omitted in the DSM-5 version.

The GAF scale represents a latent continuous measure scored from 1 to 100, where a score of 1 represents the worst hypothetical level of symptom severity and impairment of psychosocial functioning, and a score of 100 represents the, hypothetically, most optimal level. The GAF focuses on the assessment of severity. The single GAF score represents both the degree of severity of the symptom or function that is reported and, at the same time, the level most representative of the person, situation, and period in question. In certain situations, it can be crucial to avoid placing excessive emphasis on individual episodes. Symptoms and psychosocial functioning can fluctuate from week to week or even from 1 day to the next. In such instances, the critical role of the evaluator's clinical judgment becomes paramount.

The GAF scale comprises ten intervals without specific cutoff levels. These intervals are delineated using examples of symptoms and functional impairments, with "and/or" separating them in the text. Indeed, it assesses two distinct concepts—one for symptoms and another for functional impairments. However, clinicians have reported difficulties in choosing an interval or distinguishing between intervals, attributed to insufficient examples and a lack of continuity. Furthermore, there has been persistent doubt regarding the utilization of a unidimensional scale to assess both psychological symptom levels and social and occupational functioning. As these three dimensions do not consistently correlate, it presents a challenge to the reliability of GAF scores and the validity of the inferences drawn from them.

An initiative to address these issues was headed by a group of experienced researchers and clinicians from the Research Group for Personality Psychiatry at the University of Oslo. They proposed a new, revised split version of GAF, where some keywords and unambiguous examples were replaced. The most prominent changes are among the descriptions and examples at GAF levels 1–30, and

especially between 1 and 20. This newly revised GAF scale represents little change but with practical importance. In routine clinical settings, the GAF is a far more frequently used scale for the assessment of functioning [68].

7.4.3.3 Functioning Assessment Short Test (FAST)

The development of FAST also underwent a rigorous process, involving a comprehensive review of the literature regarding the primary challenges faced by individuals with psychiatric disorders. This process drew upon the clinical expertise of field experts and insights from related instruments [61]. Although the FAST scale was originally developed for bipolar disorder, it has also been validated in other clinical samples [69–76] as well as in healthy individuals [77, 78]. Recently, the FAST scale was also validated in a self-report digital format [79], and it is available in more than ten distinct languages.

The Functioning Assessment Short Test (FAST) is an interviewer-administered scale that allows the multidimensional evaluation of functioning, including aspects, such as the individual's ability to function socially or occupationally or live independently as well as financial issues and cognition. Therefore, it consists of 24 items divided into six domains of functioning:

1. **Autonomy:** refers to the person's capacity for doing things alone and making his/her own decisions.
2. **Occupational functioning:** refers to the capacity to maintain a paid job, be efficient in performing tasks at work, and work in the field in which the person was educated and whether the person earns money according to their level of employment.
3. **Cognitive functioning:** related to the ability to concentrate, perform simple mental calculations, solve problems, and learn and recall new information.
4. **Financial issues:** involve the capacity to manage finances and spend appropriately.
5. **Interpersonal relationships:** refer to relations with friends and family, involvement in social activities, sexual relationships, and the ability to defend one's own interests.
6. **Leisure time:** refers to the ability to engage in and enjoy physical activities (sports and exercise) and hobbies.

The items are rated 0 (no impairment), 1 (mild impairment), 2 (moderate impairment), or 3 (severe impairment). The overall FAST scores range from 0 to 72, where higher scores indicate greater disability, with scores above 11 indicating the presence of significant disability. The FAST provides specific cutoff scores for severity: no impairment (0–11 points), mild impairment (12–20 points), moderate impairment (21–40 points), and severe functional impairment (above 40 points). The time frame for evaluation of functioning is the past 14 days [61, 80]. It is easy to apply and requires only a short period of time for administration. Similar to the World Health Organization Disability Assessment Scale (WHODAS) 2.0, FAST has a manual that outlines guidelines for standardized administration.

7.4.3.4 World Health Organization Disability Assessment Scale (WHODAS 2.0)

The original World Health Organization Disability Assessment Scale (WHODAS)—published by WHO in 1988—was an instrument developed to assess functioning, mainly in psychiatric inpatients. Since then, the tool has undergone significant revisions by the WHO, culminating in its latest version: WHODAS 2.0.

The development of WHODAS 2.0 (<https://www.who.int>) involved a meticulous process that included a thorough review of the literature on the conceptualization and measurement of functioning and disability, as well as related instruments. Various studies were employed to assess its cross-cultural applicability, reliability, and validity, in addition to evaluating its utility in health services research. It is now available in more than ten different languages, and the psychometric properties of its different versions have been studied in community populations and clinical conditions.

WHODAS 2.0 provides a common metric of the impact of any health condition in terms of functioning. The instrument does not target a specific disease—it can thus be used to compare disabilities due to different diseases and monitor the impact of health-related interventions. It has been proposed as the standard tool for measuring functioning by the DSM-5 and the forthcoming ICD-11.

As in the ICF, WHODAS 2.0 places health and disability on a continuum, with disability defined as “a decrement in each functioning domain.” Consequently, WHODAS 2.0 incorporates the fundamental principles of the ICF. It enables the identification of limitations in activity and restrictions on participation experienced by an individual, regardless of their medical diagnosis. Six domains of functioning were assessed by the WHODAS 2.0:

1. Cognition: understanding and communicating
2. Mobility: moving and getting around
3. Self-care: attending to one’s hygiene, dressing, eating, and staying alone
4. Getting along: interacting with other people
5. Life activities: domestic responsibilities, leisure, work, and school
6. Participation: joining in community activities and participating in society

Three main versions of WHODAS 2.0 (36-item, 12-item, and 12 + 24-item) are available, which differ in length and intended mode of administration. All of them assess difficulties experienced by the respondent in the six functioning domains during the past month. The average interview time for the interviewer-administered 12-item and 36-item versions are 5 and 20 min, respectively. Both versions are available in three different forms—interviewer-administered, self-administered, and proxy-administered.

For all WHODAS 2.0 versions, respondents should answer questions with the following frames of reference in mind: (1) degree of difficulty, (2) due to health conditions, (3) in the past 30 days, (4) averaging good and bad days, (5) as the respondent usually does the activity, and (6) items not experienced in the past 30 days are not rated. More details about how to calculate the WHODAS score as well as guidelines for standardized administration are available at

<https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health/who-disability-assessment-schedule>.

In summary, the standardized rating scales presented in this chapter serve as tools for psychiatrists to gauge the severity of a patient's symptoms or evaluate critical outcomes such as cognition and functioning. Whether employed in clinical practice or research, these scales enable the ongoing monitoring of the disease and treatment response, helping decision-making and the implementation of more effective treatments.

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Chapter 8

Differentiating Bipolar and Unipolar Depression



Philip B. Mitchell and Gloria Roberts

8.1 Introduction

There has been a growing interest in differentiating bipolar depression from unipolar depression (major depressive disorder (MDD)), in terms of both phenomenological characteristics and biomarkers. This is more than a question of esoteric academic interest, as any such differentiating features would be of major clinical pertinence. They could assist in the not uncommon clinical scenarios of: first, assisting in determining the likely diagnosis in a depressed patient with uncertain or ambiguous evidence for prior episodes of hypomania or mania and, second, predicting whether a young person with a major depressive episode will go on to develop bipolar disorder or unipolar depression. Further, at a more theoretical level, if there are distinct phenomenological differences between depression in bipolar disorder and unipolar depression, that is likely to indicate a distinct underlying biology between these two disorders.

When Mitchell began to present his early research findings suggesting phenomenological differences between bipolar and unipolar depression 20 years ago, he was advised by a respected international colleague to move into other areas of research, as “there are clearly no differences between these two conditions.” In the two decades since that time, there has been growing evidence for and acceptance of such distinctions. Although the DSM and ICD classificatory systems still do not acknowledge the differences between these conditions, a high-profile *Lancet* review article [1] outlined a number of clinical features found to differentiate bipolar and unipolar depression:

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Atypical symptoms—such as hypersomnia, lability, and weight instability—are also common in bipolar depression, being reported in 90% of episodes, but they are described in only half of unipolar depressive episodes. Psychosis, psychomotor retardation, and catatonia are also more characteristic of bipolar depression, whereas somatic complaints are most frequent in unipolar depression. A family history of mania is also a relevant indicator of bipolar depression.

Chakrabarti [2], in a review of the revisions to bipolar disorder criteria in ICD-10, commented that despite the inherent difficulty for categorical diagnostic systems of incorporating a dimensional system such as the “probabilistic approach” ([3]; see below), *“the lack of distinction between unipolar and bipolar depression is problematic, because one of the reasons that the diagnosis of BD is often missed is the inability to distinguish between the two types of depression.”*

This chapter will review both the phenomenological and biological literature that has focused on this question. The authors will overview the journey of their own research, as well as the broader research literature.

8.2 A Growing Interest by International Bodies in the Question of Distinguishing Features of Bipolar Depression in the Mid-Late 2000s

In the mid-2000s, Mitchell was invited to chair a task force of the International Society for Bipolar Disorders (ISBD), focused on determining guidelines for the diagnosis of bipolar depression. This task force was part of a broader diagnostic guideline task force established by ISBD to examine the evidence base for various phases/presentations of bipolar disorder (such as mania, mixed presentations, and schizoaffective disorder), with the aim of providing evidence for revisions to the DSM-5 bipolar disorders section, as the DSM-5 working group had been recently established. An overview of this ISBD Bipolar Disorders Diagnostic Guidelines Task Force can be found in Ghaemi et al. [4], which was accompanied by the specific task force proposals in a special supplement of *Bipolar Disorders*. The invitation to Mitchell followed his authorship on relevant bipolar depression publications [5–8]. As further evidence of the contemporaneous interest in bipolar depression, the European College of Neuropsychopharmacology (ECNP) convened a workshop on bipolar depression in Nice in 2007, with a report from that meeting being published the following year [9].

8.2.1 ISBD Diagnostic Guidelines on Bipolar Depression: A Probabilistic Approach [3]

The membership of the ISBD Bipolar Depression Guidelines Task Force comprised Philip Mitchell, Guy Goodwin, Gordon Johnson, and Robert Hirschfeld. After a detailed review of the prior literature (see below), it was clear that there were no

distinct pathognomonic categorical differences between bipolar depression and unipolar depression (major depressive disorder (MDD)). There were, however, repeated findings of significant differences in the likelihood of some clinical features between these two conditions. As a consequence, rather than proposing a categorical diagnostic distinction between bipolar depression and major depressive disorder, we recommended a “probabilistic” (or likelihood) approach. We concluded that while there is no “point of rarity” between the two presentations, there was, rather, a differential likelihood of experiencing a number of specific symptoms and signs of depression. We provided a table outlining the draft proposed operationalized criteria for such an approach and commented that the specific details of such a probabilistic approach needed to be further explored, suggesting, for example, that to be useful, any diagnostic innovation should inform treatment choices.

8.3 Pre-2008 Studies That Informed the ISBD Probabilistic Approach to Bipolar Depression

In 2000, Parker et al. examined the relative prevalence of melancholic syndromes in bipolar and unipolar depression. Examining data from three prospective datasets, comprising 83 bipolar disorder and 904 unipolar patients who were assessed while depressed, in 1994, Parker et al. found that bipolar disorder subjects were significantly more likely than unipolar patients to be diagnosed as melancholic by each of the DSM and CORE (an 18-item scale with subscales for retardation, agitation, and non-interactiveness) diagnostic systems [10]. Furthermore, after logistic regression, bipolar-depressed patients were significantly more likely to demonstrate psychomotor disturbance (particularly retardation) and pathological guilt.

In a second paper from the same group, Mitchell et al. [7] undertook a “fine-grained” analysis of the most recent of these datasets. Thirty-nine of the patients had DSM-IV bipolar I (BP-I) disorder. These bipolar-depressed patients were initially compared with 39 unipolar-depressed subjects matched for age, sex, and the presence or absence of DSM-IV melancholia. Although there was no difference in the severity of depression (assessed by the Hamilton Rating Scale for Depression), those with bipolar depression were significantly more likely to have had a past psychotic depressive episode. They were more likely to currently report worthlessness, anhedonia, restlessness, leaden paralysis, and hypersomnia. Conversely, they were less likely to manifest tearfulness, anxiety, and the tendency to blame others. The most striking differences, however, were observed in the objective features of depressive psychomotor disturbance as rated by the CORE scale (see above). Bipolar patients were less emotionally reactive, had a greater delay in responding verbally, and demonstrated more slowed movement. There were no differences in agitation items. Bipolar patients rated higher on both the retardation subscale and total CORE score. Mitchell et al. then compared the 20 bipolar-depressed patients with DSM-IV-defined melancholia against age- and sex-matched melancholic unipolar patients. First, with respect to symptoms, bipolar disorder patients reported more anhedonia, a persistence of depressed mood, and hypersomnia but less initial

insomnia and anxiety. Second, bipolar disorder patients were rated on the CORE scale as demonstrating more facial immobility, slower movement, and a greater delay in initiating motor activity. Again, they had significantly higher scores on the retardation subscale of this instrument.

These findings suggested features with potential clinical utility for diagnosing bipolar depression, which were described by the authors as a “bipolar depression signature.” These were melancholic features including psychomotor retardation, unvarying mood, and marked anhedonia; “atypical” depressive symptoms such as hypersomnia and leaden paralysis; a past history of psychotic depression; and the absence of anxiety, initial insomnia, the tendency to blame others, and tearfulness. Mitchell et al. acknowledged that these features reflected differing group means and were not pathognomonic of bipolar depression. This pattern suggested that the clinical presentation of bipolar I depression is distinct from the “pure” atypical depression of, for example, seasonal affective disorder or the “pure” melancholic presentation of some patients with severe unipolar depression.

Olfson et al. [11] studied characteristics of depression in a primary care clinic, with bipolar patients identified using the self-report Mood Disorder Questionnaire (MDQ). Twenty-five percent of depressed patients were assessed as suffering from bipolar disorder according to the MDQ. Those with bipolar depression were significantly more likely than those with unipolar depression to report hallucinations, current suicidal ideation, and low self-esteem but were less likely to acknowledge disturbed appetite.

Perlis et al. [12] used three large datasets (two unipolar- and one bipolar-depressed) that had been recruited for pharmaceutical studies. The paper reported on items from two measures common to these studies, i.e., the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HARS). Perlis et al. found bipolar depression to be associated with a family history of bipolar disorder, earlier age of onset, and more prior depressive episodes. Bipolar patients reported more fears, whereas unipolar patients more commonly experienced sadness, insomnia, cognitive difficulties, and somatic symptoms.

Solomon et al. [13] used data from the NIMH Collaborative Program on the Psychobiology of Depression cohort to develop a clinical screening instrument to screen for bipolar disorder in patients presenting with a current MDE. Using a split-sample data analytic procedure, the authors first investigated the most discriminating of 59 sociodemographic and clinical variables in a comparison of an index bipolar I sample with major depressive disorder. The three most discriminating variables were: (i) the presence of delusions at baseline assessment, (ii) the number of prior episodes of major depression, and (iii) family history of major depression or mania.

Benazzi (who sadly died much too young) undertook similar studies with bipolar II-depressed patients, predominantly in a private practice outpatient context. As in a number of the studies of bipolar I-depressed patients described above, he reported an increased prevalence of “atypical” features in bipolar II compared with unipolar-depressed patients but in contrast to the bipolar I studies, found no difference in the rates of psychomotor retardation [14]. In another paper, Benazzi [15] (it was not

clear if the sample overlaps with prior reports from this researcher) reported on a comparison of the symptoms of depression in 379 bipolar II–depressed and 271 major depressive disorder outpatients. The features that were more common in bipolar II–depressed patients than unipolar-depressed patients were weight gain, increased eating, hypersomnia, psychomotor agitation, worthlessness, and a diminished ability to concentrate. “Inside-MDE hypomanic” symptoms that were more common in BP-II were distractibility, racing thoughts, irritability, talkativeness, and increased risky and goal-directed activities. Multiple logistic regression showed that hypersomnia, racing thoughts, irritability, and psychomotor agitation were independent predictors of BP-II disorder. These reports by Benazzi suggest both commonalities and distinctions between bipolar I and II depression.

8.4 Details of Recommendations of ISBD Task Force on a Probabilistic Approach to the Diagnosis of Bipolar Depression

Drawing on the studies detailed above (and others), those clinical features that had been most commonly and consistently reported in those with bipolar depression (or unipolar-depressed “converters” to bipolar disorder) were incorporated in the proposed diagnostic guidelines. As some of the reported distinguishing features such as worthlessness, low self-esteem, and social withdrawal are common in any form of depression per se, we considered these to be of low diagnostic specificity and, therefore, did not include these in the final “probabilistic” approach to the diagnosis of bipolar depression.

The proposed operationalized criteria for such an approach are detailed below. We utilized specific depressive clinical signs or symptoms (as well as characteristics of illness course and family history), rather than proposing a requirement for particular categorical presentations of depression—such as “atypical” or “melancholic” depression. We specified a particular number of features required to indicate the greater likelihood of bipolar depression or unipolar depression, respectively. The actual number of features specified was determined on the basis of both the literature reviewed and “clinical reasonability.”

We recommended that a greater likelihood of the diagnosis of bipolar I depression should be considered if ≥ 5 of the following features are present:

Symptomatology and mental state signs

- Hypersomnia and/or increased daytime napping
- Hyperphagia and/or increased weight
- Other “atypical” depressive symptoms such as “leaden paralysis”
- Psychomotor retardation
- Psychotic features and/or pathological guilt
- Lability of mood/manic symptoms

Course of illness

- Early onset of first depression (<25 years)
- Multiple prior episodes of depression (≥ 5 episodes)

Family history

- Positive family history of bipolar disorder

In contrast, we proposed that a greater likelihood of the diagnosis of unipolar depression should be considered if ≥ 4 of the following features are present:

Symptomatology and mental state signs

- Initial insomnia/reduced sleep
- Appetite and/or weight loss
- Normal or increased activity levels
- Somatic complaints

Course of illness

- Later onset of first depression (>25 years)
- Long duration of current episode (>6 months)

Family history

- Negative family history of bipolar disorder

8.5 Relevant Studies Published Subsequent to the Publication of the Probabilistic Approach to Bipolar Depression

8.5.1 Clinical Differences Between Bipolar and Unipolar Depression

In 2011, Mitchell et al. [16] tested the utility of the “probabilistic approach” in a different dataset, i.e., bipolar disorder and major depressive disorder subjects in a large sample of bipolar disorder families, all of whom had been assessed with the Diagnostic Interview for Genetic Studies (DIGS), including details of symptoms of the most severe lifetime depressive episode. The primary aim was to test the capacity of the probabilistic approach in distinguishing between unipolar and bipolar depression in this dataset. A secondary aim was to identify subgroups within the relatives with major depression, potentially indicative of “genetic” and “sporadic” subgroups. Patients with bipolar disorder types 1 and 2 ($n = 246$) and patients with major depressive disorder ($n = 120$) were assessed. Logistic regression was used to identify distinguishing clinical features and assess the utility of the probabilistic approach. Hierarchical cluster analysis was used to identify subgroups within the

major depressive disorder sample. Bipolar depression was characterized by significantly higher rates of psychomotor retardation, difficulty in thinking, early morning awakening, morning worsening, and psychotic features. Depending on the threshold employed, the probabilistic approach yielded a positive predictive value ranging from 74% to 82%. Two clusters within the major depressive disorder sample were found, one of which demonstrated features characteristic of bipolar depression, suggesting a possible “genetic” subgroup. The authors concluded that this preliminary validation of the probabilistic approach in differentiating between unipolar and bipolar depression was consistent with dimensional distinctions between the two disorders, which offered clinical utility in identifying patients who may warrant further assessment for bipolarity. The major depressive disorder clusters were considered to potentially reflect genetic and sporadic subgroups, which, if replicated independently, might enable an improved phenotypic definition of underlying bipolarity in genetic analyses.

In 2015, Mitchell’s group [17] examined the question of whether the probabilistic approach could identify differences in the features of bipolar depression between bipolar I and bipolar II disorders. As detailed above, while most of the prior studies had been in largely bipolar I populations, Benazzi had reported on distinctions between bipolar II–depressed and unipolar subjects. To answer this question, Mitchell reexamined the aforementioned bipolar disorder pedigree dataset used in the 2011 paper. Patients with DSM-IV diagnoses of BP-I ($n = 202$), BP-II ($n = 44$), and MDD ($n = 120$) were assessed. Multivariate logistic regression was used to identify distinguishing clinical features. BP-I differed from MDD in terms of greater rates of psychomotor retardation ($P < 0.05$) and psychotic features ($P < 0.05$). BP-II was distinguished from MDD ($P < 0.01$) by the greater likelihood of mixed features. Patients with BP-II had a greater likelihood of mixed features ($P < 0.001$) and a lesser likelihood of psychomotor retardation ($P < 0.05$) compared to those with BP-I. The probabilistic approach significantly differentiated both BP-I and BP-II from MDD ($P < 0.01$ to $P < 0.001$, depending on the cutoff) but did not robustly distinguish between BP-I and BP-II. The authors concluded that the probabilistic approach to bipolar depression was demonstrated for the first time to significantly distinguish both bipolar disorder subtypes from MDD. Further, in view of the debate over “mixed specifiers” for these conditions in DSM-5, the differentiation of BP-II from both BP-I depression and MDD in terms of the presence of mixed symptoms was of particular interest.

In 2015, Leonpacher et al. undertook a similar study to those reported by Mitchell et al. [16] and Frankland et al. [17] in a US sample using DIGS interviews for the NIMH Bipolar Disorder Genetics Initiative study, seeking to identify depression-related features that distinguish BP from MDD. The authors selected 34 depression-related clinical features to test across the diagnostic categories in an initial discovery dataset consisting of 1228 subjects (386 BP-I, 158 BP-II, and 684 MDD). Features significantly associated with BP were tested in an independent sample of 1000 BP-I cases and 1000 MDD cases for classifying ability in receiver operating characteristic (ROC) analysis. The authors found a number of clinical features that showed significant association with BP-I compared with MDD: delusions, psychomotor

retardation, incapacitation, a greater number of mixed symptoms, a greater number of episodes, shorter episode length, and a history of experiencing a high after depression treatment. ROC analyses of a model including these seven factors showed significant evidence for the discrimination between BP-I and MDD in an independent dataset (area under the curve = 0.83). Only two features (number of mixed symptoms and feeling high after an antidepressant) showed an association with BP-II versus MDD. Overall, this study suggested that clinical features distinguishing depression in BP-I versus MDD have important classification potential for clinical practice.

In 2019, focusing on psychomotor differences as potential differentiators between bipolar and unipolar depression (both behavioral and cognitive), the French group of Robin et al. [18] tested two groups of age-matched patients with unipolar depression ($n = 54$) and bipolar depression ($n = 20$) who completed the MADRS, the Montreal Cognitive Assessment (MoCA), and the Salpêtrière Retardation Rating Scale (SRRS, a structured instrument measuring psychomotor change). They found that the bipolar-depressed patients had higher SRRS scores and lower MoCA scores than those with unipolar depression despite no difference in the MADRS severity of depression. The authors concluded that these results highlighted the importance of psychomotor and cognitive functions in the distinction between bipolar and unipolar depression.

8.5.2 Are the Differences Between Bipolar and Unipolar Depression Also Found in Non-European Populations?

One of the limitations of this literature was that the published studies had been almost universally on European-origin subjects. It was therefore of major significance when Xiang et al. [19] published their findings in a large multicenter study of a Chinese population. Xiang et al. studied 1487 patients initially diagnosed with MDD who were consecutively evaluated in 13 centers across China. The proportions of bipolar disorder (all types), bipolar I disorder (BP-I), and bipolar II disorder (BP-II) were 20.8%, 7.9%, and 12.8%, respectively. Multiple logistic regression analyses revealed that compared to MDD patients, BP-I was significantly characterized by more atypical depressive features (increased appetite, increased sleep, and weight gain), more psychotic symptoms, more lifetime depressive episodes, and an earlier age of onset; BP-II was characterized by more psychotic symptoms and an earlier age of onset. In addition, compared to BP-II patients, BP-I patients were characterized by more frequent depressive episodes per year. This study replicated many prior findings in European-origin populations.

A recent study from China used a similar design that compared features of depression in MDD and bipolar disorder patients initially misdiagnosed with MDD in a different dataset. Studying 1463 subjects, Wu et al. [20] found that the BP-II cases were more likely than BP-I cases to report agitation. Both BP-I and BP-II cases were more likely than MDD cases to report a lifetime suicide attempt and

psychotic features. BP-II cases were more likely than MDD cases to report agitation but were less likely to report weight loss; initial, middle, and terminal insomnia; somatic anxiety; and gastrointestinal symptoms.

8.5.3 Are Depressive Episodes Different Prior to the Onset of the First Episode of Hypo/Mania?

One of the important questions concerning possible distinctions between bipolar depression and unipolar depression is whether any such differences predate the onset of the first episode of hypo/mania, i.e., do such differences directly reflect the inherent nature of the illness, or are they a consequence of prior elevated episodes? In 2018, Mitchell's group [21] studied 287 participants aged 12–30 (163 genetically high-risk (HR) with a first-degree relative with bipolar disorder (BD) and 124 controls) who were followed annually for a median of 5 years. We used the baseline presence of DSM-IV depressive, anxiety, behavioral, and substance use disorders, as well as a constellation of specific depressive symptoms (as identified by the probabilistic approach to bipolar depression) to predict the subsequent development of hypo/manic episodes. There were two particularly interesting findings. First, at baseline, genetically high-risk participants were significantly more likely to report ≥ 4 probabilistic features (40.4%) when depressed than the offspring of controls without any mental illness (6.7%; $p < 0.05$). Second, we examined the capacity of depressive features to predict later onset of hypo/manic features. Over the follow-up period, 19 HR subjects later developed either threshold ($n = 8$; 4.9%) or subthreshold ($n = 11$; 6.7%) hypo/mania. The presence of ≥ 4 probabilistic features was associated with a seven-fold increase in the risk of “conversion” to threshold BD (hazard ratio = 6.9, $p < 0.05$) above and beyond the 14-fold increase in risk related to major depressive episodes (MDEs) per se (hazard ratio = 13.9, $p < 0.05$). Individual depressive features significantly predicting conversion were psychomotor retardation and ≥ 5 MDEs. Behavioral disorders only predicted conversion to subthreshold BD (hazard ratio = 5.23, $p < 0.01$), while anxiety and substance disorders did not predict either threshold or subthreshold hypo/mania. This study suggests that specific depressive characteristics substantially increase the risk of young people at familial risk of BD going on to develop future hypo/manic episodes and may identify a more targeted HR population for the development of early intervention programs.

8.5.4 Specific Subpopulations

The issue of differences in bipolar compared to unipolar depression has also been examined in *adolescent* populations. Van Meter et al. [22] found that inpatients with bipolar disorder had more severe depression and more subthreshold manic

symptoms than those with unipolar depression. Silverman et al. [23] found that youth with BD had more severe depression and reported more irritability, anhedonia, negative self-image, hopelessness, hypersomnia, and suicidal ideation than MDD patients. Reporting on subjects with *postpartum* depression, Clark et al. [24] found that those with bipolar depression had more severe depression and were more likely to have comorbid anxiety than those with unipolar depression.

8.5.5 Are There Subtypes of Bipolar Depression?

In 2016, Mitchell's group [25] published the only report investigating subtypes of bipolar depression. Two hundred and forty-three BD subjects (170 with BP-I and 73 with BP-II) were recruited through a bipolar disorder (BD) clinic. A latent class analysis (LCA) was undertaken using symptoms reported on the structured clinical interview for DSM-IV (SCID-IV) for the most severe lifetime depressive episode, lifetime illness features such as age at first depressive and hypo/manic episodes, and family history of BD and unipolar depression. To explore the validity of any demonstrated "classes," clinical, demographic, and treatment correlates were investigated. For the combined sample, two robust LCA solutions were identified, with two and three classes, respectively. There were no consistent solutions when the BP-I and BP-II samples were considered separately. Subjects in one of the classes of the three-class solution (characterized by anxiety, insomnia, reduced appetite/weight loss, irritability, psychomotor retardation, suicidal ideation, guilt, worthlessness, and evening worsening) were significantly more likely to be in receipt of government financial support, suggesting a particularly malign pattern of symptoms.

8.6 Biomarkers

It has been proposed that biomarkers such as neuroimaging findings may help improve the differentiation between bipolar and unipolar depression. Here, we first discuss neuroimaging studies that have directly compared subjects with bipolar and unipolar depression, where the participants were aged at least 16 years, and then, second, we review other putative biomarkers.

8.6.1 Task-Based Functional MRI (fMRI) Studies

Neuroimaging studies suggest substantial overlap in the brain regions involved in unipolar and bipolar depression during the performance of a task. In a review of neuroimaging findings in unipolar and bipolar depression, the authors concluded

that both depressive types were associated with increased engagement of limbic regions and decreased activity in the prefrontal cortex compared to controls [26].

Despite the many parallels, differences also emerge although the directions of effects and regions reported have often been inconsistent. During emotional facial paradigm tasks, greater activation in the amygdala toward negative emotional stimuli and less activity toward positive stimuli were observed in unipolar depression compared to bipolar depression [27, 28]. Differential amygdala–prefrontal effective connectivity to happy faces also differentiated unipolar from bipolar depression [29]. Other studies suggested that differences in the activity of subregions of the anterior cingulate cortex (ACC) toward emotional stimuli might discriminate between unipolar and bipolar depression [30, 31].

Studies that employed cognitive tasks suggested that fronto-striatal hyperactivity or failure of deactivation of the default mode network may be present to a greater extent in bipolar relative to unipolar depression [32, 33]. During reward-related tasks, inconsistent findings have been reported regarding whether reward-processing circuits including the ventral striatum or ventrolateral prefrontal cortex show an increased brain signal in bipolar compared to unipolar depression during reward anticipation or outcomes [34–37].

In a seed-based functional connectivity study, the right posterior cingulate cortex differentiated unipolar from bipolar depression, but the connectivity of this region was associated with suicidal ideation and depression severity in unipolar but not bipolar depression [38]. More recently, using intrinsic connectivity distribution, right lateralized and interhemispheric dysconnectivity was observed in bipolar but not unipolar depression relative to controls [39].

8.6.2 Resting-State fMRI Studies

Single-site resting-state fMRI studies focused on differentiating BD from MDD depression have reported inconsistent findings. Among other findings, there are reports of reduced functional connectivity between the insular cortex and both central executive and default mode network regions in bipolar relative to unipolar depression [40, 41]. However, other studies have reported stronger or denser functional connectivity in networks in a number of regions, including the default mode network in bipolar relative to unipolar depression (e.g., [42–44]). In whole-brain resting-state studies, a recent meta-analysis reported higher resting-state activity in the left insula and the adjacent area covering the claustrum in unipolar relative to bipolar depression [45]. It is noteworthy that participants with bipolar depression in this meta-analysis had a lower severity of depression relative to those with unipolar depression.

8.6.3 *Gray Matter*

Although structural neuroimaging studies suggest a great deal of overlap in the brain regions involved in unipolar and bipolar depression, distinct differences between the two depressive types are evident. Depressed individuals with bipolar compared to unipolar disorder showed reduced middle frontal cortex thickness [46, 47] and reduced volumes in the dorsolateral prefrontal cortex [48], ACC [48–50], amygdala, hippocampus [51, 52], middle cingulate gyrus [53], superior frontal gyrus [54], fusiform, and insula [52]. In the aforementioned studies, Redlich et al. [51] also reported findings in the opposite direction for unipolar compared to bipolar depression that showed reduced volume in the left anterior cingulate gyrus, and Matsubara et al. [50] found evidence to suggest that insular volume reductions could be shared between the two depressive types. Another study showed structural deficits shared by the two depressive groups in addition to unipolar-depressed patients showing decreased gray matter volume in the left superior frontal gyrus and ACC compared with the bipolar-depressed patients [49]. In a sample of older depressed participants aged 54–80, most patients with a volume reduction in the ACC had unipolar depression, whereas those with volume reduction in the subcallosal area but not in the ACC were more likely to have bipolar depression [55]. Associations between disease severity and reduced gray matter structure have been reported in both depressive groups [56].

8.6.4 *White Matter*

Only a small number of studies have directly compared white matter in unipolar compared to bipolar depression, but overall, despite common disturbances, reports of differences between the depression types are more compelling in white matter relative to gray matter. Depressed participants with bipolar relative to unipolar depression showed reduced white matter tract integrity in the genu of the corpus callosum, posterior cingulum bundle [57], and superior longitudinal fasciculus tract [58]. A more recent study found no difference in fractional anisotropy but reported reduced axial diffusivity, believed to reflect axonal injury, in the posterior regions of the cingulum and superior longitudinal fasciculus in bipolar relative to unipolar depression [59]. Although the direction of group differences was inconsistent between studies, there was evidence of altered white matter integrity in the uncinate near the insular cortex between depressive groups [58, 60]. In a voxel-based morphometry study, white matter volume reductions within the cerebellum and hippocampus were found in individuals with bipolar relative to unipolar depression [51].

A recent study that controlled for medication load and the number of mood episodes found widespread reductions in white matter integrity in individuals with unipolar depression compared to participants with bipolar depression in an older cohort [52]. In addition to this study, other studies that reported an association

between disease severity and white matter suggest that these variables may be confounders for some of the differences observed between unipolar and bipolar depression [57, 59].

In convergence with the regions reported in resting-state functional connectivity findings [40, 41], researchers found reduced white matter integrity between prefrontal and insular cortices in bipolar relative to unipolar depression [60]. As in this unmedicated sample (unipolar depression mean age = 29 and bipolar depression mean age = 29), differences were not significantly associated with measures of disease severity, it is plausible to speculate that white matter integrity between the insular cortex and prefrontal cortex could differentiate unipolar from bipolar depression early in the course of the illness.

8.6.5 Machine Learning Neuroimaging Studies

Machine learning, also known as pattern recognition or classification, has been used to distinguish between bipolar and unipolar depression. Machine learning task-based fMRI studies that focused on the amygdala and frontal and cingulate cortices reported that although brain function in association with happy face conditions was a robust classifier (up to 90% accuracy) of unipolar and bipolar depression [28, 31, 61, 62], individuals with bipolar depression had a lower predictive probability for positive stimuli [31]. Machine learning using whole-brain resting-state functional connectivity of insular and amygdala seeds reported over 90% accuracy in differentiating unipolar from bipolar depression [63].

Studies reported a 63–79% accuracy with pattern classification of gray or/and white matter that included prefrontal and subcortical brain regions [48, 51, 52, 60, 64, 65]. One of these studies combined gray matter with functional connectivity [64], and two studies used both gray and white matter as predictors [51, 52]. Although replication is needed, these promising results suggest that multimodal neuroimaging could be used in machine learning-based pattern classification analyses to differentiate unipolar from bipolar depression.

8.6.6 Limitations of Neuroimaging Studies

As our focus has been on studies of participants in a depressed state, overall neuroimaging studies had relatively small samples. Additionally, many of the research studies did not control for confounders such as medication, illness severity, and psychiatric comorbidities.

Although our focus is on participants in a depressed state, two meta-analyses in adults are mentioned in this chapter as some findings converge with the aforementioned findings. In a meta-analysis where participants were in various mood states,

both patients with bipolar disorder (BD) and major depressive disorder (MDD) showed reduced white matter integrity in the genu of the corpus callosum, and BD compared to MDD patients showed reduced white matter integrity in the left posterior cingulum [66]. In another meta-analysis that also included participants in various mood states, individuals with MDD showed significantly reduced gray matter volume in a number of regions including the middle frontal gyrus and hippocampus compared to those with BD, and the two affective conditions demonstrated common neural correlates of smaller volume in regions including the insula [67]. In this latter meta-analysis, more patients were in a depressive state at the time of scanning in MDD studies, but the authors found no evidence for the effects of mood state in meta-regressions within disorders. Although the results of these meta-analyses are not directly comparable to studies where all participants are depressed at the time of scanning, they highlight the need to interpret state-related speculations with caution. In the absence of comparison during euthymia and mania, we cannot tell if differentiation is actually state-dependent or representative of biological vulnerability to a lifetime diagnosis of MDD or BD.

8.6.7 Blood Biomarkers

At a neurotransmitter level, bipolar and unipolar depressive episodes appear to be characterized by similar disturbed levels of dopamine [68, 69], norepinephrine [70, 71], and serotonin [72, 73] functioning. Sleep deprivation provides a challenge to the dopamine system. There is some evidence to suggest that the polarity of depression affects the response to sleep deprivation. In one study, over a seven-day period, repeated sleep deprivation resulted in a greater reduction in depressive symptoms among individuals with bipolar depression compared to those with unipolar depression [74]. In agreement with this finding, an exploratory analysis from a recent meta-analysis of sleep deprivation as a treatment for depression found a trend toward a significant improvement in symptoms in the bipolar ($p = 0.05$) but not in the unipolar depressive group [75]. It is noteworthy that when a study of late-life unipolar depression was excluded, effect sizes between unipolar and bipolar depression were numerically similar.

MicroRNAs (miRNAs) are a class of noncoding RNAs that play important roles in regulating gene expression and are considered to be one of the gene-environment interactional features of mood disorders. Notably, miRNAs are key players in different processes occurring in the regulation of basic neural processes, such as neurogenesis, neuroplasticity, and mood control [76, 77]. In the blood of 20 unipolar and 20 BD patients and 20 healthy controls who were in a depressed episode, five miRNAs (hsa-let-7a-5p, hsa-let-7d-5p, hsa-let7f-5p, hsa-miR-24-3p, and hsa-miR-425-3p) were specifically altered in unipolar and five (hsa-miR-140-3p, hsa-miR-30d-5p, hsa-miR-330-5p, hsa-miR-378a-5p, and hsa-miR-21-3p) in bipolar depression, whereas two miRNAs (hsa-miR-330-3p and hsa-miR-345-5p) were

dysregulated in both the diseases [78]. In a more recent study of 32 unipolar patients, 27 patients with BD, and 18 controls, plasma miR-19b3p was predicted to be involved in the pathway of inflammatory dysregulation associated with experiencing early childhood trauma and distinguished bipolar from unipolar disorder during a depressive episode [79]. Although sample sizes are small, evidence indicates that circulating blood miRNAs might represent potential biomarkers for distinguishing bipolar from unipolar depression.

In a review, brain-derived neurotrophic factor (BDNF) gene expression was one of the genetic biomarkers that was highlighted because of its capability to distinguish BD and MDD groups [80]. However, only one study was included where both BD and MDD participants were in a depressed state [81]. In this longitudinal study where BDNF was measured at baseline during a first depressive episode, the BD group presented the lowest BDNF gene expression levels than MDD and control groups, and MDD patients presented lower BDNF expression when compared to controls [81].

Two machine learning studies used peripheral biological markers to differentiate unipolar from bipolar depression. One study that used several peripheral biological markers found that the most relevant predictor variables to differentiate patients with bipolar depression from unipolar depression were interleukin-4, thiobarbituric acid reactive substances, and interleukin-10 (area under curve (AUC) was 0.69) [82]. In a more recent machine learning study that examined clinical and laboratory markers, self-reported symptoms primarily drove the predictions, although a number of peripheral blood markers also contributed significantly to the predictions. Notably, creatine kinase and glucose were the most important peripheral markers for separating BD from MDD, while they have no contribution to the differential diagnosis of unipolar and bipolar depression. For separating patients with unipolar and bipolar depression, in the optimum model, the test AUC was 0.77 [83].

8.6.8 Biomarkers: Overview

Despite strong parallels between bipolar and unipolar depression, structural and functional brain differences have been reported, although findings have been somewhat inconsistent. Functional MRI studies have reported distinct differences between unipolar and bipolar depression in brain regions involved in emotional processing and emotional control. The structural brain differences in white matter are more compelling relative to gray matter with suggestions of more white matter disturbances in bipolar depression than unipolar depression. Despite limitations, neuroimaging studies have identified potential regions of interest across modalities that could be targeted in the future to differentiate between the two depression types. Likely neuroimaging biomarkers across modalities include regions involved in emotion regulation with a particular focus on the insula. Peripheral blood markers may also complement clinical features and neuroimaging biomarkers for the

improvement of diagnostic accuracy. Although more research is needed in large samples, this chapter provides insights into potential clinical features and biomarkers that may be used to identify individuals with or at future risk of bipolar versus unipolar depression and targets for more personalized treatment.

8.7 Concluding Comments: Reflections on Research over the 16 Years Since the Publication of the Probabilistic Approach to the Diagnosis of Bipolar Depression and Recommendations for the Future Editions of DSM and ICD

In general, the recommendations proposed in the 2008 ISBD probabilistic approach to the diagnosis of bipolar depression have been largely supported by subsequent research studies. An increased likelihood of psychomotor retardation, psychosis, “atypical depressive” features such as hypersomnia and hyperphagia, and mixed features in bipolar depression has been strongly (though not universally) replicated. Such a “bipolar depressive signature”—distinct from pure syndromes of atypical or melancholic depression—has been largely accepted as given being the field, in contradistinction to this by dismissed by leading figures two decades ago.

Such findings have now been replicated in both European and Asian samples, suggesting that these are universally shared differences, and not culture- or ethnicity-specific. The findings suggest an underlying biology for bipolar depression distinct from that of unipolar depression, but frustratingly, many years of excellent biological research have yet to fully elucidate that.

Research since 2008 has also clarified differences between bipolar I and bipolar II depression, with psychomotor retardation and psychosis more localized to bipolar I depression and mixed features more common in bipolar II depression. Other features appear common to both BP-I and BP-II depression.

Has subsequent research suggested any necessary future modifications to the 2008 guidelines? First, one of the atypical features—leaden paralysis—has not been replicated, so that could be deleted. Second, antidepressant-induced hypo/manic symptoms have been repeatedly reported to be more prevalent in bipolar depression, so that should be incorporated in the future. Third, the cognitive component of psychomotor retardation should be more strongly emphasized in the future, as the 2008 proposals probably underemphasized the cognitive slowing that accompanies motor retardation.

What has been the impact of the recommendations of the 2008 probabilistic approach? This cannot be answered empirically, but some anecdotal evidence is, nonetheless, of pertinence. Clinicians have widely reported the clinical usefulness of this approach in assisting in ambiguous diagnostic presentations and strongly affirm that the proposals resonate with their own observations of the symptoms of bipolar depression. Further, leading experts, by lived experience, have strongly

commended that the proposals gel with their own symptomatic experience and validate symptoms, of which their own clinicians are frequently unaware.

Finally, the accumulation of empirical evidence necessitates those responsible for the future editions of DSM and ICD to incorporate these findings into future revisions of the relevant sections on bipolar depression. The status quo in the current DSM and ICD do not distinguish between the major depressive episodes of bipolar disorder and major depressive disorder, or even allude to the evidence suggesting such differences. While the research presented in this chapter does not claim to support pathognomonic or categorical differences between unipolar and bipolar depression, the evidence for dimensional differences is strong. The failure of the current classificatory systems to acknowledge those dimensional differences is, in the words of Chakrabarti [2] detailed earlier in this chapter, “*one of the reasons that the diagnosis of BD is often missed.*”

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Chapter 9

Longitudinal Course and Clinical Progression of Bipolar Disorder: An Updated Systematic Review



Lars Vedel Kessing

9.1 Clinical Considerations

- The course of illness is heterogeneous in bipolar disorder, but on average, the risk of recurrence increases with the number of prior affective episodes.
- The increasing number of affective episodes is associated with (1) an increasing risk of recurrence of episodes, (2) an increasing duration of episodes, (3) an increasing symptomatic severity of episodes, (4) a decreasing threshold for developing episodes, and (5) an increasing risk of developing dementia.
- There is evidence for the clinical progression of bipolar disorder, emphasizing the need for early intervention.

9.2 Future Perspectives

- Most of the five areas investigated in the present review are superficially investigated and hampered by methodological challenges.
- Few studies take into account the individual heterogeneity of recurrence.
- The effects of early intervention on the long-term course of illness are not clear.
- Larger, well-designed, long-term, longitudinal studies of newly diagnosed patients with bipolar disorder are needed, elucidating these areas.

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9.3 Introduction

It is a widely held belief that bipolar disorder is progressive of nature [1–4]. However, some prior reviews question this belief. Martino et al. conclude that “it is possible that cycle acceleration occurs in a subset of 25–40% of patients with bipolar disorder” only [5], and a meta-analysis on neuropsychological dysfunctions concludes that data “is not in accordance with the hypothesis of a progressive nature of cognitive deficits in bipolar disorder” [6]. Similarly, Passos et al. conclude that “illness progression is not a general rule in bipolar disorder” [7]. However, one of the reviews focused entirely on neuropsychological deficits in bipolar disorder [6], one did not systematically review the evidence for clinical progression but rather biological correlates to illness progression [7], and one was a qualitative review (or overview) [5]. In a systematic review from 2017, we concluded that although the course of illness is heterogeneous, there is evidence for the clinical progression of both unipolar disorder and bipolar disorder [8]. Since then, several studies illuminating the area have been published.

The aim of the present systematic review was to give an overall broad, updated presentation of the clinical evidence for the observation of a clinical progression of bipolar disorder and discuss the findings in relation to the conclusions in the mentioned recent reviews [5–7]. Neuroprediction may clinically be reflected by an increasing risk of experiencing new affective episodes, decreasing chances of recovery from these episodes for the individual, and increasing cognitive dysfunction during the course of illness as an expression of brain function being affected during long-term illness [9]. The author has previously, as part of a medical doctoral dissertation, defined clinical progression according to four parameters that may increase with the number of affective episodes: (1) the risk of recurrence of episodes, (2) the length of episodes, (3) the severity of episodes, (4) long-term cognitive deficits, and one parameter that may decrease: (5) the threshold for developing episodes [9]. Consequently, the aims of the present article are to review the associations between the number of affective episodes and (1) the risk of recurrence of episodes; (2) the probability of recovery from episodes; (3) the severity of episodes; (4) the prevalence of stressful life events, i.e., the threshold for developing episodes during the course of illness; and (5) long-term progression of cognitive deficits in unipolar and bipolar disorders. The article is an updated review focusing on bipolar disorder only, on these five parameters previously presented and discussed in the medical doctoral dissertation from 2001 (“Course and cognitive outcome in major affective disorder”), available electronically from 2015 [9], and the systematic review from 2017 on the evidence for clinical progression of both unipolar and bipolar disorders [8].

9.4 Methods

The systematic review is reported according to PRISMA guidelines and includes a systematic database search, conducted in cooperation with a librarian and information specialist, as well as a PRISMA flow diagram of the search procedures [10]. An extensive literature search was conducted in Medline (January 1950–September 19, 2023), Embase (1974–September 19, 2023), and PsychInfo (1906–September 19, 2023) using the following keywords:

((((((((((((((((((("Bipolar Disorder"[Mesh]) OR (bipolar disorder)) OR (bipolar disorders)) OR (bipolar affective psychosis)) OR (bipolar affective psychoses)) OR (bipolar affective disorder)) OR (bipolar illness)) OR (bipolar psychosis)) OR (bipolar depression)) OR (bipolar psychoses)) OR (mania)) OR (manic depression)) OR (manic disorder)) OR (manic disorders)) OR (manic depressive disease)) OR (manic depressive disorder)) OR (manic depressive illness)) OR (manic depressive psychosis)) OR (manic depressive psychoses)) OR (manic depressive psychosis)) AND (((((((((((((((((((("Recurrence"[Mesh]) OR ("Cognitive Disorders"[Mesh:NoExp]) OR ("Cognitive Dysfunction"[Mesh]) OR ("Social Cognition"[Mesh]) OR ("Dementia"[Mesh]) OR (recrudescence)) OR (recrudescences)) OR (recurrences)) OR (recurrence)) OR (relapse)) OR (relapses)) OR (cognitive disorder)) OR (cognitive disorders)) OR (periodic disease)) OR (disease exacerbation)) OR (disease aggravation)) OR (cognitive defect)) OR (cognitive defects)) OR (cognitive impairment)) OR (cognitive dysfunction)) OR (overinclusion)) OR (mental deterioration)) OR (social cognition)) OR (dementia)) OR (dementias)) OR (amentia)) OR (amentias)) OR (senile)) OR (senility)) OR (demention))) AND (((((((((((((((((((("Cohort Studies"[Mesh]) OR (concurrent study)) OR (concurrent studies)) OR (incidence study)) OR (incidence studies)) OR (cohort study)) OR (cohort studies)) OR (follow-up study)) OR (follow-up studies)) OR (longitudinal study)) OR (longitudinal studies)) OR (longitudinal evaluation)) OR (prospective study)) OR (prospective studies)) OR (retrospective study)) OR (retrospective studies))

Articles met the inclusion criteria if they assessed patients with bipolar disorder and investigated the association between the number of affective episodes or duration of illness and one of the following outcomes of interest: recurrence, relapse, recovery, duration of episodes, severity of episodes, life events, or cognition. Preclinical studies, studies with less than 100 included patients, studies with a follow-up period of less than 1 year, and those including only children and adolescents or only women during pregnancy were excluded. Further, cross-references were searched from identified papers and recent reviews [5–7, 11]. In this way, the present systematic review comprises an updated and shortened presentation of a comprehensive and critical review of a doctoral dissertation from 2001 ("Course and cognitive outcome in major affective disorder," available electronically from 2015 [9]) and the subsequent updated systematic journal review from 2017 [8].

Papers were excluded based on the initial screening of titles and abstracts and subsequently based on full texts due to duplicates (see Fig. 9.1: PRISMA flow diagram).

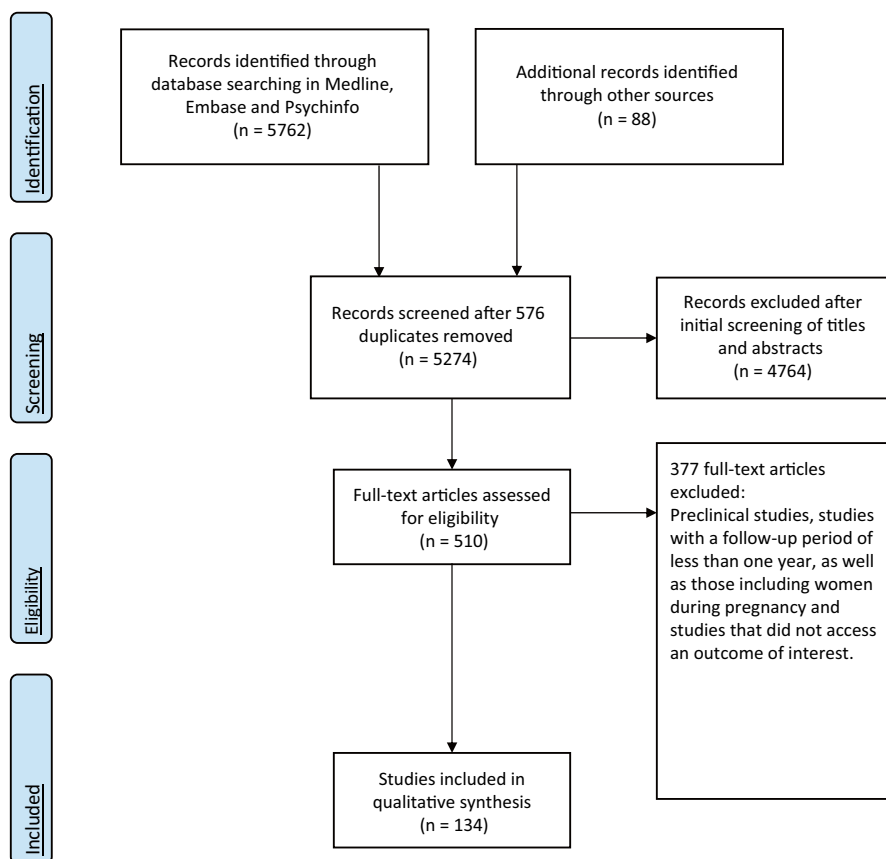


Fig. 9.1 PRISMA flow diagram

9.5 Results and Discussion

9.5.1 Literature Search

A literature search resulted in 5762 identified studies covering the five areas included in the review (see Fig. 9.1: PRISMA flow diagram). A total of 88 of the included studies were identified through other sources than the database search, and a large number of full-text articles had to be assessed ($n = 510$). The reasons for these results were that (1) there are no indexed keywords that exactly describe the five areas, resulting in a decreased hit rate of the search, (2) a substantial proportion of studies were published during the first part of the twentieth century and not included in search databases, and on the other hand (3) the author has insight into the five areas including older literature and cross-references and reviews of the areas (as illustrated by continuous publications within the areas since 1998).

9.5.2 Associations Between the Number of Affective Episodes and the Risk of Recurrence of Episodes

Regarding the recurrence of episodes, the literature search included, in addition to the database search, cross-references from the identified papers and recent reviews [5–7, 11, 12]. In addition, data on the literature published during the past century and up to the year 2017 specifically on the progression of recurrence has been comprehensively and critically reviewed in the doctoral dissertation from 2001 ([9], pp. 2–18, Tables 1–4, Figs. 1–6) and in the two subsequent updated systematic journal reviews from 2005 [13] and 2017 [8], respectively. Table 9.1 presents an updated list of studies with analyses of the relation between time to recurrence and the number of affective episodes based on the systematic literature search and prior reviews. The search resulted in 38 studies of patients with bipolar disorder and 8 studies with mixed samples of patients with unipolar and bipolar disorder, and among these studies, 25 and 4 studies, respectively, found a deteriorating course of illness, i.e., a decreasing time to recurrence with the number of episodes.

As previously reviewed and discussed in detail [9], studies on the long-term course of illness are affected by numerous challenges including biases such as selection, recall, and information biases, as well as low statistical power due to small samples and, often, short follow-ups. Furthermore, few studies consider diagnostic changes over time in the analyses or take possible confounders such as gender, age, marital status, comorbidity, etc. into account. In addition, a major challenge that affects the results of the studies is the statistical handling of data. The major proportion of the studies does not pay attention to the number of episodes in the analyses (the so-called Slater's fallacy [52]). Not paying attention to the number of episodes may result in false conclusions due to two factors [33]: (1) within a given observation period, the time under risk for experiencing new episodes will be reduced for every new episode and (2) patients with many episodes will dominate the analyses. In the analyses of time to recurrence, each factor will have the implication that the average time between episodes will decrease with each new episode, and thus, the analyses will result in artificial findings of a progressive course with decreasing intervals between affective episodes. The first factor may be compensated for by using survival analyses, as time under risk hereby is considered, and information from incomplete ("censored") intervals is utilized. The use of survival analysis in the studies in relation to study findings are indicated in Table 9.1: five out of seven bipolar studies and one out of one mixed sample study, using survival analyses, found a decreasing time to recurrence with the number of episodes. The second factor may be accounted for by using analyses that take the individual heterogeneity and the thereby induced correlation between successive episodes in the same patient into account. A few older studies have attempted to take into account the second factor by using multiple regression models correcting for the number of episodes [59] or more explicitly by breaking down the analyses according to the number of episodes [52, 60]. With the introduction of survival analyses, it became possible to take both factors involved in "Slater's fallacy" into account. One might

Table 9.1 Studies with analyses of the relation between time to recurrence and the number of episodes in bipolar disorder

Reference	Year	N	Observation period (years)	Survival analysis	Deteriorating course
<i>Bipolar</i>					
[14]	1907	25	Up to 28	—	+
[15]	1918	1995	Not recorded	—	+
^a [16]	1921	238	Up to 44	—	+
[17]	1936	34	Not recorded	—	—
[18]	1966	97	2	—	—
[19]	1969	51	4	—	—
[20]	1973	393	Up to 50	—	+
[21]	1973	160	Not recorded	—	+
^a [22]	1975	30	2–20	—	—
[23]	1980	105	Not recorded	—	+
^a [24]	1981	95	16	—	+
[25]	1983	100	12	—	—
[26]	1985	46	Not recorded	—	+
^a [27]	1990	75	4	+	—
^a [28]	1993	148	5	—	—
^a [29]	1994	131	10	—	—
^a [30]	1995	42	4.5	—	+
^a [31]	1995	51	4.5	—	—
^a [32]	1995	82	4.3	+	+
[33]	1998	2903	0–23	+	+
[34]	1999	112	10	—	—
[35]	2004	1106	0–6	+	+
[36]	2004	220	Up to 40	+	+
^a [37]	2006	858	Up to 2	+	+
^a [38]	2008	223	Up to 20	+	+
^a [11]	2012	128	5.7	—	—
^a [39]	2012	225	Up to 5	+	–/+
^a [40]	2014	300	Up to 4	+	—
^a [41]	2014	102	1	—	+
[42]	2014	255	5	+	+
[43]	2015	101	Up to 4	+	+
[44]	2016	2443	1	—	+
[45]	2016	909	5	—	+
[46]	2018	92	2	+	+
[47]	2018	256	4	—	+
[48]	2021	505	Up to 3	+	+
[49]	2023	100	10	—	+
[50]	2023	1261	1	—	+

(continued)

Table 9.1 (continued)

Reference	Year	N	Observation period (years)	Survival analysis	Deteriorating course
<i>Mixed sample of bipolar disorder or unipolar disorder</i>					
[51]	1930	633	Up to 40	–	+
[52]	1938	105	Not recorded	–	–
[53]	1945	319	Up to 30	–	+
^a [54]	1968	207	6 on average	–	–
[55]	1988	110	11	–	–
[56]	1996	30	8.2 on average	–	–
^a [57]	1998	56	3–5	+	+
[58]	2000	426	14 years on average	–	+

Deteriorating course: Decreasing time to recurrence with the number of episodes

^a Recurrence assessed prospectively following the patient’s entry into the study

expect that the actual risk of recurrence for an individual is related to the risk of recurrence at former episodes. Frailty models represent one way to handle this problem in the analyses of recurrent events in censored data [61, 62]. In these models, frailty is a random effect reflecting the individual degree of illness and thus contributes to the heterogeneity of the course of affective disorder. An alternative to frailty models would be to use nonparametric methods that are able to deal with the intra-individual correlation between successive episodes [63, 64] or dynamic survival regression models [63]. Random coefficient regression models [65] may also be used to take into account the interindividual variability in the course of illness; however, neither such analyses nor standard linear regression [11] take into account censored data and are therefore less suited in longitudinal studies.

The updated literature search identified only three studies that have presented analyses of the effect of episodes including censored observations and taking account of the individual heterogeneity: two nationwide register studies from Denmark, the first including 2903 patients with mania/bipolar disorder (in addition to 17,447 patients with a diagnosis of unipolar depressive disorder) with an up to 23 years follow-up period [33] and the second including 1106 patients with a diagnosis of mania/bipolar disorder (in addition to 9417 patients with unipolar depressive disorder) with an up to 6 years follow-up period [35], and the third, a reanalysis of data from the prospective lifelong study from Zurich by Jules Angst comprising 220 patients with bipolar disorder (in addition to 186 patients with unipolar disorder) [36].

The studies had very different designs. The Zurich study provides some major advantages with the inclusion of large populations of patients followed prospectively with rigorous definitions and assessment of episodes and recurrence during huge time periods [36]. The Zurich study included patients who were selected within specialized university centers, representing patients with the most severe disorders [36], whereas the Danish study included all first-admission patients who

were discharged from all psychiatric departments in Denmark with a diagnosis of bipolar disorder over 23 years [33] and 6 years [35], respectively. Nevertheless, because of the study design, only episodes that led to hospitalization were included in these studies. The Danish register studies were representative of patients hospitalized for affective disorders; the studies were not influenced by recall bias, and diagnostic instability was taken into account in the analyses. The effect of episodes was investigated in various age and gender groups [35, 66].

All three studies including patients with bipolar disorder found that, on average, the risk of recurrence increased with the number of episodes [33, 35, 36]. The Zurich study [36] showed that the increased risk of recurrence persisted lifelong, in accordance with results from the Danish studies [33, 35]. It has been suggested that the illness process might die out or “burn” out following a number of episodes and that the tendency toward recurrence might decrease following years of illness [22]. These theories are not supported by the three studies [33, 35, 36].

Notably, the three studies all included populations of patients from hospital settings [33, 35, 36]. It is less known whether the findings from the studies can be generalized to other populations, although an effect of depressive episodes also has been found in studies of nonclinical populations of depressed subjects [67, 68], which, however, have not taken account of the individual liability toward recurrence.

All three studies [33, 35, 36] had a “naturalistic” approach, i.e., patients may have received treatment, and the treatment was at the discretion of the responsible clinician and not directed by the researchers. Thus, treatment availability in clinical practice does not hinder the progressive course of illness that was found in each of the studies. Notably, as can be seen from Table 9.1, three out of four studies on bipolar disorder (until [18] inclusive [17]) before the introduction of ECT in the 1940s and antidepressants, lithium, and neuroleptics during the 1950s have found a shortening of intervals between episodes during the course of illness. These studies were, in general, rather lengthy and included Kraepelin’s original study with up to 44 years of follow-up [16].

9.5.3 Conclusion

It is concluded that, on average, the risk of recurrence increases with the number of episodes in depressive and bipolar disorder and that current standard treatment regimens do not stop this progression [35]. Nevertheless, the course of illness in bipolar disorders is heterogeneous, and the effect of previous episodes and their interrelation with other risk factors on the risk of relapse and recurrence warrants further research.

This conclusion is somewhat in contrast to the conclusions of the two reviews from 2016, concluding that illness progression is not a general rule in bipolar disorder [5, 7], although Passos et al. cautiously concluded that “Some hypotheses related to the neuroprogression model, such as episodes acceleration, progressive cortical

changes as a function of manic episodes, and the impact of early trauma on the course of BD, were reported in both cross-sectional and longitudinal studies” [7].

The challenge is to statistically analyze and describe the heterogeneous course of illness in affective disorders. We find it most correct to say that the “average” patient with unipolar disorder or bipolar disorder experiences a progressive course of episodes. This also means that not all patients experience such progression. The suggestion made by Martino et al. [5] that cycle acceleration may occur in 25–40% of patients with bipolar disorder is based on two studies by Kessing et al. [69] and Baldessarini et al. [11], respectively, and may be misleading. The study by Kessing et al. was an initial explorative study aiming to investigate different measures of the initial course of admission episodes and their capacity to predict further recurrence [69]; the Baldessarini et al. study included a selected population of patients ($N = 128$) with at least three recurrences [11], and none of these two studies took account of the individual heterogeneity [11, 69]. Further, by focusing only on findings that formally reach statistical significance, prior reviews [5, 7] do not give an unbiased interpretation of findings from studies. Thus, in all three studies taking account of the individual heterogeneity and quoted by the reviews, we found steadily increasing hazard ratios for new affective episodes with every prior episode [33, 35, 70]. This trend effect across episodes was less pronounced, however, still prevalent, in subgroups according to age and gender [35, 36]. In additional reanalyses of Jules Angst’s Zurich data [71], the finding of a statistically significant effect of episodes was sustained, however, at a smaller magnitude. In *sub*-analyses of the Zurich data including only patients with prospective assessments from their first affective episode, we did not find a consistent pattern, which may have been due to a small number of patients included in this tertiary analysis ($n = 119$ out of a total of 406 patients) [36, 71]. Finally, both reviews [5, 7] refer to the work by Baldessarini et al., finding a largely random course of bipolar illness [11], but this study did not take into account censored data or the individual heterogeneity of recurrence, as previously mentioned.

9.5.4 Associations Between the Number of Affective Episodes and the Probability of Recovery from Episodes

Studies of the duration of successive episodes in affective disorder during a century from Swift’s study in 1907 [14] onward have been extensively reviewed by Kessing ([9], pp. 18–23, Tables 5 and 6, Figs. 7–12), in which the individual studies are throughoutly presented. Further, based on the conducted literature search including cross-references from identified papers and recent reviews [5–7, 11, 12], an updated list of studies is presented in Table 9.2.

As extensively discussed by Kessing [9], several methodological problems involved in longitudinal studies may affect results including various degrees of selection bias, small sample sizes, lengths of follow-up, confounders such as age

Table 9.2 Studies with analyses of the duration of successive episodes in bipolar disorder

Reference	Year	N	Observation period (years)	Survival analysis	Duration of episodes
<i>Bipolar</i>					
[14]	1907	25	Up to 28	–	+
[15]	1918	195	Not indicated	–	+
[72]	1942	66	>24	–	+
[21]	1973	160	Up to death	–	+
[20]	1979	393	Up to 50	–	0
^a [24]	1981	159	16	–	–
[26]	1985	46	Not indicated	–	0
[73]	1999	2903	Up to 23	+	0
^a [74]	2013	219	Up to 25	+	0
[75]	2016	150	Not indicated	–	–
[46]	2018	193	2	+	+
<i>Mixed sample of bipolar disorder or unipolar disorder</i>					
^a [16]	1921	899	Up to 44	–	+
[51]	1930	633	Up to 40	–	–
[76]	1931	3247	Up to 11	–	0
[77]	1945	141	10–15	–	–
[53]	1945	319	Up to 30	–	–
[54]	1968	207	6 on average	–	+
[55]	1988	110	11	–	0
[56]	1996	30	>10	–	–

Duration of episodes: +: Increasing time to recovery with the number of episodes; -: Decreasing time to recovery with the number of episodes; 0: Unchanged time to recovery with the number of episodes

^a Episodes estimated prospectively following the patient's entry into the study

(and perhaps gender), and statistical approaches. Short lengths of follow-up may have increased the proportion of short episodes among patients included in the studies, while longer episodes may not have been included, and in particular, the observation period must be of sufficient length to encompass several episodes [9]. As with analyses of recurrence (see prior section), analyses without survival statistics may result in a finding of a constant or a decreasing duration of episodes during the course of illness as a consequence of Slater's fallacy [9].

Despite these methodological caveats, a strikingly clear pattern emerges from Table 9.2: the majority of studies conducted before the introduction of ECT in the 1940s and antidepressants, lithium, and neuroleptics during the 1950s have found that the duration of episodes in affective disorder increased during the illness. In contrast, such a deteriorating course was not found in studies conducted during the treatment era (in the studies by Bratfos [54] and Tashev [21], most patients had their initial episodes in the pretreatment era). It is well-known that treatment reduces the length of mood episodes and that episodes lasted longer before the introduction of effective treatment than after. It is not known, however, how treatment affects the duration of successive episodes. For ethical reasons, it is not possible to conduct a

controlled study of effective treatment versus placebo. Only two studies have systematically investigated this matter, however, within unipolar disorder. In open-trial studies, the same treatment, tricyclic antidepressants and interpersonal psychotherapy, was given across depressive episodes, and it was found that the time to remission for the subsequent episode was reduced compared with the index episode [78, 79]. Some evidence for the effect of treatment is further provided from naturalistic studies of patients in lithium treatment in which a shortening of episodes has been found over a 10-year treatment period [56].

An alternative explanation could be that the course of affective disorder has ameliorated during this century. However, no data or study supports this explanation, so it is most likely that the difference in the course of episodes before and after 1945 is due to the effect of treatment.

9.5.5 Conclusion

Although impossible to investigate in a valid way, it seems reasonable to conclude that, for untreated bipolar disorder, the duration of episodes increases as the illness progresses and that treatment can stop the deteriorating course [9].

9.5.6 Associations Between the Number of Affective Episodes and the Severity of Episodes

Several studies have found that the risk of subsequent relapse or recurrence is greater for patients with symptomatically severe episodes (e.g., [67, 80]). However, only five studies identified in the literature search have investigated the severity of successive episodes during the course of the illness, and these are mostly within unipolar disorder. Two naturalistic studies revealed that the severity of symptoms seemed to increase with the increasing number of episodes in unipolar disorder [81, 82]. This finding is partly contradicted by a study in which a highly selected subsample of mixed unipolar and bipolar patients, who adhered to lithium treatment for more than 10 years, showed decreased severity of manic episodes during follow-up, whereas no longitudinal change was found in the severity of depressive episodes [56]. Finally, only one study has systematically tested whether the severity of depressive episodes increases during the course of illness in unipolar disorder [83]. The study was a longitudinal investigation of a Danish nationwide sample of all patients (in- or outpatients, $N = 19,392$) treated for depressive disorder at first contact in psychiatric hospital settings. Data were collected as part of the daily routine and independent of research activities. The prevalence of severe depressive episodes increased substantially with the number of hospital contacts regardless of gender, age at first contact, and period of first contact.

9.5.7 Conclusion

The issue has been only superficially investigated and especially has not been systematically investigated in the era before active treatment. However, it appears from naturalistic studies mainly within unipolar disorder that the symptomatic severity of affective episodes may increase with every new episode. It is likely, although not certain, that the severity of episodes also increases progressively in untreated patients.

9.5.8 Association Between the Prevalence of Stressful Life Events and the Number of Affective Episodes

Studies of life events are complicated by a number of methodological problems of defining and measuring life events and the design of the studies [9, 84]. Nevertheless, two reviews identified in the literature search conclude that these studies demonstrate that more psychosocial stressors are involved in the first episode than in the subsequent episodes of major affective disorder ([85, 86] pp. 135–138), in accordance with findings from more recent studies [87–89] suggesting a lowered threshold for developing episodes later during the course of illness, although this relation has not been found in all studies of bipolar disorder as reviewed elsewhere [9]. Further, a history of child or adolescent physical or sexual abuse has been associated with the development of mood disorders [90–92] and faster cycling frequencies [93].

In retrospective studies of precipitating events, patients are more likely to search for stressors prior to the onset of the illness, whereas once the illness is accepted, less attention is paid to stressors, i.e., such studies are prone to recall bias ([94], p. 143; [95]). Studies with a prospective rigorous assessment of stressors are few and include a short follow-up period (up to 3 years [9]). However, two studies, one within unipolar disorder and one within bipolar disorder, identified in the literature search encompass appropriate long follow-up time to compare the presence of prospectively assessed life events before early episodes and before later episodes [96]. The first study by Kendler et al. [96] included 2395 female twins who were followed for 9 years and interviewed four times and included 1380 onsets of major depression. The associations between life events 1 year prior to the depressive episode and the depressive episode were analyzed for successive depressive episodes. In addition to the large sample size and prospective long-term follow-up, the study had two other major advantages: analyses were corrected for genetic risk (twin status), and data were analyzed using survival methods, taking the individual risk of recurrence into account. The study showed that the association between life events and depression decreased successively for the first six to eight depressive episodes, and subsequently, the association remained constantly low [96]. As emphasized by Goodwin and Jamison [85], due to the twin design, the authors were able to suggest that the relationships between life events and major depressive episodes were causal and not

simply correlational. The second study investigated the impact of life events and psychological variables on the onset and course of psychopathology in the bipolar offspring [97]. In this study, the bipolar offspring were followed for 12 years, from early adolescence ($n = 140$) to adulthood ($n = 108$). The effect of life events on the risk of developing a mood episode was especially pronounced in the early stage of mood disorders. After the first episode, the number of previous episodes became an important predictor for new episodes, with a shift in the effect of life events between the first and subsequent episodes. Thus, the pattern of precipitation of episodes during the course of illness most likely also pertains to bipolar disorder, as also pointed out by Goodwin and Jamison [85].

Long-term prospective studies may be difficult to perform in a valid way since they may be hampered by selective dropout as patients with an increased prevalence of life events seem to have an increased tendency to drop out of the study [98, 99]. Thus, it is possible that stress precipitates recurrence and increases dropout from the study. If the latter association is prominent, then the former would not be detectable ([98], p. 67). In this regard, case register data offer some remarkable advantages. Recall bias is completely avoided since data are “hard facts” collected routinely and independently of researchers. Specifically, selective dropout is for practical reasons not relevant in Danish register studies as the Danish Psychiatric Central Register covers all inpatient facilities in Denmark. Also, there is no reason to believe that patients with increased prevalence of life events who have once been psychiatrically hospitalized are less likely to be readmitted.

Psychosocial stress is not measured in register studies; instead, marital status is routinely recorded, and changes herein can be used as expressions of major life events and stress. Studies by Kessing [100] and Kessing et al. [101] showed that initially in the course of bipolar disorder (and unipolar disorder), marital status and also the type of disorder (bipolar/unipolar) and socio-demographic variables such as sex and, partly, age predicted recurrence, whereas these variables had no effect later in the course of the illnesses. Patients who had never been married had a greater risk of recurrence after the first and the second episode but not after subsequent episodes, and divorced/separated patients had a greater risk of recurrence after the first episode but not after subsequent episodes. It should be mentioned that further analyses, taking the individual liability to recurrence into account, confirmed that the effect of never engaging in marriage, the type of disorder, and age at first admission decreased during the course of illness but revealed no differences in the effect of gender and in the effect of a recent divorce between early and later episodes [102].

9.5.9 Conclusion

Studies of life events are hampered by serious methodological problems [84], and the impact of psychosocial stressors on the risk of recurrence during the course of illness has not been thoroughly investigated. A majority of studies, including studies with improved designs and statistical methods and case register studies, suggest that

early episodes are more often associated with prior life stressors than later episodes, suggesting that the threshold for developing affective episodes decreases with the number of episodes.

9.5.10 Long-Term Progression of Cognitive Deficits in Bipolar Disorder

In relation to cross-sectional studies of bipolar disorder, two recent reviews, identified in the literature search, reached contrasting conclusions in relation to the progression of cognitive dysfunction. Strejilevich et al. concluded that “evidence from cross-sectional studies did not show more severe cognitive deficits in patients with longer illness duration” [6], while Cardoso et al. concluded that “there is evidence that cognitive function in bipolar disorder is negatively associated with features of illness progression such as number of mood episodes, illness duration, and hospitalizations” [103]. Further, in a cross-sectional study investigating cognition in relation to clinical staging in bipolar disorder, patients in the late stages III and IV performed poorly in neuropsychological tests when compared with healthy controls, especially in executive function (Stroop interference), verbal learning and memory, and working memory and attention [104]. Nevertheless, a recent meta-analysis on the longitudinal course of cognitive deficits in bipolar disorder (as indicated by neuropsychological tests) found no significant differences in long-term (mean follow-up period: 8.9 years) cognitive outcomes in ten studies including 540 patients with bipolar disorder and 644 healthy individuals [105]. As acknowledged by the authors, long-term pharmacological maintenance therapy including lithium may have a protective effect on the risk of cognitive deterioration [105]. This finding is confirmed in a subsequent 6-year longitudinal study of 72 patients with bipolar disorder and 59 healthy control individuals finding no change in cognitive functioning between baseline and follow-up [106], similar to findings in a large prospective study of 266 newly diagnosed patients with bipolar disorder, 105 of their unaffected first-degree relatives, and 190 healthy controls, assessed at baseline and 16-months follow-up, in which we found no evidence of trajectory differences between patients, unaffected relatives, and controls in neurocognition and emotional cognition [107]. Patients with bipolar disorder showed stable impairments in global neurocognitive functioning over time, as well as within the domains of “working memory and executive function” and “attention and psychomotor speed,” compared to healthy control individuals [107]. Notably, early intervention as provided for newly diagnosed patients with bipolar disorder in the Copenhagen Clinic for Affective Disorders may have prevented progression in this study. Another systematic review concluded that a subset of patients with bipolar disorder presents a progressive course characterized by episode acceleration, treatment refractoriness, and functional/neurocognitive impairment [108]. This finding corroborates with recent findings from the ENIGMA Bipolar Disorder Working Group Multicenter

Neuroimaging Study of 1232 individuals showing that more (hypo)manic episodes were associated with faster cortical thinning, primarily in the prefrontal cortex [109], and with a new systematic review of longitudinal imaging studies in adolescent and adult bipolar disorder showing that the occurrence of mood episodes is associated with decreases in gray matter volumes and cortical thickness in various brain regions, including prefrontal and temporal brain regions [110].

Strikingly, no review on neuroprogression [5–7, 103, 108, 111] has included studies on the risk of developing dementia in bipolar disorder although dementia is the end stage of progression of cognitive disturbances. Nevertheless, as concluded in systematic reviews and meta-analyses from 2013 [112] and subsequently in 2020 [113], bipolar disorder increases the risk of dementia (odds ratio (OR): 2.96 [95% CI: 2.09–4.18], $P < 0.001$), even more than schizophrenia and major depressive disorder [114].

Only one study has investigated the relation between affective episodes and the risk of developing dementia, finding that the risk of developing dementia increases with the number of episodes in patients with bipolar disorder (and depressive disorder) [115]. Thus, it is possible that a major reason that *neuropsychological* functioning has not been found to decrease in longitudinal studies of bipolar disorder is the short follow-up time in these studies (mean follow-up period of 4.62 years [111]). Supporting this point of view, the longest study with a mean follow-up of 8.9 years that was included in the meta-analysis by Samame et al. [111] found a worsening of executive function over time that was positively associated with the duration of illness [116]. Finally, studies suggest that long-term treatment with lithium may decrease the risk of developing dementia [113, 117–120], further supporting a link between bipolar disorder and dementia.

9.5.11 Conclusion

Although short-term longitudinal studies have not found decreasing *neuropsychological* functioning, a single longer-term study did, in accordance with long-term studies of unipolar and bipolar disorders showing an increased risk of developing a clinical diagnosis of dementia, eventually.

9.5.12 Clinical Progression, Cognition, Brain Function, and Treatment

The associations between clinical progression, cognition, brain function, and treatment were not systematically reviewed. Nevertheless, a cross-sectional comparison of patients at different illness stages revealed more pronounced cognitive deficits during late compared with early stages in line with the staging hypothesis of bipolar

disorder [104]. Further, a number of cross-sectional studies in bipolar disorder have found associations between the number of episodes and increased ventricle volumes [121] and reduced volume of the left hippocampus [122, 123] and corpus callosum [124]. A longitudinal 6-year follow-up study of patients with bipolar disorder found that decreased volumes in dorsolateral prefrontal and inferior frontal cortex correlated with the number of previous manic episodes [125] in accordance with recent reviews of longitudinal studies, concluding that manic episodes seem to be related to accelerated cortical volume and thickness decreases, with the most consistent findings occurring in prefrontal brain areas, stressing the importance of preventing manic episodes [110, 126]. Following the same line of evidence, a longer duration of lithium treatment has been found to be related to higher white matter integrity [127], and early initiation of lithium treatment may decrease the trajectory of cognition in young people with bipolar disorder [128].

9.6 Overall Summary

Most of the five areas investigated in the present review are superficially investigated and hampered by methodological challenges. Nevertheless, studies with the longest follow-up periods, taking account of the individual heterogeneity and the thereby induced correlation between successive episodes in the same patient, all support a clinical progressive course of illness in unipolar and bipolar disorders. Overall, there is some evidence for the clinical progression of bipolar disorders in all five areas. Thus, increasing the number of affective episodes seems to be associated with (1) an increasing risk of recurrence of episodes, (2) an increasing duration of episodes, (3) an increasing symptomatic severity of episodes, (4) a decreasing threshold for developing episodes, and (5) an increasing risk of developing dementia. It is important to acknowledge that this conclusion reflects the average findings, also when taking the individual patient heterogeneity of the illness courses into account, as done with frailty models [33, 35, 36]. This conclusion is not in contrast to the conclusion in the overview by Martino et al. that “it is possible that cycle acceleration occurs in a subset of 25–40% of patients with bipolar disorder” only [5]. Similarly, it may not be in contrast to the conclusion by Passos et al. that “illness progression is not a general rule in bipolar disorder” [7], understood as *all* patients, although clinical progression occurs for the average patient as confirmed in this updated systematic review.

Early intervention may improve long-term outcomes [129–133] including cognitive functioning [132], but there is a need for prospective longitudinal studies on the effects of early intervention in bipolar disorder with more focus on cognitive and overall function and early preventive pharmacological and psychological strategies. Such studies should demonstrate scientific rigor in the conceptualization and consistent measurement of the number of (prior and future) affective episodes, as recently conceptualized [134].

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Chapter 10

Staging, Functioning, and Cognition



Ralph Kupka, Jan Scott, and Manon Hillegers

10.1 Introduction

Bipolar disorder (BD) is usually described as a chronic, recurrent, and lifelong illness. Its pathognomonic feature is the occurrence of a manic (or hypomanic) episode, differentiating it from (recurrent) unipolar depression, although in many, if not most, cases a first (hypo)mania is preceded by one or more depressive episodes. Depression is mostly the first [1] and predominant illness state in individuals with bipolar disorder [2]. The age of onset is typically in adolescence or young adulthood, and 75% of cases begin before the age of 25 years. The ‘classical’ prototype of manic-depressive illness (including both severe recurrent depressive episodes and bipolar disorders) as originally described by Kraepelin was of an episodic illness with recovery in between episodes, thus differentiating it from the chronic course and gradual decline of dementia praecox, now called schizophrenia. Still, Kraepelin himself stated that the longitudinal course of all conditions that he included in the broad concept of ‘manic-depressive insanity’ was highly heterogeneous and rather unpredictable in individual cases [3]. In today’s clinical practice,

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the borders between phenotypes of recurrent unipolar depression and bipolar disorder, and between bipolar disorder and schizophrenia, are fuzzy, and differentiating between these illnesses can be problematic. This is especially true for early-onset cases during adolescence and young adulthood as symptoms of emerging bipolar disorders overlap with many other mental health problems (ranging from anxiety states to emotion regulation problems), and longitudinally, cases of bipolar disorder may show diagnostic instability between adolescence and later adulthood. Given this scenario, it can be many years after the first symptoms occur or are reported until a definite diagnosis of bipolar disorder is confirmed.

Thus, to understand the origin and nature of bipolar disorder, one must always take a developmental perspective, since the longitudinal course of (prodromal) symptomatology at any given moment may vary and be a confusing mix of depressive, manic, psychotic, and other features. In such a longitudinal approach, there are two time frames to consider. Firstly, in the relatively short term, there is the episodic course, typically the emergence of a manic (M) episode lasting weeks or months, followed by a depressive episode (D) again lasting weeks or months, and after its remission, a symptom-free interval (I) lasting up to many years before such an 'M-D-I' (or 'D-M-I') cycle starts again. There is vast heterogeneity in this episodic course among patients: biphase D-M-I or M-D-I, predominantly recurrent depressive episodes, unipolar mania, and rapid cycling. All these phenomena are objectifiable by clinical observation, and the nomenclature to describe it, and that guides clinical management, has been proposed by a Task Force of the International Society for Bipolar Disorders (ISBD) and is now widely accepted [4]. Secondly, there is the evolution of the illness over the span of a lifetime, which again shows many variations: from a true episodic course with long intervals, in which a person completely recovers and returns to his usual level of functioning, to a gradually deteriorating course without symptomatic, let alone functional, recovery, even despite rigorous treatment. Obviously, such a very long-term perspective is not readily visible in clinical practice and is also difficult to research. If someone is diagnosed with bipolar disorder or has clinical signs that come close to a bipolar spectrum disorder, ideally, we could predict to a certain extent the course of illness, with or without treatment. Such a tentative prognosis of illness course would preferably guide both short- and long-term treatments and include the symptomatic course as well as the level of functional, occupational, and personal recovery during remission.

The personal histories of individuals diagnosed with bipolar disorder show a diverse range of clinical presentations, antecedent conditions, treatment responses, and varying degrees of residual symptoms with functional or cognitive impairments. Moreover, patients may or may not have a family history of mood disorders, a personal biography complicated by traumatic life events, or comorbid mental disorders (longitudinal or concurrent) such as an anxiety disorder, alcohol and/or substance abuse disorder (ASUD), or personality disorder. Still, treatment practice, treatment guidelines, and clinical trials tend to disregard this heterogeneity, and patients are categorized using the broader umbrella of bipolar disorders, only to be differentiated into the subcategories bipolar I, bipolar II, or unspecified bipolar

disorder. It is therefore not surprising that treatment response and outcome may differ substantially, and individual course and outcome remain difficult to predict.

To better identify and understand the early developmental features, longitudinal course, evolution, and potential progression of psychiatric illnesses, the concept of staging has been developed, in the analogy of somatic medicine. In this chapter, we will review the current status of the staging models for bipolar disorder and the evidence from clinical studies supporting these models. Since these models cover recurrent symptomatic course as well as inter-episodic functioning and cognitive impairments play an important role in the latter, we have divided this chapter into three interrelated sections—staging models, functional recovery, and cognitive impairments—and synthesized the key findings in the conclusions.

10.2 Staging and Illness Progression

The prototype of staging systems in medicine is the T(umour) N(ode) M(etastasis) (TNM) system in oncology that was introduced by the International Union Against Cancer (UICC) in 1958 and aims to encompass all aspects of cancer in terms of the primary tumour (T), regional lymph nodes (N), and distant metastasis (M). The TNM system differentiates between the clinical stage (cTNM), based on all available information from history, physical examination, blood tests, radiology, biopsy, and endoscopy, and the pathological stage (pTNM), based on microscopic examination of the tumour after surgical removal. The system can be used for choosing the most appropriate treatment and for providing patients with an estimate of their prognosis. The TNM system is adapted for various sorts of solid tumours, although it is not applicable to every form of cancer and is under continuous development. Other staging systems are used in many areas of medicine, such as cardiology, rheumatology, neurology, endocrinology, and nephrology.

The development of staging systems in psychiatry is hindered by the fact that the pathophysiology of psychiatric illness is still largely unknown and that we have, to date, no valid structural or neurobiological markers for illness recognition and progression. In classification systems such as Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and International Classification of Diseases, 11th Revision (ICD-11), disorders are defined by observable symptomatology and only to a lesser extent by their longitudinal clinical course. Moreover, these diagnostic categories were largely operationalized by observing older adults with established illnesses and show less utility for the early stages, which are less well-defined and show considerable overlap between the phenomenology of many diagnostic categories. Nevertheless, there is a need for timely recognition, application of effective treatments, and making of a prognosis, not only for a specific disorder but ideally also adapted to the personalized profile of a particular individual. Staging and profiling might help come closer to this ambition.

Although Fava and Kellner [5] published a review regarding staging in psychiatry, their description does not reflect the concept of staging as accepted in medicine

and promoted by some experts in psychiatry. For example, for mania, they merely described the bidirectional evolution of a single episode in four phases: (1) prodromal with increased self-confidence, energy, and elated mood; (2) hypomania; (3) manic episode without psychotic features; and (4) manic episode with psychotic features; their model thus did not refer to the overall longitudinal course of bipolar disorder. The first staging framework that was promoted in psychiatry was published by McGorry et al. [6]. This model was seen as underpinning trans-diagnostic early intervention services, although it was primarily applicable to the evolution of psychosis and severe mood disorders. The original model identified four clinical stages, extending from an asymptomatic at-risk stage (stage 0) to severe, persistent illness (stage 4).

Current staging models in psychiatry reflect descriptions of observable phenomena (symptomatology and psychosocial and cognitive functioning) and, thus, are merely clinical staging models. Pathological staging would go beyond clinical description and would incorporate measures of underlying pathophysiology (which would give a biological basis for illness progression), as in somatic staging models. However, most clinical staging frameworks proposed for mental disorders are designed to be ‘future proof’ such that they will be easily adapted to incorporate biomarkers of illness progression such as circadian and metabolic phenomena [7]. Importantly, at this point, they incorporate and reflect the concept of neuroprogression, which was first used in bipolar disorder [8] but has also been applied to other psychiatric conditions [9]. ‘Neuroprogression’ refers to the underlying pathophysiological processes of progressive structural, functional, and neurochemical brain changes, reflected by cognitive and functional decline, poorer treatment response, and an increasing vulnerability to relapse and chronicity. This will be discussed in detail in Chap. 20 of this book.

There are roughly three stages of life in which the first episode of bipolar disorder develops: an early age of onset of 17 years (45%), an intermediate age of onset of 26 years (35%), and a late onset age of 42 years (20%) [10, 11]. Studies show that this age of onset is important. For example, the onset at a young age often has a negative impact compared to the onset later in life and also involves other risk factors and considerations in treatment.

It is important to emphasize that illness progression is not inevitable. For example, only a minority of young people with sub-threshold manic symptoms and a family history of bipolar disorders will ultimately develop a full-threshold episode. Likewise, progression from a first episode to a recurrent course does not always occur, even in individuals with a long duration of illness or advancing age. Moreover, many persons with bipolar disorder will not progress to a stage of treatment resistance, chronicity, or significant functional and cognitive impairments, so it is important to retain therapeutic optimism.

At this point, there is debate whether staging in psychiatry in general, and for bipolar disorder in particular, is possible with the currently available evidence [12]. And if so, there is a discussion about whether staging models in psychiatry should be disorder-specific or should take a more trans-diagnostic approach [13].

10.3 Current Models for Staging Bipolar Disorder

Globally, many youth mental health services have adapted staging models for the assessment and planning of care and treatment [7]. However, some clinicians and researchers who work in other specialist mental health services or adult-only environments are more sceptical. In the context of bipolar disorders, the debates seem to fall into two broad categories. Firstly, a minority view is that clinical staging models are inappropriate for bipolar disorders [12]. However, a more nuanced argument questions whether a trans-diagnostic staging model (as originally proposed) has greater utility for clinical and research practice than disorder-specific models [13]. For the purposes of this chapter, we acknowledge these debates but have chosen to focus on the state of the art in the clinical staging of bipolar disorders.

Currently, there are at least three published clinical staging models for bipolar disorder that each approach illness progression from a different perspective. These models have been described by Berk et al. [14], Kapczinski et al. [15] (Table 10.1), and Duffy [16] (Table 10.2). The various aspects of these models should be integrated into one staging model for bipolar disorder, taking into account a trans-diagnostic approach in the early stages in order to take a broader perspective on the early non-specific developmental stage of emerging severe mental illness, especially mood and psychotic disorders, as will be discussed at the end of this chapter. The International Society for Bipolar Disorders (ISBD) Staging Task Force has published a consensus document for the nomenclature to be used in developing such a comprehensive staging model and the research that can validate it [17]. This proposed nomenclature for staging complements the previously published nomenclature for prodromal [18] and syndromal [4] bipolar disorder.

Table 10.1 Staging models of bipolar disorder as proposed by Berk et al. [14], primarily based on episode recurrence, and Kapczinski et al. [15], primarily based on inter-episodic functioning; the respective timing and numbering of stages of the two models do not correspond due to different focus

Stage	Berk et al. staging model	Stage	Kapczinski et al. staging model
0	Increased risk of bipolar disorder	Latent	Increased risk of bipolar disorder
1a	Mild or non-specific symptoms of mood disorder		Mood or anxiety symptoms without criteria for threshold BD
1b	Prodromal features: Ultra-high risk		
2	First threshold mood episode	I	Well-defined periods of euthymia without overt psychiatric symptoms
3a	Recurrence of sub-threshold mood symptoms		
3b	First threshold relapse	II	Symptoms in inter-episode periods related to comorbidities
3c	Multiple relapses	III	Marked impairment in cognition and functioning
4	Persistent unremitting illness	IV	Unable to live autonomously owing to cognitive and functional impairments

Table 10.2 Staging model for bipolar disorder as proposed by Duffy [16] with an emphasis on early development towards classical bipolar disorder or psychotic bipolar spectrum disorder

	Classical bipolar disorder ^a	Bipolar spectrum ^b
Stage 0 Confirmed familial risk	Well but at confirmed familial risk for episodic bipolar or recurrent mood disorder	Well but at confirmed familial risk for chronic fluctuating bipolar spectrum disorder
Stage 1 Positive family history + non-specific disorders and symptoms	Non-specific syndromes: Episodic anxiety and sleep disorders, clinically significant anxiety and sleep symptoms	Non-specific and developmental disorders: Chronic fluctuating anxiety and sleep disorders, ADHD, learning and motor disabilities
Stage 2 Positive family history + minor mood disorder and/or clinically significant mood symptoms	Minor mood disorders and symptoms (often episodic): Depression Not Otherwise Specified (NOS), dysthymia, cyclothymia, adjustment disorders, clinically significant depressive and hypomanic symptoms	Minor mood disorders and symptoms (often chronic fluctuating) with negative syndrome features: Depression NOS, dysthymia, cyclothymia, hypomanic symptoms, apathy, anhedonia, flattened affect, emptiness, irritability
Stage 3 Positive family history + major depressive disorder, single or recurrent	Single or recurrent (remitting) major depression (with or without psychotic features in episodes), good quality of remission	Single or recurrent (non-fully remitting) major depression, often with attenuated psychotic features: Cognitive dysfunction, decline in functioning (academically, socially)
Stage 4	A. Classical episodic bipolar disorder (BDI, BDII, NOS) with or without psychotic features in episodes and good quality of remission B. Bipolar disorder with residual symptoms: Reflecting burden of illness effects (addiction, medical comorbidity, non-optimal treatment)	A. Non-classical bipolar disorder (cyclic mania, mixed mania, BDI, II, NOS) typically not fully remitting and often attenuated psychotic symptoms B. Psychotic spectrum bipolar disorders (schizoaffective: Poorly remitting) chronic fluctuating and cognitive and functional decline

^a Classical bipolar disorder: Family history of episodic remitting mood disorders, predominantly depressive episodes, good quality of spontaneous remission, psychotic symptoms in a minority of patients and limited to mood episodes, low rate of comorbidity, excellent response to lithium prophylaxis

^b Bipolar spectrum: Family history of chronic psychotic illness or chronic atypical depression and substance use disorders, manic episodes predominate, chronic fluctuating course of illness with significant residual symptoms, not uncommonly psychotic symptoms, cognitive and functional decline, poor response to lithium prophylaxis

10.3.1 The Staging Model of Berk et al

The staging model of bipolar disorder proposed by Berk et al. [14] is based on the original trans-diagnostic staging model of McGorry et al. [6]. In Berk's model, illness progression is primarily defined by the occurrence, remission, recurrence, and persistence of mood symptomatology.

Individuals at risk (*stage 0*) are mainly those without symptoms but who have an above-average risk of developing bipolar disorder because they have a family history of bipolar disorder in first-degree relatives. In some clinical staging models, stage 0 is excluded, and the frameworks focus on stages 1–4, which typically are associated with help-seeking. However, it is worthwhile to highlight that the transition from an ‘at-risk’ stage to later stages may be associated with additional non-specific psychosocial risk factors, including childhood physical or sexual abuse, death of a close relative, and substance abuse. These factors are frequently noted by clinicians and speak to the importance of gene–environment interactions and the nature of resilience. *Stage 1* is typically associated with help-seeking. During *stage 1a*, individuals may present with mild and/or non-specific symptoms, such as mood lability, anxiety, sleep disturbances, irritability, aggressiveness, and hyperactivity. *Stage 1b* denotes the presence of attenuated syndromes (such as brief hypomania) or subsyndromal mood disorder (cyclothymia). Although this stage is sometimes addressed as ‘prodromal’, this term can only be used in hindsight if a person has developed bipolar disorder. Overall, only about 10–30% of individuals classified as stage 1a or 1b will progress to stage 2 or beyond. *Stage 2* is defined by the occurrence of the first mood episode that meets formal diagnostic criteria for bipolar disorder. If this is a manic episode, then the diagnosis of bipolar disorder is made. Since first-episode mania can present with significant psychotic features, the differential diagnosis between affective and non-affective psychosis can be difficult. In the case of a hypomanic first episode, this may not be recognized as a pathological state (as a full-threshold diagnosis would also require a history of major depressive episodes). Furthermore, a major problem for this and other staging models of bipolar disorder is the question of whether stage 2 should always include mania (meaning that hypomania or, for example, depression in those with a family history of bipolar disorders would be classified at an earlier stage). Currently, there is no satisfactory resolution, so different models have taken different approaches.

In some ways, the sequencing of depressive and (hypo)manic episodes is at the heart of many concerns about staging in bipolar disorders, as the determination of the age at onset and the age at diagnosis will be influenced by the definition of when bipolar disorder manifests. For example, a retrospective assessment of the first mood episode in 495 patients with bipolar I or II disorder revealed that in more than half of the patients, depression preceded (hypo)mania, often by many years [19]. Also, prospective assessments of offspring of parents with bipolar disorders have shown that most experience one or more depressive episodes prior to the occurrence of the first hypomanic or manic episode [1, 20, 21]. These individuals will initially be diagnosed with depressive disorder, which only in some may evolve into bipolar disorder depending on a later incidence of (hypo)mania. As such, the age at onset of bipolar disorder might be reported as the age of the first depressive episode or the age of the first (hypo)manic episode (and the age at onset and age at diagnosis can differ). When mood episodes recur, the disorder is classified as *stage 3*. Longitudinal studies give strong evidence that bipolar disorder has a recurrent course in most cases [22]. Outpatients with bipolar disorder who were prospectively followed in naturalistic studies were symptomatic, on average, half of the time, despite treatment

[2]. Subsyndromal depression prevails and is a risk factor for recurrence of any type of episode of bipolar disorder. Residual depressive symptoms may also account for a considerable degree of functional impairment in patients in stages 3 and 4. In *stage 4*, symptoms have become chronic, often manifested as either persistent depression or rapid cycling. Rapid cycling has a prevalence of about 16% in clinical research samples and generally predicts a worse outcome [23].

10.3.2 *The Staging Model of Kapczinski et al*

Most staging models are based on the notion of an illness continuum that includes at-risk and sub-threshold states as well as presentations that meet full-threshold diagnostic criteria across a wide age range (i.e. adolescence onwards). In contrast, Kapczinski et al. [15] focus primarily on adults with clinically diagnosed bipolar disorders, and staging is mainly used to categorize cases into treatment-relevant subgroups. Additionally, while the staging model of Berk fundamentally uses mood symptomatology and the pattern of episode recurrence as the main determinant of illness progression, Kapczinski and coworkers [15, 24] proposed a staging model that emphasizes the level of recovery in the inter-episode period, focussing on cognitive and psychosocial functioning. The basic assumption in Kapczinski's approach is that functional disability and cognitive decline reflect underlying neuroprogression and, as such, would be able to more accurately predict long-term treatment needs.

The *latent stage* in this model allows for the presence of subsyndromal mood and anxiety symptoms in persons at risk for bipolar disorder based on a positive family history but without cognitive impairment. In *stage 1*, the patient fully recovers from mood episodes (regardless of their number and severity) without psychiatric morbidity or cognitive impairment in the inter-episode period. It is important to notice, however, that incomplete functional recovery is common, even after the first major mood episode, especially psychotic mania [25]. In *stage 2*, psychiatric symptoms persist, either from rapid cycling bipolar disorder or psychiatric comorbidities like substance abuse, anxiety disorders, or personality disorders, but there is only transient cognitive impairment. *Stage 3* is characterized by subsyndromal symptoms of bipolar disorder and/or marked cognitive impairment associated with functional impairment, leading to inability to work or the ability to work only with very impaired performance. In *stage 4*, the patient is unable to live autonomously due to severe cognitive and functional disability.

Kapczinski and colleagues argue that the clinical stages in this model are compatible with the biological concept of allostatic load, defined as the 'wear and tear' of the body and the brain resulting from chronic overactivity or inactivity of physiological systems that are involved in the adaptation to environmental challenges [26, 27]. It is hypothesized that allostatic load progressively increases with repeated episodes as a function of cumulative stressors, mood changes, and exposure to other factors such as drugs abuse. Increased allostatic load then leads to cognitive

impairment, intermittent dysthymia, and increased rates of physical and psychiatric comorbidities. In its assumptions, the Kapczinski model thus comes somewhat closer to a pathological staging model, albeit still being based on clinical observations of functional impairment.

10.3.3 The Staging Model of Duffy

The model developed by Duffy [16] focusses on the developmental trajectory of bipolar disorder based on longitudinal prospective observations of the offspring of parents with well-characterized bipolar disorder. This model emphasizes the developmental history, clinical antecedents, and early course of diagnosable mood episodes, both depression and (hypo)mania, in children and adolescents at confirmed familial risk. The model highlights the stages leading up to a clinical presentation that meets the full criteria for a diagnosis of bipolar disorder and differentiates the trajectory of classical, episodic, lithium-responsive BD from other heterogeneous presentations such as those characterized by the presence of psychotic symptoms and a non-fully remitting course that predict non-response to lithium prophylaxis [28].

In day-to-day practice, it has also been found that only a minority of clinical outpatients have a family history of bipolar or other severe mental disorders in first-degree relatives [29]. Having said that, family history is also a proxy for genetic risk, and the emerging field of polygenic risk score and molecular genetic studies in bipolar disorders will hopefully help inform future iterations of this model.

10.4 Functional Impairment in Bipolar Disorder

The optimistic Kraepelinian view that patients with recurrent (manic-depressive) mood disorders show complete symptomatic and functional recovery in between episodes can no longer be held. Firstly, there is a high risk of recurrence of (hypo) manic or depressive episodes. In a meta-analysis, Kessing et al. [30] found that 35% of 293 adults with a first manic or mixed episode had a recurrence after 1 year, as well as 48% of 126 children and adolescents. In another meta-analysis of eight studies including 734 patients who were prospectively followed after their first manic episode, Gignac et al. [31] reported that after 1 year, 84% of patients had a syndromal recovery, while only 62% had a complete symptomatic recovery, suggesting that more than 20% had persistent subsyndromal symptoms. Moreover, 41% had a recurrence in that first year. Looking beyond a first mania, Vazquez et al. [32] found in ten naturalistic studies including 3904 adults with bipolar disorder (86% bipolar I) a recurrence rate of 26.3% per year and in 15 RCTs including 4828 individuals (96% bipolar I) a recurrence rate of 21.9% per year when treated with a mood stabilizer and 31.3% per year on placebo.

In addition to an incomplete symptomatic recovery and a substantial risk of recurrence of mood episodes, full functional recovery is not always achieved. Mood symptoms, especially those related to depression, may persist at a subsyndromal level and are associated with functional impairment [33]. Functional recovery typically lags behind the remission of the episode, which is found in recurrent depressive as well as bipolar disorders [34]. Tohen et al. [35] found that in the 2 years after the first manic episode in 166 patients, at some point, 98% had syndromal recovery (meaning that they no longer met the DSM criteria for a manic episode), 72% showed symptomatic recovery, but only 43% achieved functional recovery. In the 2 years after the first mania, 20% had another manic episode, 20% had a depressive episode, and another 19% switched phases without recovery. Burdick et al. [36] pooled 13 cohorts from seven countries, including 5882 individuals with bipolar disorder, and found rates of functional impairment ranging from 41% to 75%. Lower community functioning was associated with depressive symptoms, a greater number of prior mood episodes, more psychotropic medications, comorbid substance abuse, and lower levels of education.

10.5 Cognition in Bipolar Disorder

Most research on cognition in major mental illnesses (unipolar, bipolar, and psychotic disorders) has been focussed on findings from neuropsychology tests that estimate executive functioning, IQ, etc. [37]. These evaluations of so-called cold cognitions invariably demonstrate that cognitive impairments are associated with severe symptoms and functional disability and probably affect individuals with non-affective psychotic disorders more than those with bipolar or depressive disorders [38]. However, in recent years, this research has expanded, especially in mood disorders and in youth mental health settings, to explore social cognition and cognitive–emotional regulation (so-called hot cognitions) [39]. So, while this section predominantly reports on the established literature on neurocognition, we alert readers to emerging research that indicates that other forms of cognitive processing (especially measures of perseverative cognitions such as rumination and worry or positive basking) may be associated with illness progression in bipolar disorders and also influence treatment decisions for each clinical stage [40].

The main contributors to functional impairment in individuals with bipolar disorder are (subsyndromal) depressive symptoms and cognitive impairment [41]. While cognitive impairment is part of manic and depressive episodes, in many patients, it may persist beyond the remission of mood symptoms. Van Rhee et al. [42] reviewed the evidence of the trajectories and correlates of cognitive impairment in bipolar disorder, which we will summarize here. In contrast to schizophrenia, cognitive functioning is, in general, largely unaffected before the onset of bipolar disorder. However, there is some evidence that subtle cognitive deficits are present in some still unaffected familial high-risk individuals. Cognitive impairment is more severe in childhood-onset than in adult-onset bipolar disorder.

This is also true for multiple-episode compared to single-episode disorder, suggesting a progressive course. However, given the evidence of a genetic factor, more severe cognitive dysfunction may be a marker of a more severe illness phenotype, along with earlier age of onset, recurrent and more severe episodes, psychotic features, more hospitalizations, and longer illness duration. Longitudinal studies also suggest that apart from the domain of executive functioning, cognitive impairments, in general, do not show a progressive course. Late-onset bipolar disorder (i.e. after the age of 40) is associated with more severe and widespread cognitive deficits while these individuals have less familiar loading and more neurological comorbidities, suggesting that these cognitive impairments may have another origin. In addition, there is an increasing risk of dementia with repeated mood episodes, which again raises the question of whether cumulative toxicity of mood episodes leads to dementia, or if those who develop dementia also have a more severe form of bipolar disorder.

Cognitive impairment in bipolar disorder has been associated with inflammation and oxidative stress, decreased levels of neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF), and metabolic dysfunction. Unhealthy lifestyle habits, such as impaired sleep, inactivity, poor diet, smoking, and substance use, are also associated with increased inflammation and decreased neuroplasticity and, thus, may add to an unfavourable course.

Overall, cross-sectional and longitudinal studies of the development of cognitive dysfunction in bipolar disorder show mixed outcomes. This suggests that independent from the clinical heterogeneity of the core mood symptomatology and its longitudinal course, there may be considerable cognitive heterogeneity among subgroups of patients with bipolar disorder. With regard to the three staging models reviewed above, this is where they show their different perspectives: the Duffy model describing ‘classical’ versus ‘atypical’ developmental trajectories, the latter associated with more cognitive impairments as in schizophrenia; the Berk et al. model focussing on syndromal and subsyndromal mood symptoms; and the Kapczinski et al. model putting emphasis on inter-episodic functioning and cognition.

10.6 Clinical and Biological Evidence Supporting Staging Models

Data from various cohort studies have supplied evidence that supports the concepts of illness progression and staging by using clinical, functional, and cognitive outcomes in patients with bipolar disorder. Some studies also included potential biomarkers to investigate underlying biological processes of illness progression (‘neuroprogression’). Magalhaes et al. [43] used the data from STEP-BD to test the utility of the number of lifetime mood episodes as a relevant prognostic variable for staging. They included three groups of patients with fewer than five episodes, five to ten episodes, and more than ten episodes, respectively, and found that patients

with multiple episodes had more chronic and severe symptoms, lower levels of functioning and quality of life, and more disabilities. The authors caution however that relying on the number of episodes may be a clinically simple but also rather simplistic way of defining illness progression, and underlying biological mechanisms need to be identified.

Reinares et al. [44] separated two clusters in a sample of 106 euthymic patients with bipolar disorder, based on clinical, functional, and cognitive assessments. 'Poor' outcome (52.4%) was differentiated from 'good' outcome (47.6%) by higher episode density, more residual depressive symptoms, lower estimated verbal intelligence, and less inhibitory control. Age, age of onset, and illness duration did not differ between the two groups.

Grande et al. [45] identified two clusters (early and late stage) in a sample of 115 patients with bipolar disorder, with late-stage patients having more episodes, a younger age of onset, longer duration of illness, worse functioning, and higher levels of the pro-inflammatory cytokine Interleukin (IL)-6.

Rosa et al. [46] classified 54 euthymic patients with bipolar disorder along the four clinical stages of the model by Kapczinski (stage I $n = 16$; stage II $n = 11$; stage III $n = 13$; stage IV $n = 14$), assessed functional status and cognitive functioning, and compared these patient groups with 43 healthy controls. Except for stage I, patients had worse functional outcomes than controls. Functional impairment as measured by Functioning Assessment Short Test (FAST) increased from stage I to IV. Patients in stages III and IV had worse cognitive functioning than healthy controls.

Following the same procedure, Goi et al. [47] classified 129 patients with bipolar disorder according to Kapczinski's model (stage I $n = 31$; stage II $n = 44$; stage III $n = 31$; stage IV $n = 23$) and found that monotherapy was more frequent in stage I, two-drug combinations in stage II, and three or more medications in stages III and IV. Functional impairment as measured by FAST was correlated to the number of medications prescribed.

López-Villarreal et al. [48] followed a group of 87 patients with bipolar disorder for 5 years and found two clusters: 49.4% did show progression of functional impairment, while the other 50.6% did not. The first group had more recurrences and hospitalizations during the follow-up period, as well as worse cognitive functioning.

Tremain et al. [49] reviewed the influence of the stage of illness on functional outcomes after psychological treatment. Proxy variables of early versus later stages were the number of mood episodes, general or social functioning/disability, cognitive functioning/impairment, and psychiatric comorbidities. Their analysis of 62 studies suggests that patients in an earlier stage of illness showed more benefits for general/social functioning than those in later stages. With regard to the effect of psychological treatment on quality of life, there were no consistent differences between earlier and later stages.

In another study, Tremain et al. [50] found two clusters in a group of 302 euthymic patients with 'later-stage' bipolar disorder, defined as having ten or more lifetime episodes. The clusters differed with regard to sub-threshold depressive symptomatology, independence, energy and interest, anxiety, and cognitive functioning, among other factors. Regarding clinical variables, the cluster with an

unfavourable profile had more lifetime depressive episodes, a longer duration of illness, a higher number of hospitalizations and suicide attempts, and more rapid cycling.

van der Markt et al. [51] tested the model by Berk in lifetime retrospective mood charts of a sample of 88 patients with bipolar I disorder and 11 with bipolar II disorder, looking at the course of illness in the first 5 years after onset (stage 2, first episode). Before illness onset, 12% had at least one parent with bipolar disorder (stage 0, at-risk), and 75% had experienced prodromal symptoms (stage 1). Five years after illness onset, only 7% were still in stage 2 (i.e. no recurrence), 72% had reached stage 3 (recurrent illness), and 13% had progressed to stage 4 (chronic). Of the latter group, 8% subsequently recovered from a chronic to a recurrent course (stage 3).

Subsequently, van der Markt et al. [52] investigated the correlation between the recurrence-based model (A) by Berk and the functioning-based model (B) by Kapczinski in a cohort of 1396 individuals with bipolar I disorder. A majority (93%) was assigned to stage 3 (recurrent illness) and only 2% to stage 4 (chronic illness) of model A, while 41% and 43% were assigned to stage II (inter-episodic symptoms) and stage III (inability to work), respectively, of model B. The correlation between the two models was low (0.21), suggesting that illness progression as defined by recurrence differs from illness progression as defined by inter-episodic functioning.

In another analysis of this cohort, van der Markt et al. [53] found the following clinical profiles that predicted progression to a higher stage in the Berk model (A): familial loading, childhood abuse, earlier onset of illness, longer illness duration, psychiatric comorbidity, and treatment resistance. For the Kapczinski model (B) these were: childhood abuse, psychiatric comorbidity, cognitive functioning, and treatment resistance. In a sub-sample of the same cohort, van der Markt et al. [54] analysed MRI scans of 199 subjects with bipolar I disorder and 226 healthy controls to investigate brain age in relationship to clinical stages. They found that a higher biological than chronological brain age was correlated with a higher stage in the model (B) by Kapczinski but not in the model (A) by Berk, although the significance of that association was lost when controlling for lithium use and comorbid anxiety.

The model by Duffy [16] has been helpful in mapping the development of psychopathology in the offspring of parents with bipolar disorders and demonstrating how this differs in comparison to the offspring of 'healthy control' parents. These differences are less clear-cut when the offspring of parents with bipolar disorders are compared with the offspring of parents with other disorders [55, 56]. In a recent study of the development of psychopathology in the offspring of parents affected with either bipolar or psychotic disorders and controls [57], the Duffy model was slightly adapted allowing a cross-disorder approach that acknowledges the heterotypic nature of schizophrenia and bipolar disorders. Stage 0 (well) was divided into stage 0a (well, without familial risk) and 0b (well, with familial risk). Stage 1 is referred to as the non-mood stage. Within stage 1, 'developmental', 'anxiety', 'alcohol/substance', and 'other non-mood' disorders were distinguished. Psychosis was clustered with manic episodes in stage 4. The total number of transitions

between ages 13.2 and 17.1 was significantly higher in the familial high-risk offspring as compared to controls, but staging did not reveal clear differences between schizophrenia and bipolar offspring. By evaluating survival curves of the diagnoses clusters as well as clinical stages, we could confirm that non-mood disorders are more prevalent at a younger age in the offspring of schizophrenia patients, which confirms a more prominent neurodevelopmental origin.

Grewal et al. [58] reviewed 35 studies that investigated biomarkers of neuroprogression and late-stage bipolar disorder, including neurotrophic factors (BDNF), inflammatory markers (IL-6, IL-10, and Tumor Necrosis Factor-alpha (TNF- α)), oxidative stress markers, telomere length, and structural brain changes. Included studies either used a staging model to classify patients or correlated biomarkers to clinical variables associated with illness progression (age at onset, duration of illness, number of episodes and hospitalizations, and symptom severity). If a specific staging model was used, it was the Kapczinski et al. model. Although findings are sometimes conflicting among studies, and any conclusion is therefore preliminary, the authors hypothesize that inflammation plays a prominent role in illness progression and functional and cognitive impairments. Inflammatory markers are already increased in the early stages when compared to healthy controls, suggesting that inflammation is a trait marker for bipolar disorder. Moreover, inflammation worsens towards the later stages of the illness, suggesting that inflammatory processes contribute to progressive biological alterations such as brain changes and impaired immune system response. An increase in ventricular size and the reduction of grey matter volume were the most pronounced brain changes associated with illness progression. The authors emphasize that similar changes have been identified in schizophrenia and major depressive disorder, suggesting that illness progression may be a trans-diagnostic phenomenon.

10.7 Towards an Integrated Staging Model for Bipolar Disorder

There is a growing understanding of the early stages of bipolar disorder and the risk factors that play a role in the onset. At the same time, it presents the clinician with the dilemma of how and when to express these concerns and when and how to intervene [59]. In addition to different risk groups, the period in life in which the first symptoms or the first episode of illness (and any comorbidities) manifest itself is also of great importance in interpreting the disease stage and providing appropriate psycho-education and treatment advice.

To enable further study of clinical staging in bipolar disorder, there is a need for one model that draws on the perspectives of the models described earlier [17]. This could be a multidimensional model, such as the T(umour) N(ode) M(etastasis) model in medicine and the consensus trans-diagnostic staging framework advocated for youth mental health [7]. The existing medical and trans-diagnostic models have clinical utility because they (a) use relevant information about the current clinical presentation to determine the stage of illness, (b) elucidate decisions about the

choice and sequencing of treatment, and (c) make predictions about future clinical course and illness progression. An integrated staging model for bipolar disorder could describe (1) the evolution of its core phenomenology (i.e. mood) symptomatology, including prodromal, subsyndromal, and syndromal (full episode) (as in the Berk and Duffy models); (2) the degree of inter-episodic functional and cognitive impairment (as in the Kapczinski and Duffy models); and (3) the degree of psychiatric and somatic comorbidity (as in the Duffy and Kapczinski models).

10.8 Conclusion

This chapter highlights the current state of the art in the staging of bipolar disorders and how multidimensional frameworks that incorporate clinical phenomenology alongside cognitive and social functioning underpin the three most widely quoted models (Berk, Kapczinski, and Duffy). These models undoubtedly shed light on the treatment needs of individuals with different clinical stage presentations of bipolar disorder and help make predictions about the likelihood of illness progression. However, the models are best suited to the clinical settings in which they were developed and, as yet, we have no consensus staging model of bipolar disorders that generalizes across different clinical and research settings. This is a disadvantage to clinicians as treatments recommended for, for example, ‘stage 2’ illness in one model may not apply to ‘stage 2’ illness in another model. It also undermines collaborative research as it is not possible to combine data from different studies (that use different staging models) to examine the risk and protective factors for illness progression in a reliable and valid manner. Furthermore, if experts in bipolar disorders begin to develop a consensus staging model, one cannot simply combine current models as, for example, they will need to determine whether and how to include evidence regarding other aspects such as social cognition and illness extension (describing how a mental illness may expand beyond the diagnostic boundaries of the index disorder).

To design a unified staging model for bipolar disorder, one may learn from transdiagnostic staging models that have further evolved and are beginning to differentiate factors associated with illness progression and extension [7, 60] (Scott et al., in review).

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Chapter 11

Substance Use Disorder in the Course of Bipolar Disorder



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11.1 Introduction

Bipolar disorder (BD) is the 17th leading cause of disability among all diseases along with other mental health diseases such as major depression, anxiety disorders, and schizophrenia [1]. The global estimates of lifetime and 12-month prevalence of BD are 2.4% and 1.5%, respectively [2]. It is worth noting that the identification and accurate diagnosis of BD can be challenging due to its complex nature, symptom overlap, and heterogeneous trajectories. Furthermore, BD imposes a significant burden on society, both in terms of economic costs [3] and social impact. In a recent Canadian cohort on the early burden of disability in subjects with common mental disorders in Ontario that included almost two million individuals, it was found that the incidence of entries into the local provincial disability support program was greater among subjects with mood disorders than those without mood disorders (aHR 2.03; 95% CI [1.95, 2.11]), and this rate was even greater in individuals with BD (rate ratio: 4.31 [95% CI: 3.56–5.17]) than in those with major depression (rate ratio: 1.82 [95% CI, 1.36–2.43]) [4]. In addition to its direct impact on disability,

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BD can also influence the risk of developing other diseases, including increased rates of stroke mortality [5]. Chen et al. assessed the incidence and 5-year trend of medical illnesses following a BD diagnosis in a sample of almost 60,000 subjects. The findings highlight an increased risk of various medical conditions, particularly in the first year after diagnosis, underscoring the need for careful evaluation and management of comorbidities in individuals with BD to reduce mortality rates associated with medical illnesses [6].

Additionally, to explore the impact of BD, it is important to examine overall risk factors associated with the condition. Based on a systematic review from the International Society of Bipolar Disorders (ISBD), family history of BD, subthreshold hypomania symptoms, recurrence of depressive episodes, and psychotic features could be relevant prodromes of the disease [7]. Andrade-González et al. (2020) also explored some initial prodromes for BD onset and identified subthreshold symptoms such as the most cited ones in the literature [8]. Regarding the impact of substance use, specifically, Lalli et al. found in a systematic review ($n = 22$) that six out of nine studies assessing overall substance use found that substance use was a risk factor for developing BD. Cannabis use, nonmedical use of prescription medication (NUPM), nicotine use, and alcohol use were risk factors for BD in approximately half of the assessed studies [9]. In addition to substance use as a predictor for BD onset, there is evidence that suggests worse outcomes regarding functional and cognitive measures [10]. Cannabis use could be associated with a higher number of suicide attempts and an increased risk for manic symptom onset [11, 12], although studies regarding the relationship between cannabis and cognition are not homogeneous [13]. In relation to comorbidity, there is evidence indicating a strong association between substance use disorder (SUD) and BD, identifying that individuals with an alcohol use disorder (AUD) were found to be at a 4.1 times greater risk of presenting BD compared to those without an AUD. Moreover, the risks were even more pronounced for illicit drug users, who exhibited a five times greater risk of having BD compared to nonusers [14]. In this chapter, we will delve deeper into the relationship between BD and SUD. We will explore how these two conditions interact and the potential underlying causes that contribute to the occurrence of both SUD and BD. Finally, we will discuss the evidence-based treatment strategies for this condition.

11.2 Substance Use in the Offspring of Parents with Bipolar Disorder

It is known that BD is highly heritable, and individuals with a family history of BD in their first-degree relatives present an almost eight times greater risk of having BD as compared to individuals without a family history of BD [15]. Thus, many studies have been focused on understanding the clinical trajectories of the offspring of parents with BD.

A recent prospective cohort study from Colombia [16] compared the offspring of parents with BD ($n = 131$) with a community control offspring group ($n = 150$). The authors found that the offspring of parents with BD had a higher frequency of psychoactive substance use during both assessments (baseline and 4-year follow-up). The magnitude of differences between groups increased at the 4-year follow-up. In addition, the BD offspring group had a younger age of onset for psychoactive substance use compared to control offspring [16].

Another prospective cohort study by Duffy and colleagues [17] provided a comprehensive analysis of the trajectory of the offspring of parents with BD. They included data from 229 high-risk offspring and 86 control offspring, followed for up to 16 years. In this cohort study, authors found that BD in young people at familial risk is often preceded by years of impairing psychopathological presentation. The cumulative incidence of substance use disorder (SUD) was 30.36% among the high-risk offspring of parents with BD versus 15.70% among control offspring, with a trend to be statistically significant ($HR = 2.56, p = 0.053$). Moreover, they found that a family history of SUD increases the risk of their offspring developing an SUD at a mean age of 17.46 years, and this age is convergent with the onset of mood disorders.

Additional prospective longitudinal studies including the offspring of parents with BD also found higher rates of SUD in high-risk individuals. Axelson et al. [18] found that high-risk offspring ($n = 391$) had significantly higher rates of SUD (19.9%) than control offspring ($n = 248$, 10.1%), in a mean follow-up of 6.8 years. Nurnberger et al. [19] also found that high-risk offspring ($n = 141$) followed by a mean of 2–3 years, had two times greater rates of SUD (18%) than control offspring ($n = 91$, 9%), but this difference was not statistically significant. Preisig et al. [20] conducted a 10-year follow-up study of the offspring of parents with BD ($n = 81$) and found that the risk of developing any SUD was 28% for high-risk proband and 19% for control proband ($n = 63$). Additionally, they found that the offspring of parents with early-onset BD presented a five times greater risk of substance use disorders than those with later onset and controls. Altogether, these studies indicate that the offspring of parents with BD are more likely to develop SUD than the offspring of parents without BD.

11.3 Substance Use as a Risk Factor for Bipolar Disorder: Evidence from Prospective Cohort Studies

Assessing whether substance use is a risk factor for BD is highly relevant clinically because this is a modifiable risk factor. There is evidence showing that even in utero exposure to substances may play a role in externalizing the outcomes for the offspring from childhood to adulthood. Data from 79 individuals with BD from a birth cohort shows that the offspring exposed to maternal smoking during pregnancy exhibit a twofold higher risk of developing BD. After adjusting for maternal race,

alcohol use, psychiatric history, and birth weight, none of these variables changed the associations by more than 10%. In this cohort, smoking during pregnancy was the strongest and only significant predictor of BD in the offspring [21].

A recent systematic review [9] including prospective and retrospective cohort studies that (a) included individuals without BD at baseline, (b) assessed preexisting substance use, and (c) assessed the presence of BD or hypomanic/manic symptoms at follow-up found substantial evidence showing that substance use is a risk factor for BD. This systematic review found that six out of nine (66.7%) studies that assessed any type of substance use found that substance use was a significant risk factor for BD. When looking at specific types of substance use, cannabis use was the most investigated one, and five out of nine studies (55.6%) showed that cannabis use was a risk factor for BD. Interestingly, it was shown that a greater frequency of cannabis use was associated with a greater risk of developing BD or hypomanic/manic symptoms. Among the least investigated specific substances are (1) alcohol use: three out of seven studies (42.9%) found alcohol use as a risk factor for bipolar disorder or hypomanic symptoms, (2) nonmedical use of prescription medications (NUPM): one out of two (50%) studies found that NUPM was a risk factor for bipolar disorder or hypomanic symptoms, and (3) cocaine use: only one study included in this systematic review had specifically assessed whether cocaine use was a risk factor for developing BD and found that individuals that reported lifetime cocaine use at baseline had a 3.41 times greater risk to develop BD in the follow-up of 3 years as compared to individuals that did not report lifetime cocaine use at baseline. An important limitation of this systematic review is that the frequency of substance use varied across the studies included. For example, some studies assessed lifetime use, while others assessed current use/abuse/dependence or substance use disorder, and this limitation added a large heterogeneity to the findings.

A recent population-based cohort study using Danish nationwide registers included 6,651,765 individuals and assessed whether cannabis use disorder is associated with an increased risk of psychotic and nonpsychotic unipolar depression and BD [22]. This study found that individuals with cannabis use disorder had a greater risk of developing any type of BD. Importantly, individuals with cannabis use disorder had a four times greater risk of developing psychotic bipolar disorder as compared to individuals without cannabis use disorder (HR: 4.05 [95% CI: 3.52–4.65]), even after adjusting for potential confounders (e.g., sex, alcohol use disorder, substance use disorder, parental mood disorders, parental alcohol use disorder, cannabis use disorder, and substance use disorder, among others). When evaluating the risk of developing BD in relation to the time of the first diagnosis of cannabis use disorder, it was found that the highest risk of developing BD was within the first 6 months of diagnosis of cannabis use disorder (HR: 16.45 [95% CI: 13.97–19.38]). However, the risk of BD among those with cannabis use disorder remained elevated even after 10 or more years. Although there is a lack of evidence supporting that cannabis use cessation can reduce the risk of developing BD, these findings reinforce the importance of developing public health strategies focused on reducing cannabis use. Prevention programs should offer accessible psychoeducation and support to mitigate risk factors, such as avoidance of substance use [23].

Although the use of tobacco and alcohol as a risk factor for developing BD has been less explored, a recent study using data from the Northern Finland Birth Cohort 1986 Study, which included 7660 participants, assessed whether alcohol use, cigarette smoking, and coffee consumption at the age 15–16 were risk factors for a subsequent diagnosis of BD at the age of up to 32–33 years [24]. The study found that the mean number of cigarettes/day (OR: 1.23 [95% CI 1.01–1.50]) as well as the mean volume of alcohol consumption, characterized by the total grams of ethanol per day (OR: 1.22 [95% CI 1.01–1.47]) but not the frequency of excessive drinking (which was assessed by the frequency they reported on how many times during the past 30 days they had had six (for boys) or four (for girls) drinks or more), in adolescence (15–16 years old) were associated with an increased risk of subsequent BD after adjustment for sex, parental psychiatric disorders, family structure, illicit substance use, and emotional and behavioral problems at baseline. There was no association between coffee consumption in adolescence and subsequent diagnosis of BD during adulthood. This study showed that a greater amount of alcohol and cigarettes during adolescence was a risk factor for developing BD during adulthood.

Another important clinical consideration is that the use or abuse of substances with psychotomimetic properties (e.g., cocaine, amphetamines, hallucinogens, and cannabis) may induce psychotic symptoms. A recent study using data from the Norwegian Patient Registry, which included 3187 individuals with a diagnosis of substance-induced psychosis from 2010 to 2015, found that the 6-year cumulative transition rate from substance-induced psychosis to BD was 4.5% (95% CI = 3.6–5.5), and the risk of this transition was higher for women than for men [25]. The median time from the diagnosis of substance-induced psychosis to a diagnosis of BD was 1 year. These findings suggest that clinicians should be aware of the risk of transition from substance-induced psychosis to BD and carefully observe the clinical evolution of these cases, providing the care needed to prevent a worse prognosis.

The literature in the field shows that substance use is an important risk factor for developing BD, and it seems that there is a dose-dependent relationship, especially for cannabis, alcohol, and cigarettes.

11.4 Substance Use and Bipolar Disorder: Evidence from Machine Learning Studies

Machine learning (ML) is a set of techniques that can teach a computer to learn patterns from data and make predictions or decisions based on a model [26]. ML has been evolving as an alternative to traditional approaches to statistics to map newly associated factors with BD, as well as create predictive models to further understand the disorder trajectory [27–30].

Previous studies that aimed to predict BD incidence identified substance use–related features as important factors for the onset of BD. A recent study that aimed

to build a predictive model to detect BD early in a large birth cohort ($n = 3748$) identified cannabis use at 18 years old as an important risk factor for BD onset 4 years later [31]. The same study showed that the high-risk subgroup presented an increased frequency of drug use [31]. Recent data on another prediction study on BD onset in young adults (aged 18–24 years at baseline) found lifetime cocaine use as the sixth most important feature in the model [32], and potential alcohol abuse or dependence was a relevant variable in a supplementary model for BD onset without depression-related features as predictors.

ML approaches play a crucial role in capturing nonlinear associations and complex relationships, especially when examining the intricate dynamics between SUD and BD. Traditional statistical methods often struggle to uncover these intricate connections due to their linear assumptions and limited ability to handle large and diverse datasets, increasingly common within mental health research. Despite the models so far presenting good performances and relevant insights regarding BD research, we still face some barriers to the generalizability of these models (e.g., a lack of external validation and small sample sizes) [33] and especially in the deployment, in the form of risk calculators—tools that output risk probabilities for a given clinical outcome—for example, which may be one of the best ways to bring the benefits of predictive modeling to clinical practice since it could assist on early BD risk identification.

11.5 Bipolar Disorder as a Risk Factor for Substance Use Disorder

Regarding the reverse pathway, there is evidence showing a bidirectional association between mood disorders and SUD [34].

According to findings from the 10-year follow-up of the US National Comorbidity Survey, mood disorders are risk factors for the subsequent onset of SUD, with stronger associations observed for BD [35]. The risk of SUD onset generally increased as a function of the number of preexisting disorders [35]. Moreover, BD significantly predicted the transition from illicit drug use to illicit drug abuse and the transition from illicit drug abuse to illicit drug dependence. Compared to major depression and dysthymia, BD is more strongly associated with any alcohol-related condition [36].

Regarding BD specifically, a strong association was found between BD and the subsequent development of SUD in the Zurich Community Cohort [36]. Manic symptoms put individuals at a 2.4 times greater risk for later alcohol use and a 4.4 times greater risk for later onset of alcohol dependence, despite the fact that the overall number of persons who developed later alcohol abuse was greater than the number with alcohol dependence. The risk of later onset of cannabis use was 2.2 times greater in individuals with manic symptoms, and the risk of cannabis abuse/dependence was 4.8 times greater in the same population. Regarding benzodiazepine, the risk of later use was 3.6 times greater, and the risk of abuse/dependence

was 11.5 times greater in individuals with manic symptoms. The same study found that BD type II (BDII) is a strong predictor for alcohol abuse (OR: 9.1), alcohol dependence (OR: 21.1), benzodiazepine use (OR: 6.9), and benzodiazepine dependence (OR: 14.1). In opposition to manic symptoms, BD type II did not predict the development of cannabis use or abuse/dependence. The authors suggested that manic symptoms, even below the diagnostic threshold for hypomania, may be a consistent and comprehensive risk factor for the future development of SUD [36].

Furthermore, an epidemiologic study with a community sample ($n = 34,653$) shows that baseline lifetime mood disorders (major depressive disorder and BD) were associated with incident nonmedical prescription opioid use at follow-up, adjusted for demographics, comorbid mood/anxiety disorders, and other substance use [37].

A recent study using machine learning techniques to identify the predictors of illicit substance abuse/dependence among young adults has also found that the lifetime history of a manic episode was a strong predictor for illicit substance abuse/dependence in this cohort of young adults [38].

Since BD and SUD are strongly associated, it is suggested that they share physiological mechanisms. They both can be understood as systems related to regulation of motivation, reward, and the initiation of behavior [39]. Individuals with BD may have an increased susceptibility to the rewarding effects of substances [39]. In addition, individuals with SUD and BD have impaired decision-making. They also share mechanisms such as poor modulation of motivation and susceptibility to behavioral sensitization [39].

Another important mediator is impulsivity, the disposition toward rapid reactions without regard to the negative consequences, which is a frequent element in the course of BD, particularly during manic episodes but also during depressive, mixed, and euthymic periods [40]. Impulsivity also plays a crucial role in the starting and maintenance of substance use [41]. Impulsivity is even higher when the individual has comorbid BD and SUD, and it is associated with serious behavioral consequences for both disorders [41]. Thus, the impulsivity often observed in individuals during a manic episode may potentially contribute to an increased risk of substance consumption in this population.

11.6 Bipolar Disorder and Substance Use Disorder Comorbidity

As previously mentioned, the comorbidity between SUD and BD is common. A systematic review and meta-analysis showed that the pooled lifetime prevalence of any SUD was 35.7% (95% CI 27.2–44.3%) for individuals with BD type I (BDI) and 28.1% (95% CI, 21.8–34.3%) for individuals with BDII [42]. This systematic review also showed that males with BD had an almost 3 times greater probability of having alcohol use disorder, a 2.4 times greater probability of having cannabis use disorder, and a 2.2 times greater probability of having any type of SUD as compared

to females with BD. Finally, this systematic review showed that individuals with BD with comorbid SUDs presented an earlier age of onset of BD and a greater number of hospitalizations, indicating a worse clinical course for individuals with this comorbidity.

A cross-sectional study including an outpatient sample of 187 children and adolescents with BD, 29 with BD and SUD comorbidity, and 115 healthy controls showed that children and adolescents with BD and SUD comorbidity presented a worse clinical course, marked by greater rates of lifetime history of suicide attempts and lifetime hospitalization, as well as greater functional impairment, as compared to children and adolescents with BD and without SUD comorbidity [43]. In line with these findings, a recent systematic review included 14 studies and concluded that individuals with comorbidity of BD and SUD have increased cognitive impairment as compared to individuals with BD and without SUD comorbidity [44]. Importantly, executive functioning, which includes verbal fluency, working memory, and attention, was the most impaired cognitive domain found across the studies included in this review.

Oliva et al. [45] aimed to identify demographic and clinical factors associated with different types of SUD in BD using machine learning techniques. The classifier for alcohol use disorder (AUD) and SUD in BD presented a sensitivity of 75% and specificity of 75%. Hypomania as the first mood episode (OR: 4.34, 95% CI [1.42, 13.31]) and the presence of hetero-aggressive behavior (OR: 3.15, 95% CI [1.48, 6.74]) were important features to explain AUD co-occurrence with at least another SUD. In a recent study, the authors aimed to predict the predominant mood polarity of patients with BD based on demographic and clinical variables [46]. Based on a sample of 148 patients, the model presented an receiver-operating characteristic curve (ROC) area under the curve (AUC) of 74.7%, and comorbid substance dependence, especially comorbid alcohol dependence, was a key variable when classifying between manic or depressive predominance.

Altogether, the literature indicates that the comorbidity between BD and SUD has an impact on a worse clinical progression. Post [47] emphasized that this progression can involve the accumulation of and sensitization and cross-sensitization to stressors, mood episodes themselves, and bouts of substance abuse. In order to prevent this malignant transformation from a manageable disease to a treatment-resistant condition, it is essential to promote early strategies targeting stress reduction and modulation, as well as treat and prevent mood episodes and substance abuse.

11.6.1 Bipolar Disorder and Substance Use Disorder: Treatment Implications

It is crucial to acknowledge that comorbid conditions, such as SUD, may contribute not only to a delay in BD diagnosis [48] but also to a worse course of BD, for example by raising the rate of nonadherence to medication, which is a frequent

cause of recurrence [48]. A recent cross-sectional study showed that in subjects with BD with comorbid SUD, antidepressant-induced manic switch and poor treatment response to mood stabilizers occur more often than in individuals with BD and without SUD [49].

Comorbid SUD also raises the likelihood of suicide attempts [49, 50]; however, the effect on suicide death remains unclear [50]. In children and adolescents with BD, the risk of death by suicide was significantly associated with comorbid SUD (OR: 17) [51]. Furthermore, lifetime mixed features, psychotic symptoms, and aggression are more frequent in individuals with BD and comorbid SUD than in individuals with BD and without this comorbidity [49].

Taking into consideration the pernicious clinical manifestation of individuals presenting BD and comorbid SUD, SUD comorbidity should be managed as early as possible, preferably simultaneously [52]. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) provide some general principles to guide pharmacological treatment in their most recent guidelines, as described below:

Alcohol Use Disorder (AUD) For patients with BD presenting AUD comorbidity, the combination of divalproex and lithium has the strongest level of evidence (level 2). This combination showed a significant reduction in the number of drinks per drinking day and per heavy drinking day, compared to the group with lithium in monotherapy, adjusting for adherence to treatment. Lamotrigine, divalproex monotherapy or add-on, and lithium meet the criteria for a lower level of evidence (level 3). Quetiapine is not recommended due to the lack of efficacy [52].

It is important to be cautious with lithium use in heavy drinkers, considering the potential of electrolyte imbalance due to synergistic effects. Lithium itself may cause alterations in electrolyte excretion [53]. Alcohol consumption can also affect electrolyte balance in several ways. Patients with AUD may present electrolyte abnormalities due to alcohol-induced diseases, such as vomiting, diarrhea, and malnutrition [54], which can lead to lithium intoxication. Regarding some antiepileptic drugs, such as divalproex, liver function tests are recommended before starting treatment and during the first months due to the potential of drug-related hepatotoxicity [55]. If the patient has a severe hepatic impairment, the use of divalproex is contraindicated [56].

Cannabis Use Disorder Although this is a common comorbidity in BD [42], there are limited treatment options designed for this specific comorbidity. With level 3 of evidence, there is lithium and/or divalproex. Quetiapine did not prove benefits [52].

Stimulant Use Disorder For cocaine use disorder, the best evidence is that bupropion add-on therapy (level 2), and lithium and/or divalproex might be useful (level 4). Quetiapine and risperidone, both of them in monotherapy or as adjunctive agents, showed efficacy for cocaine and methamphetamine use disorders (level 3) [52].

Opioid Use Disorder (OUD) Methadone has the best evidence of efficacy for individuals with BD and OUD comorbidity (level 3). Due to growing concern regarding the risk of overdose, CANMAT [52] advises clinicians to consult the Canadian Research Initiative in Substance Misuse (CRISM) guidelines for further advice in this matter.

Psychosocial interventions are important treatment strategies as an adjunct to pharmacological treatment. Colom and Vieta [57] built a structured psychoeducational program, which consists of 21 weekly sessions, with a duration of 90 minutes per session. This intervention is focused on five main areas: (a) illness awareness, (b) adherence enhancement, (c) detection of early awareness signs, (d) substance misuse avoidance, and (e) lifestyle regularity. A recent systematic review including 47 studies showed that psychoeducation as an adjunctive to the pharmacological treatment in BD led to the reduction of new mood episodes, a reduction in both the number and the duration of hospitalizations, and an increased adherence to the pharmacological treatment [58]. Specifically, in the treatment of the comorbidity between BD and SUD, a randomized controlled trial including 62 individuals with BD and current substance dependence, treated with mood stabilizers, tested the efficacy of integrated group therapy (20 weeks), which addresses the two disorders simultaneously, when compared to group drug counseling (20 weeks), which focuses on substance use. The results showed that individuals receiving the integrated group therapy presented significantly fewer days of substance use during treatment and a follow-up of 3 months [59]. Similar results were found for the shorter version of the integrated group therapy (12 sessions), showing a trend toward a greater reduction in days of substance use during the follow-up of 6 months and a greater decrease in risk of mood episodes during treatment for individuals receiving the intervention [60].

Regarding other types of psychosocial interventions and psychotherapies, according to the most recent Cochrane review on this matter, due to several reasons—the large variety of study designs, methodological differences, and difficulties with data pooling and data interpretation—it is not possible to rule in favor of any specific psychosocial treatment over another for this population of comorbid SUDs and severe mental illness [61].

11.7 Clinical Tips

- Clinicians should be aware of the greater risk of developing SUD seen in individuals with a family history of BD.
- About 5% of individuals with a substance-induced psychosis will present a transition to a BD diagnosis, and the median time for this transition is 1 year.
- Early and adequate treatment of BD may prevent the development of SUD and vice versa.
- SUD may delay the appropriate diagnosis of BD, so an appropriate investigation of the history of mania is highly relevant in individuals with SUD.

- Some medications may be useful in the management of the comorbidity between BD and SUD, and they vary according to the type of SUD.
- Clinicians should be aware of the risk of electrolyte imbalance when using lithium in individuals with AUD and BD.
- Clinicians should be aware of the liver function and/or liver damage before starting treatment with antiepileptics in individuals with AUD and BD.

11.8 Future Perspectives

The understanding of the relationship between SUD and BD is an ongoing area of research, and there are some future perspectives that can further advance the study of this interface. In regard to research, long-term longitudinal studies tracking individuals with BD and SUD over time can help unravel the potential outcomes and a better comprehension of the possible trajectories. Mechanistic studies focusing on the underlying mechanisms of both conditions can provide valuable insights into the shared etiological factors and neurochemical pathways involved, paving the way for targeted interventions.

As our understanding of the heterogeneity within BD and SUD grows, there is a need for personalized approaches to treatment. Future research should focus on identifying subtypes or phenotypes within this comorbidity spectrum (e.g., using unsupervised ML techniques) and developing personalized treatment algorithms based on individual characteristics, including biomarkers and clinical features. It can lead to more targeted and potentially effective interventions for these individuals. Not only algorithms for treatments at individual-level could be developed but also risk calculators with enough complexity—i.e., more robust models with enough multimodality from multiple sources of data [62]—to predict alternate trajectories outside of a pure BD progression (e.g., BD with SUD comorbidity).

Comorbid SUD in individuals with BD has significant implications for diagnosis, treatment, and prognosis. It can contribute to delayed BD diagnosis, worsen the course of the illness, increase the risk of nonadherence to medication, and raise the likelihood of suicide attempts. Individuals with BD and comorbid SUD also exhibit higher rates of symptoms such as mixed features, psychosis, and aggression. Early and simultaneous management of SUD comorbidity is crucial. Pharmacological treatment options vary depending on the specific SUD, and psychoeducation plays a vital role in providing information about the illnesses, their consequences, and coping strategies. However, more research is needed to determine the most effective psychosocial interventions for individuals with comorbid SUDs and BD. Preventive measures include promoting healthy lifestyles and minimizing the use of alcohol, tobacco, and other drugs.

11.9 Conclusion

Figure 11.1 summarizes the clinical aspects emphasized in this chapter. There is a bidirectional association between BD and SUD. Substance use is an important risk factor for the onset of BD, according to prospective cohorts and ML studies. Since it is a modifiable risk factor, efforts should be made to prevent and treat SUD. Regarding individuals with a high risk of developing BD, prospective cohort studies indicate that the offspring of parents with BD are more likely to develop SUD and that they start substance consumption at an earlier age than control offspring.

At the same time, BD and, particularly, manic symptoms are risk factors for the development of SUD, according to cohort and ML studies. BD also predicts the transition from drug use to drug abuse and from drug abuse to drug dependence. In machine learning models, cannabis, alcohol, and cocaine use were important risk factors preceding BD onset. ML also identified demographic and clinical factors associated with different types of SUD in BD. Given its strong and complex

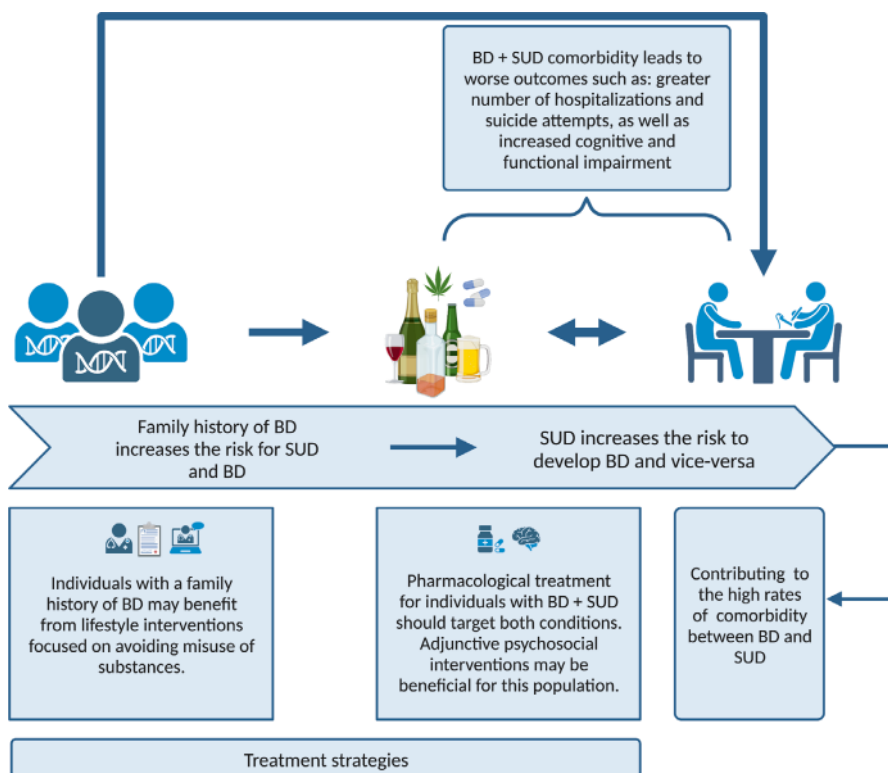


Fig. 11.1 Interplay between bipolar disorder and substance use disorder. There is a bidirectional relationship between BD and SUD that may be built up by a family history of BD. Integrated and preventive treatment strategies are highly recommended

association, it is suggested that BD and SUD share physiological mechanisms, such as impaired decision-making, impulsivity, poor modulation of motivation, and abnormal reward responses.

Regardless of which disorder comes first, the comorbidity rate between BD and SUD is high, and it contributes to a worse clinical progression. Earlier age of onset, a greater number of hospitalizations, greater rates of suicide attempts, and greater cognitive and functional impairments are some of the outcomes seen in individuals with this comorbidity. In order to prevent these outcomes, BD and SUD should always be treated early and intensively.

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Chapter 12

Bipolar Disorder and Clinical Comorbidities



Natalie Palma and Fabiano Alves Gomes

12.1 Introduction

Individuals living with psychiatric illnesses face an increased risk of impaired functionality, poorer indicators of quality of life, and associated medical conditions, ultimately leading to higher mortality compared to the general population [1]. Among the major groups of mental disorders, bipolar disorder (BD) results in a twofold increase in mortality risk compared to the population free of mental disorders, ranking second only to the group of psychotic disorders and ahead of depressive and anxiety disorders [2].

Comorbidity is defined as the presence of two or more clinical entities in the same patient [3]. Nonetheless, it is always necessary to differentiate clinical conditions that present with symptoms similar to bipolar disorder in its various phases, which would be diagnosed as bipolar disorder due to another medical condition, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). In such cases, identifying and appropriately treating the underlying disease results in the remission of mood symptoms.

Bipolar disorder is a chronic, longitudinally monitored illness with a tendency for recurring episodes throughout life. The onset of symptoms commonly occurs in early adulthood, with the first mood episode occurring rarely (less than 5%) after the age of 60 [4]. It is crucial to note that these patients have a higher risk of

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developing clinical conditions associated with the treatment of bipolar disorder itself, in addition to age-related diseases, and the psychiatrist should be competent in recognizing them. Furthermore, the pathophysiology of bipolar disorder may contribute to accelerated aging and an increased incidence of clinical conditions due to allostatic load and neuroprogression phenomena [5]. A therapeutic focus on mood stabilization may lead to the underdiagnosis and undertreatment of associated clinical conditions.

12.2 Main Comorbidities Associated with Bipolar Disorder

Medical conditions that coexist with this mood disorder are mainly associated with the treatment of the disease, although they can also be directly linked to depressive or manic/hypomanic episodes [6]. Clinical comorbidities are common in patients with bipolar disorder, with an average of 3–4 associated health conditions, tending to increase with age. The most common groups of diseases include metabolic syndrome (up to 50%), hypertension (45–49%), cardiovascular disease (9–49%), respiratory problems (4–15%), arthritis (16–21%), endocrine disorders (17–22%), and atopic diseases such as allergic rhinitis and asthma (6–20%) [7]. It is often challenging to determine whether the clinical condition results directly from the side effects of psychotropic drug treatment, from a patient's own pathophysiological mechanisms and lifestyle, or from an interaction between both factors.

Although these comorbidities may be present even in young patients, the incidence of general medical comorbidities tends to increase with age. A Brazilian study with 94 outpatients diagnosed with bipolar disorder type I, with an average age of 50 years, identified systemic arterial hypertension as the most frequent clinical comorbidity, present in almost 30% of the sample, followed by dyslipidemia (22.3%), hypothyroidism (19.1%), and diabetes mellitus (17%) [8].

Even within the mood disorders group, bipolar patients exhibit a higher burden of clinical diseases compared to those with unipolar depression. Moreover, these patients almost entirely receive prescriptions for lithium, anticonvulsants, or atypical antipsychotics, which are known to increase the risk of hypothyroidism, weight gain, and diabetes [9]. This increased burden of clinical diseases in patients with bipolar disorder results in polypharmacy and a reduction in life expectancy by an average of 10 years [7].

12.2.1 Metabolic Diseases

12.2.1.1 Obesity and Overweight

Weight gain is a common issue in bipolar patients, even without the prescription of medications known to be associated with appetite changes [10], and can be a factor associated with the disease, leading to poorer functionality [11]. Obesity, defined as

an excess of fatty tissue in relation to lean body mass, complicates the treatment of these patients [12]. Individuals with bipolar disorder may struggle to maintain a balanced dietary pattern and exercise, predisposing them to weight gain. Conversely, obese individuals may exhibit alterations in the hypothalamic–pituitary–adrenal axis, with increased secretion of leptin and other hormones released by the adipose tissue, affecting normal mood modulation [12].

There is no perfect measure to assess overweight and obesity since the interaction between body mass and fat distribution can vary according to ethnicity and genetics. The body mass index (BMI), calculated by dividing weight in kilograms by height in meter squared (kg/m^2), is a good indicator due to its practicality, although it may be less accurate in older individuals due to the loss of lean mass and decreased weight. A Brazilian study with 255 bipolar outpatients found a prevalence of 33.7% for overweight and 31.4% for obesity in the sample, defined as BMI 25–29.9 and BMI ≥ 30 , respectively. This same study detected an almost twofold higher chance of obese bipolar individuals having a history of suicide attempts. Obesity is also correlated with alcohol use disorders and comorbid anxiety disorders [13].

12.2.1.2 Diabetes

Studies indicate that bipolar disorder patients have a risk of up to three times higher for type 2 diabetes mellitus compared to the population without psychiatric disorders [14]. Various pathways could explain this association between bipolar disorder and type 2 diabetes, involving behavioral, sociodemographic, and biological factors; therefore, the evaluation of our patients should address physical activity practices, dietary patterns, comorbidities with eating disorders, smoking, thyroid diseases, and weight and BMI measures [15].

The use of medications can contribute to this association. Lithium and valproic acid are known to induce weight gain, which can lead to glucose metabolism alterations, in addition to atypical antipsychotics directly associated with the development of metabolic syndrome. However, diabetes is also found at an increased frequency in people with bipolar disorder even before the advent of second-generation antipsychotics and in treatment-naïve patients [14].

The diagnosis of diabetes is confirmed by laboratory testing of altered glucose results using fasting blood glucose, oral glucose tolerance test, or glycated hemoglobin. Repeat testing of abnormal results is necessary for diagnostic confirmation, except when the patient presents unequivocal symptoms of hyperglycemia: polyuria, polydipsia, polyphagia, and weight loss [16]. The presence of type 2 diabetes mellitus concurrent with bipolar disorder is associated with increased morbidity, poorer treatment response, greater chronicity of the disease, and dysfunctionality, contributing to high cardiovascular mortality in these patients. Brain alterations such as reduced hippocampal volume and gray matter reduction are also associated with this comorbidity [17]. Both insulin resistance and the diagnosis of type 2 diabetes mellitus are also associated with a worse response to lithium use [18].

12.2.1.3 Metabolic Syndrome

The growing association found between obesity and an increased risk for cardiovascular events, cancer, and higher mortality led to the creation of the term “metabolic syndrome” to define individuals in this risk group. The syndrome is characterized by a common pathophysiological basis involving insulin resistance, dyslipidemia, hypertension, and central obesity, possibly orchestrated by the latter component [16].

A meta-analysis of 37 studies, with a total of 6983 bipolar patients, found an average prevalence of 37.3% for metabolic syndrome, with the highest rates in those patients using antipsychotics [19]. However, more recent studies have shown that even treatment-naïve bipolar individuals also present an increased risk of metabolic syndrome [20].

12.2.2 Cardiovascular Diseases

Bipolar disorder has been progressively associated with an increased risk of cardiovascular mortality, although this risk is similar to that observed in studies of bipolar depression. Pharmacological treatment contributes to this increased risk, but this correlation was perceived even before the currently available treatments. Inadequate diet, sedentary lifestyle, and smoking are other factors that also favor an increase in cardiovascular risk in this group [21].

The risk of systemic arterial hypertension is increased by 27% for patients with bipolar disorder compared to the general population. Additionally, bipolar disorder is also associated with poorer blood pressure control. Once again, factors such as medication use and a sedentary lifestyle are linked to this increased risk [22].

The increased cardiovascular risk contributes to a reduction of 10–15 years in life expectancy for patients with bipolar disorder compared to the general population [23].

12.2.3 Chronic Pain

People with bipolar disorder are more than twice as likely to experience chronic pain compared to the general population, with a relative risk of 2.14, according to the results of a meta-analysis involving data from 22 cross-sectional studies totaling 171,352 bipolar patients. This same study found a prevalence of 28.9% for chronic pain among bipolar individuals, with the most common forms being generalized pain (23.5%) and migraines (14.2%) [24].

The central processing of pain involves various brain areas in connections that include the thalamus, prefrontal cortex, primary and secondary somatosensory cortices, and anterior cingulate and insular cortices. The medial and lateral pain systems, regulating the affective-emotional and sensory-discriminative aspects of pain, respectively, are altered in patients with schizophrenia and bipolar disorder type 1, indicating a central processing issue in these patients [25].

There is a significant interface between medications for the treatment of chronic pain and mood disorders, but therapeutic options are more limited when it comes to bipolar disorder since dual and tricyclic antidepressants, which have a well-known action for pain, should be avoided. Pregabalin and gabapentin are anticonvulsants considered first-line for the treatment of chronic pain but without a known mood-stabilizing effect. In the therapy of migraines, we have more options, as several anticonvulsants, such as valproate, lamotrigine, and topiramate, as well as atypical antipsychotics like olanzapine and quetiapine, can be used in both pathologies without the risk of mood alterations [26]. Carbamazepine has good potential for the treatment of neuropathic pain, with attention to the risk of weight gain and interaction with other medications [27]. It is important to note that conditions associated with chronic pain are linked to an increased risk of suicide, which should lead to special attention in the elderly population with bipolar disorder [28].

12.2.4 Other Clinical Diseases

The prevalence of respiratory diseases in patients with bipolar disorder is almost twice that of people without mental illnesses, especially chronic obstructive pulmonary disease. There also seems to be an increased incidence of bipolar disorder in patients with asthma, especially those using prednisolone [29].

Data on the increased incidence of cancer diagnoses in people with bipolar disorder are still conflicting, with studies indicating this association and others finding no differences compared to the general population. Recent studies have also pointed to an increased prevalence of Parkinson's disease and viral hepatitis in this population [28].

It should be emphasized that patients with bipolar disorder often do not receive diagnostic investigation or even appropriate treatment for somatic comorbidities, simply due to the psychiatric diagnosis or the presumption of incapacity to adhere to treatment regimens due to mental illness [29].

Regarding the SarsCov-2 virus pandemic that began at the end of 2019, large cohort studies have shown an increased risk of contracting the disease and also higher mortality among patients with mental disorders [30, 31], as well as a higher risk of needing rehabilitation and specialized care after discharge among patients with mood disorders [32].

12.3 Comorbidities Associated with Treatment

Pharmacotherapy is the main strategy for managing mood episodes and remains central in the maintenance treatment of bipolar disorder. Therefore, it is important to be aware of the main clinical implications of the prolonged use of medications, given the chronic nature of the disease. The main side effects associated with mood-stabilizing medications are listed in Table 12.1 [10].

Table 12.1 Side effects of classic mood stabilizers

Neurological
Tremor: lithium
Gastrointestinal
Nausea, vomiting, and diarrhea: lithium, valproate
Metabolic
Weight gain: lithium, valproate
Endocrine
Hypothyroidism: lithium, carbamazepine, valproate
Nephrogenic
Polydipsia, polyuria, and renal failure, lithium
Dermatological
Acne, psoriasis: lithium, lamotrigine
Hair loss: lithium, lamotrigine, valproate
Cognitive
Cognitive decline: lithium, valproate, carbamazepine
Sexual
Decreased sexual desire: lithium
Sexual dysfunction: carbamazepine, valproate
Hepatological
Elevation of transaminases: valproate
Hepatitis: carbamazepine
Hyperammonemia: valproate
Hematological
Serious blood dyscrasias: carbamazepine

Adapted from [10]

12.3.1 Lithium

The first important aspect of lithium use is its interaction with other frequently used medications: thiazide diuretics, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs can increase lithium levels (RISE 2016). Adequate hydration should also be encouraged since dehydration increases the risk of kidney injury and lithium intoxication [33].

In most chronic lithium users, there is a reduction in the ability to concentrate urine, which can lead to interstitial nephropathy [28]. The two main forms of kidney involvement associated with this medication are nephrogenic diabetes insipidus and chronic kidney disease.

Nephrogenic diabetes insipidus results from the inhibition of water reabsorption stimulated by antidiuretic hormone in the collecting ducts due to the direct effect of lithium causing polyuria, dehydration, increased thirst, and polydipsia. If such symptoms appear, it is important to exclude other causes, such as central diabetes insipidus, side effects from the use of anticholinergic medications, and even psychogenic polydipsia. Treatment usually involves the use of diuretics [7].

Chronic kidney disease occurs in 5% of patients using lithium and seems to be more associated with multiple daily doses and blood levels above 0.8 mmol/L than with the duration of treatment. Therefore, monitoring renal function throughout treatment and avoiding supratherapeutic lithium levels are important [7, 33].

The use of lithium is associated with a twofold increased risk of hypothyroidism, which usually appears in the first years of use [33]. About 2% of patients will need levothyroxine, with attention to the fact that treating hypothyroidism can improve bipolar disorder treatment outcomes [7].

Dermatological side effects such as acne and psoriasis are also associated with lithium use, but their preexistence does not constitute a contraindication to the medication. Up to 10% of patients using lithium may experience some degree of alopecia [10].

Despite the possible side effects and special precautions needed, lithium carbonate continues to be a first-line treatment for bipolar disorder, and it is believed that up to 40% of elderly individuals with bipolar disorder may experience symptom remission with lithium monotherapy. Additionally, lithium users have lower rates of dementia, diabetes, stroke, and cancer compared to bipolar individuals using other medications, which may be linked to its anti-inflammatory, antioxidant, endothelial, and intracellular signaling effects inhibiting the GSK3 β pathway [33].

12.3.2 Anticonvulsants

Asymptomatic elevation of liver transaminases can occur in up to 40% of patients using valproic acid, but these changes are generally nonprogressive and do not imply discontinuation of the medication. Severe hepatotoxicity is rare, occurring in 0.01%, and is often potentiated by the combination with other anticonvulsants [10]. A similar effect is observed with the use of carbamazepine. Attention should be given to the induction of liver enzymes caused by carbamazepine, which can alter the metabolism of various other drugs, even reducing its own serum concentration.

Transient leucopenia may occur in up to 10% of patients using carbamazepine, with a reduction of up to 25% in the white blood cell count. However, an improvement is observed even with the continuation of treatment, persisting in only 2% of cases. The elderly are at an increased risk of blood dyscrasias induced by carbamazepine, although severe reactions such as aplastic anemia, agranulocytosis, and thrombocytopenia are rare [10]. An important effect, particularly in chronic users and the elderly, is the reduction in bone mineral density associated with the use of anticonvulsants. Carbamazepine can reduce the levels of vitamins D and K, besides interfering with the intestinal absorption of calcium. Valproic acid can cause bone problems by directly suppressing the activity of osteoblasts and may increase the risk of fractures by inducing cerebellar alterations. Therefore, consideration should be given to annual dosages of vitamin D, calcium, phosphate, and alkaline phosphatase, in addition to supplementation with calcium and vitamin D3 [34].

A recent systematic review found a higher risk of fractures in individuals with bipolar disorder regardless of age, sex, or comorbidities and, curiously, independent of the medications in use (however, the use of benzodiazepines, serotonin reuptake inhibitors, and tricyclic antidepressants are already known to be associated with a higher risk of fractures and are medications sometimes used in the treatment of the disorder) [35]. Elevations in serum ammonia levels without alterations in liver function can frequently occur in patients using valproic acid, but they are asymptomatic in most cases. However, the appearance of tremors, ataxia, confusion, lethargy, and disorientation should alert to the suspicion of hyperammonemic encephalopathy induced by the medication. Confirmation is achieved through an increase in ammonia levels (usually twice the baseline) and a generalized slowing of cerebral electrical activity on the electroencephalogram, promptly leading to a reduction in dose or discontinuation of valproic acid [10]. Older anticonvulsants, such as carbamazepine and valproic acid, are associated with a worse profile of cognitive side effects. On the other hand, oxcarbazepine seems to have a less negative impact on cognition, and lamotrigine has been shown to be free of such effects [34]. Despite the association of lamotrigine with severe skin rash, Stevens–Johnson syndrome, and toxic epidermal necrolysis, the occurrence of dermatological complications is rare if the adjustment is gradual [10].

12.4 Clinical Monitoring

Due to the frequent presence of clinical comorbidities in patients with bipolar disorder, the evaluation of these patients should include physical examination, neurological assessment, and complementary laboratory tests. Neuroimaging is indicated in the presence of neurological signs or symptoms, in the investigation of associated cognitive conditions, and even in the presence of mood episodes with atypical presentations [36].

In the initial assessment of the patient, it is important to gather information about preexisting medical comorbidities, smoking, alcohol use, family history of clinical comorbidities, and cardiovascular risk factors. This investigation also aims to rule out possible contraindications and guide the monitoring of adverse effects in the choice of medication therapies.

Blood pressure, heart rate, waist circumference, and BMI should be checked for all patients before starting treatment, and the following complementary tests are also indicated for everyone: complete blood count, fasting blood glucose, total cholesterol and fractions, and triglycerides. Other complementary tests may be indicated depending on the choice of medication. Anthropometric measurements and blood pressure should be repeated during patient follow-up, being indicated in assessments at 3, 6, and 12 months. In case of changes in measurements or laboratory tests, a general clinical evaluation and a reassessment of the medications in use should be carried out, taking into consideration the risk–benefit of their use and the possibility of switching to other strategies [36].

Table 12.2 Baseline laboratory investigation for patients with bipolar disorder

CBC
Fasting glucose
Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
Platelets
Electrolytes and calcium
Liver enzymes
Serum bilirubin
Prothrombin time and partial thromboplastin time
Urinalysis
Urine toxicology for substance use
Serum creatinine
eGFR
24 h creatinine clearance (if history of renal disease)
Thyroid-stimulating hormone
Electrocardiogram (>40 years or if indicated)
Pregnancy test (if relevant)
Prolactin

CBC complete blood count, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *vLDL* very low-density lipoprotein. Adapted from [36]

The guidelines published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) in 2018 propose, in addition to the complete clinical history and physical examination, an extended laboratory panel for the evaluation of all patients with bipolar disorder (Table 12.2), which includes, in addition to the previously indicated tests, the following: electrolytes and calcium, liver enzymes and bilirubin, prothrombin time and partial thromboplastin time, creatinine and estimated glomerular filtration rate, thyroid-stimulating hormone, electrocardiogram, prolactin, urine analysis, urine toxicology screening, and 24-hour creatinine clearance (in case of a history of kidney disease) [36].

12.5 Conclusion

Patients with bipolar disorder have high rates of clinical comorbidities, especially with cardiovascular and metabolic diseases, resulting in increased mortality compared to the general population. The increase in life expectancy exhibited by humanity as a whole in recent decades, resulting from improvements in sanitary conditions, greater access to health services, and technological advancements, has not been reflected to the same extent in individuals with severe mental disorders [37].

A multi-professional approach and a collaborative care model, in which patients are treated in a chronic disease model, can contribute to reducing the physical and mental burden of bipolar disorder for both bipolar patients and their families [38].

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Chapter 13

Circadian Rhythms in Patients with Bipolar Disorder



Aline Zimmerman, Camila Zimmer, Bruno Braga Montezano,
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13.1 Introduction

Humans have internalized daily cycles of light and dark in the form of circadian rhythms—named after the Latin expression “*circa diem*,” which means “about a day” [1]. The circadian clock synchronizes biological and behavioral processes to the external temporal environment [2], including sleep. Each person presents a different circadian preference, and these preferences are divided into morning and evening types [3]. These types indicate at which time of the day the individual prefers to perform intellectual-heavy or physical activities [4]. Bipolar disorder consists of mood episodes that deviate from the typical behavior of the patient and may have significant changes in activity, energy, and sleep levels. The sleep disturbances these patients may face depend on the accompanying mood episode [1]. Regarding circadian preferences, previous investigations indicate that patients with bipolar disorder prefer the evening [5, 6].

In the literature, associations between bipolar disorders and multiple genes of the molecular circadian clock have been reported [2, 7]. Most of the studies exploring the relationship between circadian rhythm and bipolar disorder are based on cross-sectional designs, which may lead to unclear directionality of the association [6]. In brief, it appears that disruptions in circadian rhythms may be considered an additional state marker of bipolar disorder, which is also a trait of the disorder [2]. In a

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meta-analysis from 2022 with 56 studies, data supported that subjective sleep disorders may predict unipolar depression onset, which illustrates the interplay between mood disorders and disruptions in the circadian rhythm [8]. In addition, a similar pattern was observed in a recent study where circadian phase disturbances preceded mood symptoms in bipolar disorder and major depression [9]. Previous studies have shown that patients with bipolar disorder present with significantly higher rates of abnormal sleep and circadian rhythm disturbance when compared to control samples. It is important to note that these changes in sleep patterns are observed not only in the acute phase of the disorder but also in euthymic periods [10, 11]. Gershon demonstrated in a 2-year follow-up on euthymic patients with bipolar disorder that abnormal sleep duration may accelerate the recurrence of depressive episodes [12].

13.2 Circadian Disruption in Bipolar Disorder

As circadian rhythm disruption has been studied extensively in recent years, new insights into the directionality of the association with bipolar disorder are coming to light. In 2023, a systematic review that included 14 studies on the relationship between sleep disturbance and cognitive impairment in patients with mood disorders found preliminary evidence suggesting a significant association between the two after controlling the analysis for demographic and clinical covariates. In contrast, the association was not significant in healthy individuals [13]. This is an example of an interplay between circadian rhythm and bipolar disorder in the clinical context. In the following subsections, we will address the role of disruptions in the circadian rhythm in the onset and trajectory of bipolar disorder, as well as present evidence related to the circadian rhythm of patients diagnosed with bipolar disorder.

13.2.1 Circadian Disruption as Bipolar Disorder Predictor

Recent research underscores the significance of circadian rhythm disturbances in predicting bipolar disorder onset. In 2022, Xu aimed to build a predictive model for major depression to bipolar disorder conversion. The model consisted of clinical and genetic factors and was trained based on 5-year follow-up data. The best-performing model was based on clinical characteristics—i.e., age of first onset, gender, previous suicide attempts, and number of hospitalizations—and single nucleotide polymorphisms (SNPs) of the circadian rhythm genes, achieving an area under the receiver operating characteristic (ROC) curve of 78% [14]. A systematic review that aimed to evaluate sleep and circadian disorders as risk factors for bipolar disorder [15], based on 30 articles ($n = 7451$), found that these disturbances are

common in people at risk for bipolar disorder, in addition to high cortisol levels at different times of the day. However, the pathophysiology is unclear, and the included studies presented high heterogeneity in study design and population definition.

In a 2021 meta-analysis, the authors aimed to describe sleep alterations among the offspring of parents with bipolar disorder compared to the offspring of controls. The study included ten studies, of which four were eligible for meta-analysis. The findings suggest that the offspring of parents with bipolar disorder have greater daytime sleepiness, and the overall studies indicate that the at-risk population also has an increased likelihood of experiencing adverse sleep patterns [16].

In 2023, Cordeiro et al. aimed to identify triggers of acute mood episodes in bipolar disorder in a systematic literature review. Based on a total of 108 studies, pharmacotherapy presented to be one of the most studied triggers of manic or hypomanic episodes, especially antidepressants. It is interesting to note that the review also identified other triggers for mania, such as the use of energy drinks [17]—which may affect sleep patterns and cause insomnia [18]. Regarding depressive relapses in bipolar disorder, decreased sleep was found as a potential trigger, along with stressful life events and fasting [17].

In terms of sleep characteristics of subjects at a high risk of bipolar disorder or presenting an early onset of the disorder, Scott et al. published a review to explore sleep patterns and circadian rhythm and describe these factors as potential risk markers. Out of 76 studies in the systematic review, 35 were included in the meta-analysis. Self-rated and actigraphy data showed a greater preference for eveningness and increased dysregulation of social rhythms in subjects at risk for bipolar disorder or presenting with full-fledged bipolar disorder. Even though results should be interpreted considering study heterogeneity, preexisting circadian rhythm disturbances were associated with a 40% increase in bipolar disorder onset risk. At-risk individuals and subjects with full-threshold bipolar disorder also presented with longer total sleep time, taking into account that psychopathology manifestation and use of psychotropic medications moderated the effect size [19].

In the past few years, the role of disturbed sleep as an early marker for bipolar disorder has been investigated. A systematic review that included three cohort studies found that sleep disturbances frequently precede bipolar disorder by several years and increase the long-term risk for mood disorders in general. These circadian rhythm problems usually emerge in early adolescence and remain chronically present in at-high-risk subjects [20]. A more recent systematic review from 2019 assessed the relationship between sleep alterations and full-blown bipolar disorder onset—general onset and specific manic or depressive episode onset. Based on the 16 studies included, the results indicate that sleep disturbances typically appear 1 year prior to bipolar disorder onset, usually during childhood and adolescence. A decreased need for sleep often precedes a manic episode, and hypersomnia may predict bipolar depression. Insomnia may anticipate both manic and depressive episodes [21].

These insights may assist in the comprehension that alterations in circadian rhythm and sleep disturbances, in general, can function as both risk markers for bipolar disorder and as a prodromal symptom of the disease. Furthermore, patients with bipolar disorder and subjects at risk may present specific sleep profiles in comparison to healthy subjects. In the subsequent chapter, we examine the overlap between bipolar disorder and sleep and how the disorder trajectory may affect the circadian rhythm health.

13.2.2 Circadian Disruption Influenced by Bipolar Disorder

In 2015, Ng et al. aimed to compare sleep–wake patterns in subjects with inter-episode bipolar disorder against healthy controls and individuals with primary insomnia using meta-analysis. Twenty-one studies were eligible for the review, adding up to 24 sleep-related variables. The analyses demonstrated that individuals with inter-episode bipolar disorder present with worse sleep patterns when compared to controls in most variables and comparable to subjects with primary insomnia. Sleep onset latency, wake after sleep onset, and variability in sleep–wake patterns—namely total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency—showed very low heterogeneity and presented the most consistent evidence for impairment in inter-episode bipolar disorder [22].

In 2016, Stubbs aimed to describe the prevalence and predictors of obstructive sleep apnea in major depression, bipolar disorder, and schizophrenia. The systematic review included 12 articles and found that 24.5% of patients with bipolar disorder present with obstructive sleep apnea, while the prevalence for obstructive sleep apnea are 35.3% and 15.4% for major depression and schizophrenia, respectively. The study found age and BMI as relevant predictors for obstructive sleep apnea in samples with serious mental illness [23].

Meyer aimed to describe the sleep-circadian alterations in remitted schizophrenia and compare them with those in inter-episode bipolar disorder. According to the 30 included studies ($n = 1770$), both patients with schizophrenia and bipolar disorder had significantly longer total sleep time, longer time in bed, greater sleep latency, and reduced motor activity in comparison to controls [12]. In another systematic review, Melo aimed to define current evidence regarding chronotype and circadian rhythm patterns in patients with bipolar disorder. They found that depression was more frequently associated with circadian rhythm alterations than euthymic periods, and few studies evaluated mania directly, but those that did showed irregular rhythms [6]. In a similar idea, based on 30 studies with more than 6000 participants in total, Meyrel found that individuals with bipolar disorder exhibited greater

eveningness, lower flexibility of rhythms, lower amplitude of rhythms, and more disturbances across a range of circadian rest/activity rhythms [5].

In the scope of actigraphy-based studies, De Crescenzo et al. aggregated data from 13 studies in a meta-analysis that aimed to understand the role of actigraphy as an objective measure of sleep-related patterns in bipolar disorder. The authors found a decrease in activity mean and an altered pattern of sleep in patients with bipolar disorder. Furthermore, the findings suggest that the sleep signature observed in the studies might be generalized to the whole bipolar spectrum, which comprises manic, depressive, and euthymic phases [24].

By looking at the onset of the disease, studies such as that by Dondé can shed light on the panorama of sleep disturbances in the early clinical stages—considered the clinical ultra-high-risk and first episodes of psychotic and bipolar disorders. Thirteen studies compared sleep measures between subjects with an early clinical stage and controls. The clinical group presented poorer sleep quality, shorter total sleep time, longer sleep onset latency, longer wake duration after sleep onset, and lower sleep efficiency than controls. Based on meta-regression analysis, the study demonstrated that age and antipsychotic status may have a significant effect on subjective sleep measures. No differences in sleep parameters in electroencephalography (EEG) were observed [25].

Considering that understanding the presentation of circadian rhythm and sleep in patients with bipolar disorder in remission is essential, Geoffroy et al. carried out a meta-analysis of studies using actigraphy for sleep monitoring in remitted bipolar disorder. Nine studies met eligibility criteria, and the results showed significant differences in sleep latency, sleep duration, wake after sleep onset, and sleep efficiency between remitted bipolar disorder cases and controls—with poorer parameters for the clinical group [26].

Previous studies investigated the effect of different substances on the circadian rhythm. Lithium is widely used for bipolar disorder treatment [27]. Xu et al. published a meta-analysis that included four observational studies and one experimental study aiming to review the effect of lithium on circadian rhythm in patients with bipolar disorder. The results suggest a potential association between lithium and a shift toward morningness, but the pattern should be further validated [28]. Frigerio aimed to examine whether caffeine intake or withdrawal may impact the natural course of bipolar disorder regarding clinical outcomes—including the onset of mood symptoms. The authors observed that acute increases in caffeine consumption may precede manic symptoms. The direct stimulant effect of caffeine on sleep or its effect on the metabolism of lithium or other medications may explain this phenomenon. However, caffeine intake could also be a sign that a manic relapse is starting [29].

13.3 Biological Mechanisms

13.3.1 Genetic and Epigenetic

Studies have identified specific clock genes, particularly the *CLOCK* gene, as critical elements influencing bipolar disorder susceptibility and its clinical progression. The *CLOCK* gene regulates other circadian-related genes, and variations within these genes have been linked to disrupted circadian rhythms [30].

Takaesu et al. focused on the association between clock genes and bipolar disorder in his review of the literature and found several studies that linked the *CLOCK* gene to bipolar disorder susceptibility [31]. Also, Benedetti et al. reported that a single nucleotide polymorphism (SNP) in a specific region of *CLOCK* is associated with a higher recurrence of mood episodes in bipolar disorder patients [30]. Further research suggests that this SNP is also linked to a delayed sleep–wake phase and an eveningness chronotype [32]. Findings are not universally consistent, as Kishi et al. found no significant association between *CLOCK* and bipolar disorder, suggesting that *CLOCK* may not play a primary role in bipolar disorder pathophysiology [33].

Gene–environment interactions also significantly affect circadian rhythm regulation in the disorder. Zeitgebers are external cues that help an individual’s internal rhythms align with their environmental ones. While light exposure, the primary zeitgeber, helps align circadian rhythms with the environment, individuals with bipolar disorder may exhibit hypersensitivity to light, particularly in the morning, which can destabilize mood [34]. Other environmental cues, such as social interactions and physical activity, also impact circadian alignment, with disruptions in these rhythms linked to precipitating a manic or depressive episode [35, 36]. Figure 13.1 illustrates the interaction between genetic predispositions and environmental cues in circadian rhythms in bipolar disorder.

13.3.2 Neurobiological

Neurotransmitters important for mood regulation, such as serotonin, dopamine, and norepinephrine, present circadian fluctuations impacting patients with bipolar disorder. These neurotransmitters follow circadian patterns in their levels, release, and synthesis-related enzymes, suggesting that these entire signaling systems are regulated by the body’s internal clock [37].

Serotonin is particularly significant due to its role as a precursor to melatonin, a hormone essential for regulating sleep–wake cycles. Research shows that disruptions in serotonin pathways, such as variations in serotonin transporter genes, are linked to sleep disturbances in bipolar disorder [38]. These disruptions may

exacerbate mood instability, as low serotonin levels reduce the body's capacity to stabilize mood following sleep deprivation. Benedetti et al. found that bipolar disorder patients with specific serotonin-linked gene polymorphisms experienced poorer mood regulation after sleep deprivation, highlighting serotonin's key role in maintaining mood stability under disrupted sleep conditions [39]. This serotonergic dysregulation likely worsens emotional regulation challenges in bipolar disorder, with melatonin synthesis playing a crucial role in mediating these effects.

13.3.3 *Endocrine*

As mentioned, the endocrine system, responsible for hormonal balance, influences mood and energy, with hormones such as cortisol and melatonin being tied to the circadian rhythm to reach homeostasis. The primary hormone responsible for regulating sleep–wake cycles is melatonin. Commands from the hypothalamus's suprachiasmatic nucleus (SCN), which depend on circadian signals, secrete melatonin. Because of that, disruptions in circadian rhythms can impair melatonin secretion, leading to sleep disturbances and abnormalities in melatonin secretion commonly observed in bipolar disorder [40, 41].

Mood states may also influence variations in the quantity and timing of melatonin secretion. Research has shown that depressive and euthymic states are associated with a delayed peak and reduced melatonin levels [42], while in manic states there is an earlier peak and a higher level of melatonin secretion [41]. Research examining melatonin levels across these mood phases in individuals with bipolar disorder found that melatonin levels were consistently lower in bipolar patients than in healthy controls, regardless of mood state. This suggests that low melatonin secretion may serve as a characteristic marker of bipolar disorder, rather than changing with mood states [43]. Figure 13.1 illustrates the variation in melatonin levels across the circadian rhythm, comparing healthy controls with bipolar patients.

The other hormone closely tied to circadian rhythms is cortisol, released as a stress response. Research shows that bipolar disorder patients often experience disruptions in cortisol [6]. A study by Girshkin et al. found that bipolar disorder patients displayed higher cortisol levels at waking and heightened responses during stressful situations, compared to those with schizophrenia, though not differing significantly from healthy controls. Also, these alterations were associated with specific variables across disorders: in bipolar disorder, lower cortisol levels at waking were related to a longer illness duration [44]. Despite these findings, studies have yet to consistently demonstrate clear connections between cortisol levels and mood symptoms in bipolar disorder [45].

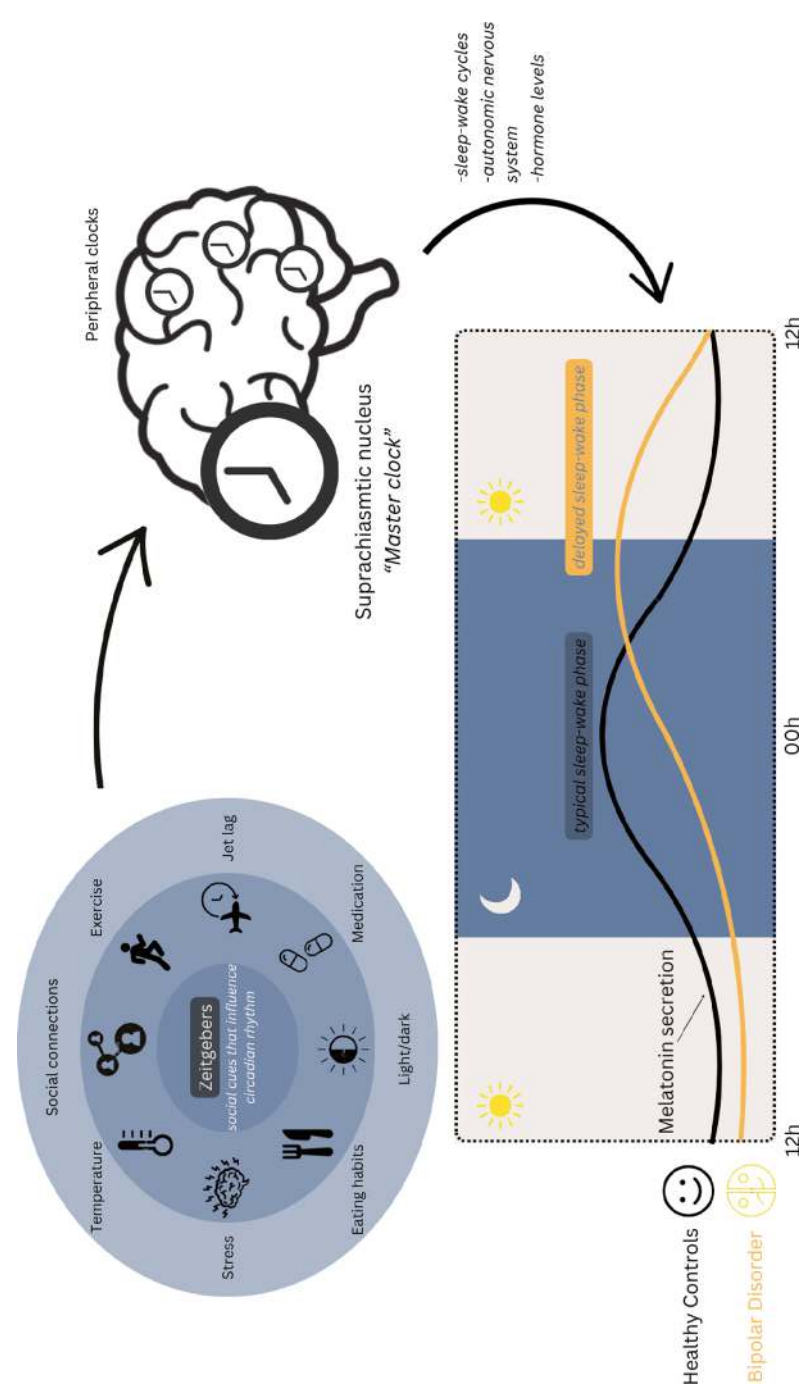


Fig. 13.1 The interaction between zeitgebers, genetic predisposition, and circadian rhythms, highlighting how external time cues and genetic factors influence sleep-wake patterns in bipolar disorder

13.4 Actigraphy/Digital Phenotyping

The constant presence of smartphones and wearables in daily life offers a path to revolutionize psychological practice, providing an opportunity to refine diagnostic processes, identify mood episodes earlier and with greater precision, and deliver more targeted treatment. More specifically, digital phenotyping is an approach that uses digital tools to objectively measure health aspects such as mood, sleep, and activity—essential aspects for understanding and managing bipolar disorder [46]. By passively collecting continuous data through actigraphy, digital phenotyping can create personalized digital signatures for bipolar and other psychological disorders, providing insights that guide more effective interventions.

13.4.1 *Sleep–Wake Patterns*

Actigraphy studies show significant differences in sleep–wake patterns between bipolar disorder patients and controls across various mood states, indicating that individuals at risk for bipolar disorder exhibit a lower relative amplitude of the rest–activity cycle and more sleep irregularity than controls [22]. Also, Faedda et al. found that bipolar patients generally display lower activity levels and longer sleep durations, take longer to fall asleep, and spend more time awake during the night, all contributing to a more variable sleep–wake pattern with greater intradaily variability and lower interdaily stability [47].

As expected, manic episodes are typically associated with reduced total sleep time and more variable sleep onset and offset, leading to hyperactivity and decreased sleep need. In contrast, depressive episodes show patterns of prolonged sleep duration, increased daytime sleepiness, and delayed circadian rhythms, with greater variability in mean activity levels. In a study with 260 patients, circadian disturbances were more frequent in depressive states than in euthymia or in comparison to controls [48].

Additionally, studies found variability within bipolar disorder in sleep parameters like total sleep time and wakefulness after sleep onset, even though these measures did not differ significantly from controls [49]. Geoffrey et al. demonstrated that bipolar disorder is linked to greater interdaily stability [50], and Stanislaus et al. further reported that bipolar patients experience greater daily variability in total sleep time and shorter sleep durations during specific periods compared to healthy controls [51]. In younger bipolar patients, one study found no eveningness preference in children, though it is present in adolescents with BD [52].

13.4.2 Activity Levels and Energy Expenditure

Studies using actigraphy also consistently show that individuals with bipolar disorder have distinctive patterns in activity levels and energy expenditure, marked by variability and instability in circadian rhythms. Four studies involving 105 patients confirmed that bipolar patients display less stable and more variable circadian activity patterns, even during euthymia, highlighting ongoing circadian rhythm disruptions in this population, while four other studies also indicate a smaller amplitude and alterations in mean activity levels in bipolar disorder [6].

Monassian et al. observed that bipolar disorder patients in manic states exhibit higher levels of motor activity when exploring new environments, a behavior that reflects heightened energy and reduced inhibition of mania [53]. Krane-Gartiser's findings further reveal that bipolar disorder patients in both manic and depressive episodes show lower activity in the morning compared to controls. However, this difference dissipates in the evening, suggesting a disrupted rhythm in daily activity levels [54].

Additionally, mania and mixed states are associated with an advanced acrophase—where peak activity occurs earlier in the day—and reduced daily activity compared to controls, showing a shift in the timing and intensity of activity from healthy patterns [55]. There is also evidence suggesting that greater severity of manic symptoms correlates with less robust locomotor rhythms, demonstrating a relationship between symptom intensity and circadian rhythm disruption [56].

13.4.3 Social Interaction

Social rhythm activities, such as communication frequency and location-based social engagement, are crucial markers of mood stability in bipolar disorder, reflecting shifts in emotional well-being and the regulation of social behavior [57].

Beiwinkel et al. used the Social Information Monitoring for Patients with Bipolar Affective Disorder (SIMBA) system to assess social activity through objective data from smartphone sensors and subjective self-reports of mood symptoms over 12 months. Findings indicated that social communication patterns could reflect mood states. For example, a decline in social communication, such as fewer outgoing text messages, was associated with an increase in depressive symptoms. On the other hand, increased social communication was linked to higher levels of clinical manic symptoms, suggesting that manic episodes may involve heightened social engagement [58].

Social activity patterns, including metrics like communication frequency, can also serve as indicators of rhythmicity—a marker of stability in bipolar disorder. Disturbances in these rhythms may signal an increased risk of mood episodes [59].

13.5 Effective Management of Bipolar Disorder

13.5.1 *Psychosocial Interventions for Circadian Rhythm Regulation*

Cognitive and behavioral interventions addressing sleep aspects and irregular circadian rhythms have shown positive results, indicating that restoring these patterns can effectively manage bipolar disorder. Among these approaches, interpersonal and social rhythm therapy (IPSRT) emphasizes stabilizing circadian rhythms, psychoeducation, and resolving conflicts in interpersonal relationships as targets in bipolar treatment. This approach provides patients with tools to monitor daily activities affecting circadian rhythm and social contacts and activities throughout the day. Clinical trials evaluating the effectiveness of IPSRT have shown positive impacts on reducing depressive and manic symptoms in this population [60]. Additionally, it has reduced recovery time after mood episodes, increased the likelihood of achieving stability [61], and extended periods without new affective episodes [62].

Another approach focuses on exposing patients to sunlight as part of treating circadian rhythm disturbances in bipolar patients [63]. Sunlight serves as the primary marker of biological rhythm, ensuring the proper functioning of all other biological processes. To investigate the effects of light exposure on symptoms of bipolar depression, a study divided adults with this condition into two groups. One group received treatment with bright white light at 7000 lux, while the other received placebo red light at 50 lux. After 6 weeks of study, both groups showed improved sleep quality, but only the group treated with bright white light had greater remission of depressive symptoms (68.2% vs. 22.2%).

Conversely, for bipolar patients in a manic state, the treatment adopts an opposite approach. Instead of light exposure, it proposes blocking blue light through glasses, simulating a “virtual darkness” [64]. This approach aims to mitigate melatonin suppression, aiming to improve both insomnia and bipolar disorder symptoms [65]. Two randomized clinical trials investigated the effects of blue light-blocking glasses on manic patients. Compared to the placebo group using clear glasses, participants who received blue light-blocking glasses showed significant improvements in sleep, with fewer interruptions during the night [66]. Additionally, there was a reduction in manic symptoms assessed by the Young Mania Rating Scale (YMRS) [67].

Similarly, cognitive behavioral therapy for insomnia in bipolar disorder (CBTI-BD) has also proven to be a promising approach to reducing manic symptoms. CBTI-BD includes components of the therapies mentioned above, such as increasing and decreasing light exposure, regular activity habits, and relaxation practices [68]. Additionally, it aims to restructure distorted thought patterns regarding sleep and provide education on sleep hygiene. A comparative study between eight sessions of CBTI-BP and psychoeducation revealed that CBTI-BP reduced relapse rates of mood episodes and significantly improved the severity of insomnia [68].

Overall, effective management of bipolar disorder benefits from regulating circadian rhythm through psychosocial approaches. These interventions not only improve patients' quality of life but also demonstrate significant impacts on extending periods of remission and reducing the incidence of mood episodes. This emphasizes the importance of adopting and adapting treatments that directly address biological rhythms, considering their interactions with the psychosocial functioning of individuals with bipolar disorder.

13.5.2 Pharmacotherapy for Circadian Disruptions in Bipolar Disorder

In bipolar patients, sleep disturbances are often observed and are associated with potential impairment in the release of melatonin, which is why agomelatine, an agonist of melatonin receptors, MT1 and MT2 receptors, has been tested as an adjunct treatment in bipolar 1 disorder. The study included patients in a depressive episode: fourteen on lithium treatment and seven on valproate. They received agomelatine as an open-label addition to their standard treatment, at a dose of 25 mg/day, for at least 6 weeks, followed by an option for extension of up to an additional 46 weeks. The results demonstrated that nearly half of the participants responded positively in the first weeks of treatment, and over 80% showed significant improvement on the Hamilton Depression Rating Scale (HAM-D) by the end of the study. However, over a year, one participant experienced a manic episode that was associated with the treatment [69].

Another study compared the efficacy of agomelatine versus placebo as an adjunct to lithium or valproate in bipolar participants in a depressive episode. Participants were randomized to receive agomelatine ($n = 172$) or placebo ($n = 172$) over 52 weeks. However, in contrast to the previous result, this study did not reveal significant differences in symptom improvement between the groups at any stage of the treatment, suggesting that agomelatine was not superior to placebo for bipolar depression treatment [70]. Finally, ramelteon, which also acts as a melatonin agonist, was investigated as an adjunct treatment in a randomized clinical trial. Participants were required to be stable for more than 7 weeks and were randomized to receive 0.1 mg ($n = 164$), 0.4 mg ($n = 160$), or 0.8 mg of ramelteon ($n = 154$) or placebo ($n = 164$). Similar to the study mentioned above, participants showed no significant differences in treatment compared to placebo [71].

The impact of lithium on the circadian rhythm of bipolar patients has also been explored. Studies in animals and humans have shown that lithium can delay or prolong the biological clock [72]. Similarly, a systematic review pooling results from 95 studies demonstrated that lithium also affects the amplitude of activity rhythms and acts on the retinal–hypothalamic–pineal pathway, influencing sleep regulation [73]. Lithium may affect the circadian rhythm through the inhibition of glycogen synthase kinase 3 beta (GSK3B) protein [74]. This molecule plays a vital role in the cellular clock, regulating body rhythms such as the sleep–wake cycle [74]. The

OPHYMUM multicenter study conducted in France compared sleep patterns in 525 stabilized outpatient patients who were either on lithium treatment or not. Those on lithium treatment ($n = 149$) showed better sleep quality and duration compared to those not using lithium ($n = 376$), indicating that the medication may favor circadian rhythm regulation [75].

In general, these findings suggest that while melatonin and its agonists may offer some benefits in treating sleep disturbances associated with bipolar disorder, lithium remains a valuable option due to its positive impact on circadian regulation and sleep quality. More studies are needed to better understand the complex interactions between pharmacological treatments and circadian regulation in bipolar patients.

13.5.3 Assessing Sleep in Bipolar Disorder: Screening and Tools

The high prevalence of sleep and circadian rhythm disorders in bipolar patients, coupled with their bidirectional relationship with mood episodes, highlights the need to prevent and treat these symptoms to reduce episode recurrence. This emphasizes the importance of regular screening using validated scales and tools to assess sleep disorders and sleep hygiene, providing crucial guidance for more effective treatment [76].

In 1989, Buysse et al. developed the Pittsburgh Sleep Quality Index (PSQI), which assesses subjective sleep quality and possible disturbances [77]. The questionnaire consists of questions about quality, latency, duration, efficiency, sleep disturbances, medication use, and daytime dysfunctions. Similarly, the Insomnia Severity Index (ISI) can also be used to investigate sleep problems. The scale comprises questions similar to the PSQI, differing mainly in the reduced number of questions [78]. Both scales are accurate in identifying cases and non-cases according to the international classification of diseases, 10th revision (ICD-10) criteria [79].

However, few scales have been designed to measure sleep specifically in mental health disorder settings. The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was designed to assess biological rhythms in the clinical setting, specifically regarding patients with bipolar disorders. The BRIAN evaluates sleep quality and clinically prevalent rhythm disturbances by considering four domains: sleep, activities, social rhythm, and eating pattern. This semi-structured scale is able to discriminate between euthymic bipolar subjects and healthy controls in all four domains [80].

In addition to assessing sleep problems, researchers have also developed scales aimed at measuring behavioral aspects that may lead to poor sleep quality. The sleep hygiene index consists of questions such as “Within 4 hours of going to bed, do you use caffeine or other stimulating substances?” or “Do you use the bed for anything other than sleeping or sexual activity?” These questions can be used both for screening for poor sleep habits and as targets for intervention. A large study investigated the impact of sleep hygiene on daytime sleepiness, which was assessed using the

Epworth Sleepiness Scale, and sleep quality, which was assessed using the PSQI. The study, involving over 600 participants, confirmed the relationship between poor sleep hygiene, poor sleep quality, and perception of daytime sleepiness, indicating that interventions in this direction may improve sleep and regulate the circadian cycle in people with bipolar disorder [81].

In conclusion, integrating regular screening for sleep disorders and poor sleep hygiene into the treatment protocols for bipolar patients can provide significant benefits. These screenings facilitate early identification and intervention, potentially reducing the recurrence of mood episodes and improving the overall quality of life. Additionally, such interventions may help regulate the circadian cycle, further enhancing the management of bipolar disorder.

13.6 Conclusion

This chapter reveals the close relationship between circadian rhythm and bipolar disorder. Disruptions in circadian rhythms and sleep patterns are strongly associated with the occurrence and recurrence of mood episodes, acting as both a risk marker and a prodromal symptom. A network of genetic, neurobiological, endocrine, and environmental factors mediates this relationship, which can be seen in Fig. 13.1.

Genetic factors play a critical role in this dynamic, with circadian rhythm-regulating genes, such as *CLOCK*, significantly impacting the susceptibility to bipolar disorder. These genes influence standard sleep patterns and mood stability. The effects of these genetic factors are compounded by neurobiological mechanisms, where circadian dysregulation affects the rhythmic oscillation of critical neurotransmitters, including serotonin, dopamine, and norepinephrine, further exacerbating mood dysregulation. Additionally, alterations in hormonal patterns, notably cortisol and melatonin, observed in bipolar disorder patients indicate endocrine dysregulation that aggravates sleep disturbances and, consequently, mood instability. Environmental cues or zeitgebers further impact circadian alignment, with disruptions in these cues often triggering or worsening mood episodes.

In light of these findings, recent studies have revealed significant differences in sleep–wake patterns, activity levels, and social interactions between bipolar patients and healthy controls, depending on the mood state. These differences persist even during euthymia, suggesting a continuous circadian dysfunction that may contribute to the vulnerability to mood episodes. Digital phenotyping, through actigraphy, provides a valuable tool for capturing these sleep, activity, and social patterns, providing a detailed perspective on circadian disturbances in bipolar disorder patients.

Given these persistent circadian disruptions, psychosocial interventions, such as IPSRT and CBTI-BD, have demonstrated efficacy in stabilizing circadian rhythms and reducing the severity of mood episodes. Light-based therapies, such as bright light exposure for bipolar depression and blue light blocking for mania, complement these approaches by managing circadian dysfunction. In pharmacotherapy,

lithium is notable for its dual role in regulating circadian rhythms and stabilizing mood, while melatonin agonists, such as agomelatine and ramelteon, have yielded mixed results.

Clinically, a comprehensive approach to managing bipolar disorder is crucial, including regular monitoring of circadian rhythms. Tools like the PSQI, the ISI, and the BRIAN are essential for identifying sleep disturbances and inadequate sleep habits. Integrating these tools into clinical practice allows for early detection of circadian dysfunctions, facilitating timely interventions to prevent the recurrence of mood episodes and improve patient outcomes. Thus, bipolar disorder management should focus on circadian regulation as a critical target, promoting long-term stability and improved quality of life.

13.7 Future Perspectives

Advancing research in chronobiology is crucial for deepening our understanding of the interplay between circadian rhythms and bipolar disorder. Future studies should focus on identifying specific biomarkers of circadian dysfunction in bipolar patients, which could inform more personalized treatment approaches. Digital health interventions, such as mobile apps, offer promising tools for real-time monitoring and management of circadian disruptions. Furthermore, digital phenotyping can provide data on sleep–wake patterns and activity levels, allowing early detection and management of social rhythms’ dysregulation.

Moreover, integrating chronotherapy and environmental interventions into the management of bipolar disorder should be a key focus of future research and clinical practice. Chronotherapy, which involves interventions such as light exposure and pharmacological treatments, can directly target the circadian disruptions commonly observed in bipolar disorder patients. Future studies must refine these interventions and establish standardized protocols that maximize therapeutic outcomes.

Additionally, environmental interventions should be further explored as potential adjunctive therapies in bipolar disorder management. Encouraging regular sleep–wake cycles, optimizing light exposure, and creating environments that promote circadian alignment could significantly enhance mood stability and reduce the recurrence of mood episodes. Further studies in this direction could lead to more personalized and comprehensive treatment strategies.

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Part II

Biological Underpinnings

Chapter 14

Blood Biomarkers in Bipolar Disorder



Ning Olivia Zhao, Sarah Chiang, Rohit Jha, and Gabriel Rodrigo Fries

14.1 Introduction

Bipolar disorder (BD) is a severe mood disorder that heterogeneously affects more than 1–3% of the world's population and is associated with high clinical morbidity and mortality [1]. Unlike some medical conditions in which the underlying mechanisms are well-understood and there are specific biomarkers or tests that can aid in diagnosis, the diagnosis of BD remains purely clinically based on behavioral and psychological assessments. Additionally, BD is often comorbid with other psychiatric disorders such as attention-deficit/hyperactivity disorder, autism, borderline personality disorder, and substance use disorders, making identifying and correctly diagnosing BD particularly difficult [2–4]. For this reason, the investigation of biomarkers in BD is an area of increasing focus and importance as it has the potential to aid in diagnosing and distinguishing mood phases in BD. In particular, blood and serum biomarkers are of importance as they would provide a minimally invasive and cost-effective method of diagnosis. This chapter will delve into current research on the main classes of blood biomarkers in BD, their limitations, and future directions and applications of the field.

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14.2 Neurotrophic Factors

Among the most studied BD biomarkers are neurotrophic factors. In particular, the most replicated finding is the decreased serum levels of brain-derived neurotrophic factor (BDNF) [5] in individuals with BD. In its mature form, BDNF is a polypeptide that plays an essential role in neurogenesis and neuroplasticity [5] and is detected throughout the brain, especially in the hippocampus and cerebral cortex [6]. Multiple meta-analyses have shown that decreased peripheral BDNF levels can be a marker of disease activity [7–9]. Studies also agree that circulating BDNF levels are more prominently decreased in acute patients compared to euthymic patients [7, 8], with evidence that BDNF is negatively correlated with disease progression and severity [10]. In particular, a study demonstrated that variations in serum BDNF levels can distinguish between individuals diagnosed with BD for under 3 years and those diagnosed for over a decade [11]. Studies have shown that blood BDNF levels normalize after appropriate treatment of acute mania [12], with evidence that plasma BDNF levels are higher in patients who have an excellent response to lithium compared to patients refractory to treatment [13]. Interestingly, a recent systematic review found that psychotherapy can also increase BDNF levels in individuals with BD, further indicating its potential as a biomarker for therapeutic efficacy [14].

Other neurotrophic factors have not been as widely analyzed compared to BDNF, but studies have found associations between other factors and BD. In particular, insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2, and nerve growth factor (NGF) have all been associated with the pathophysiology of BD, with evidence that the administration of lithium can impact their concentrations [15, 16]. IGF-1 has diverse metabolic functions throughout the body and within the brain, including aiding in neurogenesis, impacting central nervous system (CNS) plasticity, and enhancing cellular viability [17, 18]. High serum IGF-1 levels have been reported in BD and major depressive disorder [19]. One possible explanation is that decreased IGF-1 expression disrupts neuroplasticity in regions of the brain responsible for emotional and cognitive processes. Therefore, increased systemic levels of IGF-1 in patients with mood disorders could be considered a compensatory mechanism in response to insufficient IGF-1 levels in the brain [20]. Other factors such as plasma levels of VEGF were shown to be increased in manic and depressive phases [21], whereas FGF-2 and NGF were found to be significantly higher during mania compared to controls [22]. VEGF and FGF-2 are considered angiogenic factors that play important roles in vascular development throughout the body and the central nervous system (CNS) [23]. In particular, VEGF has been shown to induce blood-brain barrier (BBB) breakdown and allow immune cell infiltration into the brain [24]. A recent study showed that VEGF and FGF-2 may be potential biomarkers of BD in children and adolescents with autism spectrum disorder [25]. In contrast to IGF-1, VEGF, and FGF-2, NGF levels have been found to be lower in mania and negatively correlated with the severity of manic episodes [26]. NGF is important for neuronal survival by protecting sympathetic and cholinergic neurons from degeneration, in addition to

also playing a role in learning and memory [27, 28]. Studies of NGF levels in BD remain limited [29], but one study showed that individuals with BD had lower NGF levels compared to controls and found a negative correlation between NGF levels and mania severity [26]. Interestingly, another study showed that elevated levels of NGF might be a useful biomarker for detecting conversion to BD in women with major depressive disorder [30]. Overall, neurotrophic factors continue to show significant potential as biomarkers for BD, in addition to enhancing our comprehension of its pathophysiology.

14.3 Inflammatory Markers

Multiple studies have suggested that inflammation contributes to mood disturbances in BD. At the CNS level, elevated cytokines could disrupt neural circuits and ultimately affect mood regulation [31]. The role of inflammation in BD pathophysiology and progression was initially proposed due to the hypothesis that lithium helps stabilize mood by modulating the immune system [32]. Research has since shown that inflammatory pathways are activated in both the manic and depressive phases of BD, as indicated by increased levels of acute-phase proteins and pro-inflammatory cytokines [33–35]. In particular, pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α), soluble TNF receptor type 1 (sTNFR1), soluble interleukin-6 (IL-6) receptor (sIL-6R), C-reactive protein (CRP), and interleukin-6 (IL-6) have all been found to be elevated during manic and depressive episodes of BD [36, 37]. A recent meta-analysis showed that IL-6 is elevated in BD depression, mania, and euthymia, indicating its potential as a trait marker for BD [38]. Interestingly, this study also found that CRP (a widely accepted inflammatory marker used in clinical settings) and TNF- α levels were increased in mania and major depressive states but not during euthymia, indicating that they could be regarded as state markers [38]. Inflammatory markers could also help distinguish between BD and unipolar mania. Unipolar mania is no longer recognized in the DSM-5 but has been described as a form of BD with recurrent manic and hypomanic episodes without depressive phases [39]. A recent study showed a significant increase in CRP and IL-6 levels in patients with unipolar mania compared to BD patients [40]. Elevated CRP levels are most likely attributed to the increase in IL-6, as IL-6 stimulates the production of CRP [40].

Recent research has transitioned from investigating cytokine concentrations to examining cytokine receptor levels due to their potential higher reliability as markers of inflammation [41]. For example, IL-6 can activate the classical signaling pathway by binding to the IL-6 receptor, and it also can trans-signal by binding to sIL-6R. The classical signaling pathway activates both anti- and pro-inflammatory cascades, whereas trans-signaling engages just the pro-inflammatory pathways [43]. Therefore, measuring sIL-6R levels can be a more accurate measure of pro-inflammation compared to measuring IL-6 [44]. A recent study examining cytokine receptors found that higher baseline depression levels in individuals with BD

correlated with higher serum levels of sTNF- α R1. They also found that higher baseline sTNF- α R1 levels positively predicted depressive symptoms in euthymic individuals with BD who later became depressed, with sadness in patients with bipolar depression predicting future increases in sTNF- α R1 [45]. This study showcases the hypothesized bidirectional inflammation–depression relationship in BD.

In recent years, there have been efforts to synthesize the body of research regarding neurotrophic, oxidative, and inflammatory biomarkers in BD. One meta-analysis involving 2467 individuals with BD and 2360 controls showed that no biomarker could differentiate mood phases individually. However, the following five biomarkers were found to differentiate BD from controls and correlate with specific BD mood phases: TNF- α , sTNFR1, high-sensitivity (hs) CRP, IL-6, and BDNF. Specifically, the manic phase was found to be associated with a decrease in BDNF and an increase in TNF- α , sTNFR1, IL-6, and hs-CRP. Similarly, the euthymic phase of BD was associated with increased levels of IL-6 and hs-CRP, and the depressive phase of BD showed a decrease in BDNF and an increase in TNF- α levels [46]. More recently, another meta-analysis looked at 4547 individuals with BD [47] and reported that BDNF clearly plays a role in the depressive phase of BD. However, it found mixed and contradictory evidence regarding the association between neurotrophic and inflammatory markers with the clinical features of BD, with poor consistency in inflammatory factors such as IL-6 and TNF- α [47]. In summary, studies have shown that cytokine levels fluctuate with different phases of BD [48], including a negative correlation between pro-inflammatory markers, namely sTNF- α R1, and cognitive function in patients [49]. More highly controlled and large-sample-size studies are needed to identify precise inflammatory biomarkers and their potential clinical utility in BD.

14.4 Oxidative Stress Markers

Studies have shown that oxidative stress plays a key role in the pathophysiology of BD [50]. Among multiple markers, a meta-analysis showed that lipid peroxidation, DNA/RNA damage, and nitric oxide (NO) were significantly increased in BD compared to controls. Notably, lipid peroxidation had a high effect size [51]. Since the CNS, and in particular the brain, have high lipid concentrations, they are especially vulnerable to oxidative stress [52]. Accordingly, increased lipid damage was found in the prefrontal cortex and anterior cingulate cortex in BD patients, further establishing that oxidative stress plays a role in the pathophysiology of BD [53]. By-products of lipid peroxidation, such as thiobarbituric acid reactive substance (TBARS) and malondialdehyde (MDA), have been repeatedly used as peripheral markers of oxidative stress. Of note, a meta-analysis reported increased TBARS levels during mania, euthymia, and depressive phases, indicating that TBARS may be an oxidative stress trait marker in BD [54]. Studies also showed a significant positive correlation between TBARS level and the severity of BD symptoms [55, 56], suggesting it as a state marker for BD as well [54]. Oxidation of proteins has

also been associated with the pathophysiology of BD. In particular, 3-nitrotyrosine (3-NT), which is a marker of protein oxidation, was elevated during depressive episodes in individuals with BD [11], although a more recent meta-analysis found no statistically significant difference in 3-NT levels [51]. NO, which is derived from the endothelium and released during times of oxidative stress, has been shown to be elevated in BD [53, 54], with one study noting elevated NO levels specifically in mitochondrial proteins [57].

Blood antioxidant levels have also been used to indirectly measure oxidative stress. Antioxidants such as glutathione (GSH), uric acid, zinc, and antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) have all been shown to be associated with BD [54]. A recent meta-analysis found that BD was associated with elevated levels of glutathione S-transferase, zinc, uric acid, CAT, and SOD levels [54]. However, a recent review noted discrepancies among studies with regard to SOD and CAT [58]. While most reports show increased SOD levels in individuals with BD during manic and depressive episodes compared to those in euthymia and controls [54, 59–61], other studies reported decreased SOD levels in individuals during mania [62, 63]. Similarly, there are conflicting studies on the association between CAT and BD, with some studies showing increased [54] or decreased [63] CAT levels in patients compared to controls. Additionally, decreased GSH and increased uric acid levels were found in mania and euthymia, indicating that GSH and uric acid could be trait markers since their association with BD did not change during euthymia [54]. A recent review also recognized these findings but highlighted that certain studies indicated no distinction between control groups and individuals with BD [64].

14.5 Neuronal and Glial Markers

Postmortem studies have provided evidence that mood disorders are affected by neuronal and glial histopathology [65]. In BD specifically, morphologic changes such as decreased neuronal and glial density have been found [66]. Therefore, there has been a growing interest in neuronal and glial markers measured in blood, in particular S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE). S100B, a type of glial marker, is concentrated in the cytoplasm of astrocytes and oligodendrocytes [67] and functions to promote cell proliferation and inhibit apoptosis [68]. S100B can also be found in the extracellular space, whether through active release or through glial cell damage [69]. S100B can enter the blood if it accumulates in the extracellular space following cell damage. Therefore, S100B levels in the blood could indicate CNS injury [70]. NSE is an isoenzyme involved in the final steps of glycolysis that mainly acts on neuronal and neuroendocrine tissues [71]. NSE also plays a role in neuroprotection and protects against neurodegeneration in the CNS [72]. Unlike S100B, NSE is not secreted into the extracellular space under normal conditions. Only during times of cellular injury or death will NSE be leaked into the extracellular space, making it a useful biomarker for structural damage to neuronal cells [73]. Studies have shown that S100B levels are

increased in manic and depressive episodes compared to controls [74–76]. However, other studies have shown that NSE levels are significantly decreased in BD patients compared to controls [77, 78]. In an effort to clarify possible differences between S100B and NSE levels in relation to BD, a recent meta-analysis looked at 11 studies involving 599 BD patients and 378 controls [79]. The study found that blood S100B levels were significantly higher in BD patients compared to controls; however, no difference in NSE levels was identified [79]. Although S100B levels were found to be elevated in BD, S100B is nonspecific, and elevated levels can be found in other mental disorders as well, such as depression and schizophrenia (SZ) [80, 81].

14.6 Metabolic Markers

People with BD often exhibit metabolic dysfunction, making metabolic biomarkers a logical area of focus. Specifically, investigations into lipid and glucose metabolism hold great promise for the identification of novel biomarkers for BD. Lipid metabolism dysfunction may play a key role in the pathophysiology of BD as well as other neuropsychiatric disorders. This can be attributed to the high abundance of lipids in the brain and the strong association between neuropsychiatric disorders and developing dyslipidemia [42]. Interestingly, a lipidomics study found over one hundred lipids to be significantly different between BD and controls [82], further supporting the potential of lipids as biomarkers.

A recent scoping review of 99 papers sought to summarize the research on lipid biomarkers in BD [83]. Four routine makers in clinical practice, namely total cholesterol, high-density lipoproteins, triglycerides, and low-density lipoproteins, were commonly studied; however, few studies showed replicable associations between those markers and BD. One study found that depressive episodes often correlated with elevated lipid levels, while manic episodes tended to be linked with reduced lipid levels [83]. Of note, the use of targeted and global lipidomics for researching lipid biomarkers in BD is relatively new with only a few recent publications [84–86]. Targeted lipidomics involves analyzing a predetermined set of lipids; however, current studies are heterogeneous in their investigation of lipid classes, making it difficult to deduce generalized findings [83]. On the other hand, studies that used global lipidomics, which analyzes all lipid molecules present in a sample, found that glycerophospholipids, sphingolipids, glycerolipids, and fatty acids were potential biomarkers for BD [83, 85].

Insulin resistance and type 2 diabetes (T2DM) occur frequently in individuals with BD [87], indicating that glucose metabolism dysfunction may play a role in the pathophysiology of BD. In patients, brain imaging studies have shown changes in cerebral glucose metabolism in certain regions of the brain [88–90], further supporting the connection between glucose dysregulation and BD. Studies have also shown decreased levels of glucagon and glucagon-like peptide 1 in patients compared to controls [91, 92] and may represent a marker of late-stage disease in BD [92]. Impaired glucose metabolism may also affect the efficacy of BD treatment, with

evidence that patients with insulin resistance or T2DM have a worse response to mood stabilizers compared to patients with normal glucose metabolism [93].

It is important to note that many of the medications that treat mood disorders can potentially cause metabolic side effects [94]. For example, second-generation antipsychotics such as olanzapine and quetiapine are associated with weight gain and increased blood LDL, triglyceride, glucose, and total cholesterol levels in BD and SZ patients [95]. Consequently, studies have indicated that BD patients are less likely to adhere to their medication regimens when they encounter a higher number of side effects [96]. Medication nonadherence further complicates metabolic studies due to the heterogeneity of the study participants. It is important for research studies to differentiate the inherent biological association between BD and metabolic markers with secondary effects due to BD pharmacological treatment.

14.7 Epigenetic Markers

Epigenetic mechanisms can regulate gene expression without directly altering genetic change and have been suggested to play key roles in the pathophysiology of BD [97]. DNA methylation, one of the most well-studied epigenetic mechanisms, involves the addition of a methyl group to the DNA molecule at cytosine residues, typically silencing gene expression [98]. Studies have shown that DNA methylation might be linked to the pathophysiology of BD. For instance, an early postmortem study of individuals with BD showed increased expression levels of membrane-bound catechol-O-methyltransferase (MB-COMT) in the left frontal lobe due to hypomethylation of the *COMT* promoter [99]. Additionally, *COMT* expression levels in peripheral blood were found to be increased in individuals with BD compared to controls [100]. Recent studies have also examined the methylation of dozens of candidate genes, including genes from the hydroxytryptamine receptor (*5-HTR*) family and *BDNF* [101]. Studies have also shown an association between DNA methylation in the promoter region of *BDNF* and BD, ultimately resulting in decreased expression of this protein (discussed earlier in this chapter). This effect was ameliorated by treatment with medications such as lithium and valproate. Also of note was the fact that this effect was more pronounced in patients in a depressive episode compared to mixed or manic episodes, indicating its possible clinical use as a biomarker to help differentiate or predict the onset of a mood episode in patients [102]. Similarly, the serotonergic transporter and receptor genes have been shown to present increased DNA methylation levels in BD, supporting the narrative of a relationship between dysfunction within the serotonin pathway and BD [103]. Interestingly, DNA methylation of the serotonin 3A receptor has been shown to be correlated with adverse childhood experiences and also mediates the severity of BD; patients tested in this study with traumatic childhood experiences showed significantly higher methylation of this receptor and also presented with more severe BD symptoms [104]. Finally, one study found that guanosine oxidation (8-OHdG), which demethylates DNA by decreasing the binding affinity of methyl groups, was significantly increased during manic and depressive episodes but not during euthymia [105].

Noncoding RNAs regulate gene expression by altering chromosome structure, splicing, and transcription [106]. Studies have shown associations between BD and different types of noncoding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Importantly, miRNAs can be released from cells and can stably enter systemic circulation, making them possible blood biomarkers [107, 108]. Specifically, MiR-144-5p, considered to be a “common RNA signature” to many tumors, is also thought to be implicated in neurological pathways. One study found its down-expression to be associated with depressive disorders, with treatments such as cognitive behavioral therapy helping return levels of MiR-144 to nearly baseline levels [109]. Additionally, MiR-134, localized to the brain, is hypothesized to play a role in mood disorders as well. Interestingly, while MiR-134 overexpression generally correlates with depression-like symptoms, its circulating levels have been shown to be decreased in untreated individuals with BD compared to patients under treatment and controls [110]. Finally, elevated MiR-34a levels have been found in BD, and analogously to MiRNA-144, treatment (usually with lithium and valproic acid) was shown to decrease their levels nearer to normal [111, 112]. Of note, this miRNA is associated with a variety of pathways, including the regulation of the plasticity of the CNS [113]. A recent review identified several circulatory miRNAs that differed in individuals with BD compared to controls. These included miR-106b, miR-125a, miR-142, and miR-221, although the studies selected frequently presented conflicting findings regarding the precise relationship of each of these miRNAs with BD [114].

lncRNAs function as posttranscriptional regulators and chromatin modifiers, and studies have shown that they may play an important role in the pharmacological response in BD. One genome-wide association study (GWAS) of 2563 patients found two regions on chromosome 21 that encode for lncRNAs (*AL157359.3* and *AL157359.4*) to be significantly associated with lithium response [115]. In recent research, additional lncRNAs were observed to be downregulated in the peripheral blood of individuals with BD compared to controls, specifically *MEG3* and *RMST* [116]. Of note, decreased *MEG3* expression has been associated with increased oxidative stress and increased hippocampal neuron apoptosis via inactivation of the PI3K/AKT/mTOR pathway [117], suggesting that *MEG3* may contribute to the pathogenesis of BD by regulating this pathway [116].

14.8 “Omics” Research

Advances in neuroimaging, genetics, and data analysis techniques may eventually contribute to the development of more reliable biomarkers. Additionally, the integration of clinical data and multiple types of biomarkers in “omics” research may offer a more comprehensive understanding of the disorder and improve diagnostic accuracy in the future. “Omics” research involves the comprehensive analysis of biological molecules within an organism or a system. Various “omics” approaches, including proteomics, transcriptomics, methylomics, and metabolomics, have been utilized to explore the molecular underpinnings of BD. These approaches have the

potential to pinpoint novel biomarkers and enhance our understanding of the disorder.

Transcriptomics focuses on the study of gene expression levels, which can help identify genes that are upregulated or downregulated in BD as well as the impact of differential splicing and expression [118]. A recent transcriptome meta-analysis of peripheral blood identified 19 genes, 60 biologically annotated gene sets, and 4 gene co-expression modules that differed between individuals with BD and controls [119]. The genes that were upregulated played a role in oxidative stress, immune signaling, and apoptosis, whereas downregulated genes were primarily involved with histone modification, DNA repair, and RNA processing and splicing [119]. This study also found no significant differences in gene expression between individuals with BD and patients with SZ [119]. Of note, one study created a multi-class classification transcriptomic model that identified genes in postmortem brains that could differentiate between BD and SZ [120]. Specifically, when examining the anterior cingulate cortex and amygdala from postmortem brains, one study found two transcriptional changes in individuals with BD compared to controls [121]. The identified genes encompassed those implicated in inflammation, while another gene was found to be associated with the postsynaptic membrane [121].

Proteomics involves the study of all proteins in a biological sample. A recent meta-analysis of proteomics studies in BD identified the following five proteins as potential biomarkers for discriminating between BD patients and controls: C3, insulin-like growth factor (IGF)-1, transferrin (TF), apolipoprotein AI (APOA-1), and alpha-2-macroglobulin (A2M) [122]. These proteins are involved in various biological processes, namely growth and endocrine regulation (IGF-1), iron transportation (TF), protease inhibition (A2M), protection against pathogens (C3), and cholesterol transport (APOA-1). However, the definitive links between each of these proteins and BD were inconclusive due to conflicting results across studies [122].

Metabolomics focuses on the profiling of small molecules (metabolites) within cells, tissues, or bodily fluids. Metabolomic studies have identified alterations in the multiple metabolic profiles of individuals with BD, including changes in neurotransmitter metabolites, energy metabolism, and oxidative stress markers [123]. As is the case with other “omics,” studying metabolites can also help delineate BD from other diagnoses. A recent study identified 17 metabolic biomarkers in dried blood spots that could differentiate BD from major depressive disorder during low mood phases [124]. Another study identified 22 metabolites as biomarkers for BD using nuclear magnetic resonance (NMR). Among them, the following molecules were confirmed for the first time in BD serum samples: aspartate, threonine, gamma-aminobutyric acid (GABA), 2-hydroxybutyric acid, serine, and mannose [125], which play a role in amino acid metabolism, the tricarboxylic acid cycle, and glycolysis.

Overall, while “omics” research has advanced our understanding of BD and provided potential biomarkers and therapeutic targets, it is still an evolving field. Validation and translation of these findings into clinical practice require further research and collaboration. Ultimately, a combination of multiple “omics”

approaches and clinical data may provide a more accurate and personalized diagnostic and treatment approach for BD.

14.9 Clinical Applications and Future Perspectives

While there is much we have yet to confirm, there is significant potential in the ability of blood biomarkers to advance our diagnosis, management, and understanding of BD [31]. Assessing biomarkers in the blood of patients may hold the key for an objective way to untangle BD from the myriad of other mental health conditions with similar symptoms that BD is often misdiagnosed for, potentially reducing the years of diagnostic delay often seen in individuals with BD. Blood biomarker profiles are also hypothesized to be able to differentiate between BD subtypes, allowing us to categorize them more easily and craft more effective treatment plans [126]. Furthermore, there is hope that such biomarkers could aid in the early detection of BD and identify risk factors to help diagnose high-risk individuals, especially in cases where individuals have a family history or other risk factors [127]. This would allow clinicians to identify the condition before severe mood episodes occur (which can lead to earlier intervention and improved outcomes for patients). Early intervention strategies may be especially effective given that it has been theorized that the response to treatment is greater in the early phases of BD [128].

Blood biomarkers also have prospects beyond facilitating diagnosis. Levels of one or multiple biomarkers could be used to monitor the progression of BD over time, helping clinicians assess treatment effectiveness and disease stability and severity to advance our understanding of the implications of certain treatment plans to more effectively care for patients [122]. Moreover, identifying biomarkers that predict an individual's response to specific medications or therapeutic interventions can enable more personalized treatment plans tailored to an individual's unique biology. Blood biomarkers could potentially assist in tailoring psychotherapeutic approaches to individual patients. For example, biomarker profiles might inform the choice between cognitive behavioral therapy, psychoeducation, or other psychotherapeutic modalities. Biomarkers might be used to guide recommendations for lifestyle modifications, such as exercise, diet, and sleep, which can impact mood stability. Biomarkers might be used to assess the severity of mood episodes, allowing for the optimization of medication selection and dosing to improve symptom management and quality of life to reduce the trial-and-error approach often seen in psychiatric medication management [129]. Blood biomarkers may also be used to monitor whether patients are taking their prescribed medications regularly, an important factor because nonadherence to medication regimens is a common challenge in BD treatment. Blood biomarkers may also be useful for monitoring the safety of medications. Some medications used in BD treatment can have side effects that affect the liver, kidney, or blood cell counts; biomarkers could help detect these effects early. Similarly, certain biomarkers may be associated with an increased risk of comorbid conditions, such as substance use disorders or cardiovascular

problems. Identifying these risks early can inform preventive measures and additional treatment considerations.

Certain biomarkers may even serve as prognostic state indicators, helping clinicians predict the long-term course of the disorder in individual patients [130]. This information can guide treatment planning and patient education. Additionally, blood biomarkers can be especially useful in a phasic disorder like BD as a tool to predict the onset of a new episode or a relapse in individuals beyond the measures currently used [131]. Biomarkers may help identify specific subgroups of individuals with BD who are at a particularly high risk of specific outcomes, such as rapid cycling or suicide risk. Additionally, biomarkers may hold the key to empowering individuals with BD to learn more about and more objectively track and manage their condition; increased beliefs in self-efficacy in psychiatric conditions tend to be correlated with better outcomes. Biomarkers can also enhance shared decision-making between clinicians and patients by providing objective data about the course and prognosis of the disorder. This can help patients make informed choices about their treatment and management.

The potential for using blood biomarkers in combination with other diagnostic methods, such as clinical interviews and brain imaging, is an exciting area of research in BD. Integrating multiple diagnostic approaches can enhance the accuracy of diagnosis, improve treatment planning, and provide a more comprehensive understanding of the disorder. Clinical interviews with trained mental health professionals are a crucial component of BD diagnosis. However, mood disorders can present with overlapping symptoms, making diagnosis challenging. Blood biomarkers can provide objective biological data that may help confirm or refine the diagnosis. Neuroimaging techniques, such as magnetic resonance imaging (MRI) and functional MRI, can reveal structural and functional brain abnormalities associated with BD [132]. Combining imaging data with blood biomarker information can provide a more comprehensive understanding of the disorder's neurobiological basis. Blood biomarkers can assist in subtyping BD and identifying specific features, such as rapid cycling or psychotic symptoms. These subtypes may have different treatment responses and clinical courses, guiding personalized treatment plans [133]. Combining clinical interviews, biomarker profiles, and brain imaging data can help tailor treatment approaches to address individual symptom profiles and neurobiological characteristics.

14.10 Limitations of Blood Biomarkers

Blood biomarkers present many advantages such as their ease of use; however, peripheral levels might not be an accurate representation of the pathological processes occurring in the brain [134]. Additionally, samples at specific points in time might also be misleading due to fluctuations related to medications, environment, or stress levels. Currently, there is still a lack of longitudinal studies that would be needed in order to establish the clinical utility of biomarkers in practice.

One major limitation of studying biomarkers is that no single biomarker can establish the causality of disease severity, duration, or progression. Although the exact pathophysiology of BD has not been elucidated, research has suggested that it is most likely a multitude of factors that impact its pathogenesis [135]. Furthermore, most of the identified peripheral biomarkers have also been found in other neuropsychiatric disorders, making it difficult to isolate biomarkers specific to BD [31]. Therefore, studies should examine groups or categories of biomarkers instead of individual factors in order to differentiate BD from other psychiatric disorders such as SZ and major depressive disorder [136, 137]. Notably, GWAS studies have found *loci* that differentiate BD from SZ [138], and further genetic studies offer the potential to gain additional insights into the underlying distinctions between neuropsychiatric disorders.

The limited reproducibility of results from different studies is a major drawback of utilizing biomarkers. Factors such as sample size, patients with diverse subtypes of BD or phase states, and differences in sample collection methodology all contribute to the heterogeneity of studies [134, 139]. For example, a previously mentioned meta-analysis of inflammatory and neurotrophic biomarkers found poor consistency in IL-6 and TNF- α levels despite their status as some of the more extensively researched biomarkers in BD [47]. Furthermore, not all studies control for confounding factors such as body mass index, age, sex, and pharmacological treatment, which could result in misleading findings [140]. This raises the question of whether identified biomarkers can be universally applied across diverse cultures and ethnic backgrounds, a critical consideration when contemplating the translation and utilization of biomarkers in clinical practice [141]. It is also important to note that publication bias toward positive results is likely to occur in the field of biomarkers according to two meta-analyses [134, 140].

There are also practical, clinical limitations to utilizing biomarkers in everyday practice. Not all biomarkers can be readily extracted from the blood or serum. In addition, currently, there is no established practice to obtain serum biomarkers to examine psychiatric pathology for clinical diagnosis. The lack of accuracy and/or precision in current diagnostic tools pose a barrier to patient refusal and resistance to acceptance by clinician utilization. Furthermore, diverse perspectives persist on the underlying causes of BD, and not everyone subscribes to BD having a biological origin. This could make implementing biomarkers as a widely utilized diagnostic tool difficult.

14.11 Conclusion

The exploration of biomarkers coupled with technological advances has significantly enhanced our understanding of the biological mechanisms underlying the expression, susceptibility, and treatment response in BD. The various biomarker classes and mechanistic pathways discussed including neurotrophic, inflammatory, oxidative stress, neuronal and glial, metabolic, and epigenetic markers are all candidate biomarkers to identify BD pathogenesis, progression, subtype, and severity (Table 14.1).

Table 14.1 Selected blood biomarkers commonly investigated in bipolar disorder (BD)

	Biomarker	Main function	Relation to BD
Neurotrophic factors	BDNF	Neuroplasticity; neurogenesis: stimulates growth, differentiation, synapse assembly, and survival of neurons	Decreased during mania and depression
	IGF-1	Aids neurogenesis and enhances cellular viability; impacts synapse structure and function	Increased
	VEGF	Angiogenic factor: promotes vascular development in CNS	Increased
Inflammatory markers	TNF- α	Involved in neuroprotection and neuroinflammation; increases the permeability of the BBB	Increased during mania and depression
	IL-6	Involved in neuroprotection, neuroinflammation, and synaptic plasticity; increases the permeability of the BBB	Increased
	CRP	Acute-phase response; inflammation	Increased during mania and depression
Oxidative stress markers	TBARS	Measure of lipid peroxidation	Increased
	NO	Increased oxidative stress	Increased
	SOD	Antioxidant enzyme	Increased in most studies (but inconclusive)
	CAT	Antioxidant enzyme	Increased in most studies (but inconclusive)
	GSH	Antioxidant with neuroprotective effects	Decreased in mania and euthymia
Neuronal and glial markers	S100B	Glial markers used to promote the proliferation of brain cells; indicate nervous system injury or BBB dysfunction	Increased during mania and depression
	NSE	Protects against neurodegeneration in the CNS	Decreased in most studies (but inconclusive)

Legend: *BDNF* brain-derived neurotrophic factor; *CAT* catalase; *CRP* C-reactive protein; *GSH* glutathione; *IGF-1* insulin-like growth factor; *IL-6* interleukin-6; *NO* nitric oxide; *NSE* neuron-specific enolase; *S100B* S100 calcium-binding protein B; *SOD* superoxide dismutase; *TBARS* thiobarbituric acid reactive substance; *TNF- α* tumor necrosis factor alpha; *VEGF* vascular endothelial growth factor

The integration of new “omics” technology in the field has contributed to a more comprehensive understanding of the disorder by analyzing groups of molecules. A biomarker-driven approach in psychiatry could substantially improve the efficiency and cost-effectiveness of interventions, ultimately enhancing the quality of life for patients.

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Chapter 15

Mitochondrial Dysfunction



Tadafumi Kato

15.1 Introduction

Bipolar disorder is characterized by recurrent manic and depressive episodes with a lifetime prevalence of around 1% and is one of the major mental disorders along with schizophrenia [1]. The high concordance rate between monozygotic twins clearly indicates that genomic factors are involved. Recent genome-wide association studies [2] and case–control exome analysis [3] and our exome analyses in trio families [4, 5] have found associations with genes related to intracellular Ca^{2+} signaling including Ca^{2+} channel genes and have pointed to commonalities with related neuropsychiatric disorders such as schizophrenia.

On the other hand, mitochondrial disease [6]; Darier's disease [7] caused by mutations of the endoplasmic reticulum (ER) Ca^{2+} pump gene, *ATP2A2*; and Wolfram's disease [8] caused by mutations of the ER (endoplasmic reticulum) stress-related gene *WFS1* are known as genetic disorders with a high frequency of comorbid bipolar disorder. Therefore, intracellular Ca^{2+} signaling abnormalities due to the dysfunction of mitochondria and ER, which act as intracellular Ca^{2+} stores, may also cause bipolar disorder.

Mitochondria are intracellular organelles surrounded by inner and outer membranes, and the proton ion gradient between the inner membranes, formed by the respiratory chain, is the driving force for ATP production. Mitochondria also take up calcium ions using a proton ion gradient between the inner membranes. Mitochondrial calcium regulation is thought to be involved in exocytosis, postsynaptic calcium-dependent synaptic plasticity, and other cellular functions.

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Bipolar disorder is currently treated with lithium that inhibits inositol monophosphatase and three anticonvulsants, valproic acid, lamotrigine, and carbamazepine, as well as atypical antipsychotics such as quetiapine, olanzapine, aripiprazole, and lurasidone, among others [1]. Their pharmacological actions are different, the relationship to abnormal intracellular Ca^{2+} signaling is unknown, and the mechanisms by which these medications stabilize bipolar disorder are largely unknown. Therefore, there have been no successful attempts at developing drugs acting directly on the pathophysiology of bipolar disorder.

Based on the hypothesis that intracellular Ca^{2+} signaling abnormalities due to the dysfunction of intracellular Ca^{2+} stores, namely mitochondria and ER, are involved in bipolar disorder, we have obtained findings from genomic studies, cellular and animal model studies, and brain imaging studies. These multimodal studies provide clues to understanding the pathophysiology of bipolar disorder across the molecular, cellular, and organ levels. This chapter will especially focus on mitochondrial dysfunction.

15.2 History of Mitochondrial Dysfunction Hypothesis of Bipolar Disorder

In 1994, we reported altered brain energy metabolism in bipolar patients by magnetic resonance spectroscopy [9], and in 1996, we reported the accumulation of mitochondrial DNA deletions, one of the causes of mitochondrial disease, in the postmortem brains of bipolar patients [10]. Based on these findings, we proposed the mitochondrial dysfunction hypothesis of bipolar disorder in 2000 [11].

Subsequently, it was reported that mitochondrial disease and bipolar disorder are linked in a family [12]. In 2004, a series of reports supporting this hypothesis drew attention to the mitochondrial dysfunction hypothesis of bipolar disorder [13, 14]. In 2006, we created mice with an accumulation of mutated mitochondrial DNA in the brain alone by expressing a mutant of mitochondrial DNA polymerase only in the brain [15] and reported that periodic behavioral changes appeared, which were suppressed by lithium. These studies further endorsed the role of mitochondrial dysfunction in bipolar disorder.

15.3 Pharmacology

Chen et al. treated rats with valproate or lithium and identified mRNAs commonly induced by both drugs. The gene identified by differential display was bcl-2 encoding an antiapoptotic protein located on the mitochondrial outer membrane [16]. Mitochondria play a major role in apoptosis, and various apoptotic stimuli induce the formation of the mitochondrial permeability transition pore (mPTP). mPTP is a

multi-protein complex that opens in two distinct modes: low conductance mediated by the adenine nucleotide translocator and high conductance mediated by the F_1F_0 ATP synthase [17]. The former mediates Ca^{2+} release from mitochondria. On the other hand, irreversible dissociation of F_1 from ATP synthase F_0 causes sustained opening of mPTP, induces mitochondrial expansion, and releases large molecules such as cytochrome c. Bcl-2 suppresses mPTP opening and prevent apoptosis. Thus, the upregulation of bcl-2 by mood stabilizers may well explain their neuroprotective effects.

15.4 Genetics

We found that individual differences in mitochondrial DNA (mtDNA) affected intracellular calcium signaling by studying the transmitochondrial cybrids, that is hybrid cells made by the fusion of mtDNA-deficient cells (rho-zero cells) and platelets derived from patients or controls [18].

Though initial studies reported the association of bipolar disorder with mitochondrial DNA variants, they are generally underpowered. A recent study of 1,001 patients with bipolar disorder and 1,034 controls showed the nominally significant association of 15452C>A (rs3088309 and Leu236Ile) in *MT-CYB* defining haplogroup JT with bipolar disorder ($p = 1.4 \times 10^{-4}$) [19]. In spite of that tens of thousands of patients were examined by recent genome-wide association studies, the large-scale association analysis of mitochondrial DNA in bipolar disorder is an underexplored area.

We reported that loss-of-function mutations in mtDNA polymerase (polymerase γ [*POLG*]) [20] and ANT1 [21], which are the causative genes of chronic progressive external ophthalmoplegia (CPEO), are common in bipolar disorder, but the results of exome analysis in 13,933 patients did not reproduce these findings [3].

We found increased mtDNA deletions in the postmortem brains of bipolar patients [10]. Although there was no difference in the Stanley Brain Bank sample [22–24], Vawter and colleagues examined mtDNA deletions in 27 bipolar and 30 schizophrenic patients and 45 controls and reported an increase in mtDNA deletions in the dorsolateral prefrontal cortex in bipolar patients [25].

We reanalyzed the results of gene expression analysis focusing on mitochondria-related genes and found elevated expression of *LARS2* [26]. *LARS2* encodes a mitochondrial leucyl tRNA (transfer RNA) synthetase. mtDNA 3243A>G mutation, the causative mutation of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), decreases the efficiency of aminoacylation of tRNA^{Leu}(UUR). The overexpression of *LARS2* reportedly rescues the phenotype of cells carrying the mtDNA 3243A>G mutation [27]. We found that *LARS2* was upregulated in the cybrids carrying the mtDNA 3243A>G mutation. We found that the levels of the mtDNA 3243A>G mutation were increased in the postmortem brains of patients with bipolar disorder. In patients with mutations in the brain, mutations were also found in the liver. Recently, we replicated this finding in a

completely independent study. We performed a comprehensive analysis of somatic mutations by deep exome sequencing including mtDNA in trio families and cases of bipolar disorder and found that the frequency of somatic mtDNA mutations of tRNA genes including 3243A>G in blood or saliva DNA was significantly increased [5].

15.5 Comorbidity with Mitochondrial Diseases

Chronic progressive external ophthalmoplegia (CPEO) is a relatively mild, adult-onset mitochondrial disease caused by multiple deletions of mtDNA that results in ptosis and other symptoms including depression. Suomalainen et al. reported that a case developed CPEO after many years of severe depression [28]. At autopsy, the brain showed a higher level of multiple deletions of mtDNA than muscles. Depression was also seen in other affected family members of this case, suggesting that depression in this family was a manifestation of mitochondrial dysfunction in the brain. After this report, many cases of mitochondrial disease presenting with depression or bipolar disorder have been reported [6].

In particular, three studies using structured interviews in patients with mitochondrial disease [29–31] found that the frequency of bipolar disorder in patients with mitochondrial disease is high, ranging from 16 to 21%. More recently, Colasanti et al. screened 52 patients with mitochondrial disease for bipolarity using the Mood Disorder Questionnaire (MDQ) [32]. The results showed that bipolar I disorder was found in 12.2% (6/49) of the patients, with an odds ratio of 7.8 compared to the general population in the United Kingdom, suggesting that bipolar I disorder is more common in patients with mitochondrial disease. In particular, bipolar I disorder was common in patients with 3243A>G mutation (17.4%, 4/23) with an odds ratio of 12.8 [32].

15.6 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) studies have indicated changes in brain energy metabolism in ³¹P-MRS, including decreased creatine phosphate and decreased intracellular pH, and changes in plasma membrane phospholipids, including changes in phosphomonoesters [33]. ¹H-MRS studies showed decreased *N*-acetyl aspartate (NAA), increased glutamine/glutamate, decreased creatine, increased choline, and increased lactate [34, 35]. In a meta-analysis of ¹H-MRS, NAA in the left prefrontal white matter was significantly lower in bipolar patients [36]. Many of these findings by MRS have been pointed out as being univocally understandable as being due to mitochondrial dysfunction [34].

15.7 Postmortem Brains

Konradi et al. performed gene expression analysis in the postmortem brains of bipolar patients and reported that the expression of mitochondria-related genes was generally decreased, consistent with the mitochondrial hypothesis [14]. This finding was confirmed by other researchers [37–39]. It was pointed out that the decreased expression of mitochondria-related genes is strongly influenced by the agonal state [40]. The global decrease of mitochondria-related genes is also associated with medication and the pH of brain samples [37]. Thus, there was a discussion about whether the global decrease of mitochondria-related genes is an artifact or reflects the pathology of bipolar disorder. Konradi et al. suggested that this finding suggests mitochondrial dysfunction in bipolar disorder because lymphocytes derived from patients cultured in low-glucose medium failed to show the increased expression of mitochondria-related genes seen in healthy controls [41]. Recently, Hagihara et al. argued that the decrease in brain pH is a trans-diagnostic endophenotype of neuropsychiatric disorders involving cognitive impairment, based on the low pH of postmortem brains of patients with mental disorders and animal models of neuropsychiatric disorders [42, 43].

In a study of microarray analysis of dissected pyramidal cells in the prefrontal cortex [44], mitochondria-related gene expression changes were found in schizophrenia, but no significant expression changes were found in bipolar disorder.

Lewis et al. analyzed the results of gene expression analysis by RNA sequencing of the dorsolateral prefrontal cortex in schizophrenia and bipolar patients conducted as part of the CommonMind Consortium [45], focusing on mitochondria-related gene expression [46]. The results showed that the nature of mitochondrial dysfunction in schizophrenia and bipolar disorder is different, as changes in mitochondrial functional pathways associated with reduced energy production were found only in schizophrenia but not in bipolar disorder.

15.8 Cellular Models

Cataldo et al. reported that mitochondrial structure is altered in fibroblasts of patients with bipolar disorder [47]. Mitochondria were concentrated within the perinuclear region than in distal processes in patients with bipolar disorder.

In 2015, a report from Mertens et al. published in *Nature* attracted attention. They generated hippocampal dentate gyrus granule cells from the induced pluripotent stem (iPS) cells of six bipolar patients (three lithium responders and three nonresponders) and analyzed them. Patients' neurons exhibited phenotypes of increased mitochondrial membrane potential, smaller mitochondria, and increased expression of mtDNA-derived transcripts. Patients' neurons showed hyperexcitability, and this phenotype was improved by lithium only in lithium responders. These findings indicated that hyperexcitability may be a phenotype of bipolar

patients' neurons [48]. The findings of this paper were subsequently confirmed in an independent sample set [49].

Results of animal models also support the role of hyperexcitability in bipolar disorder. We focused on *ANT1* (*SLC25A4*), the gene responsible for CPEO and reported in a family of CPEO and bipolar disorder, and generated brain-specific mutant mice of *Ant1* [21]. In these mice, we found increased excitability of serotonergic neurons [21]. Brain-specific conditional knockout mice of *Atp2a2*, a causative gene of Darier's disease, showed hyperactivity of dopaminergic neurons [50]. These results suggest that neuronal hyperexcitability may be involved in the pathogenesis of bipolar disorder.

To study the mechanisms of lithium responsiveness, Paul and colleagues generated neural progenitor cells from iPS cells derived from lithium-responsive and lithium-nonresponsive bipolar patients in multiple families and performed RNA sequencing, mitochondrial membrane potential (MMP) analysis, and cell viability assays. These parameters were also examined in cultured lymphoblastoid cells from 25 BD patients (16 lithium responders and 9 nonresponders) and 12 controls. They found that MMP was lower in the cells of patients with bipolar disorder and reversed by lithium treatment in cultured lymphoblastoid cells [51].

A group at Harvard University reported a study using brain organoids. They generated brain organoids from iPS cells from eight bipolar patients and eight control subjects, performed RNA sequencing, and examined them using microelectrode arrays. In bipolar patients, gene expression of pathways involved in cell adhesion, neurodevelopment, and synapses was decreased, while gene expression involved in immune signaling was increased. Since the involvement of the endoplasmic reticulum was suggested by gene ontology analysis, they performed a proximity ligation assay (PLA). The mitochondria-associated endoplasmic reticulum membranes (MAMs) were decreased in the neurons derived from bipolar patients. This suggests that MAMs are impaired in bipolar disorder. Functional analysis using microelectrode arrays of brain organoids cultured for 9 months showed a lack of increase in firing frequency by electrical stimulation or potassium addition [52].

15.9 Biomarkers

Various blood biomarkers have been proposed for bipolar disorder [53]. These include neurotrophic factors including brain-derived neurotrophic factor (BDNF), immune parameters such as cytokines (interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , IL-2, IL-6, interferon (IFN)- γ , etc.), S100B, C-reactive protein, the kynurenine pathway, matrix metalloproteinases, neurotransmitter systems, mitochondrial markers such as reduced activity of mitochondrial complex I, oxidative stress markers including thiobarbituric acid reactive substances (TBARS), and neuroendocrine factors, among others. These biomarkers are discussed in other chapters.

The elevation of inflammatory markers is a well-corroborated finding in bipolar disorder as written above. However, it is still unclear why inflammation is increased

in bipolar disorder. As discussed in this chapter, the accumulation of deleted mitochondrial DNA (mtDNA) in the brain is reported in bipolar disorder. mtDNA, unlike chromosomal DNA, is not subject to DNA methylation, and when it leaks out of cells, it is misidentified by the immune system as exogenous DNA from bacteria or other sources. In fact, mtDNA is known to induce inflammation and increase cytokines [54]. We hypothesized that mtDNA released from the brain and other cells, especially partially deleted mtDNA with a small molecular weight due to deletion, may be involved in the cytokine elevation observed in bipolar disorder. In a mouse model of brain-specific accumulation of deleted mtDNA by neuron-specific expression of mutant *Polg*, the amount of deleted mtDNA was also increased in plasma, suggesting the presence of mtDNA released from the brain in the plasma [55]. Therefore, we measured plasma mtDNA levels and four cytokines in 109 depressed patients. As expected, mitochondrial DNA concentrations were positively correlated with three cytokines, IL-4, IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF), in depressed patients [56]. In bipolar patients, plasma mtDNA levels tended to be higher in depression than in remission, but this was not statistically significant ($p = 0.06$) [55]. Plasma mtDNA levels are reported to be negatively correlated with the mitochondrial health index, suggesting the role of plasma mtDNA in the pathophysiology of bipolar disorder [57].

The results so far do not allow us to conclude whether leaked mtDNA is a cause of inflammation in bipolar patients, but further studies will be needed to reach a conclusion.

15.10 Drug Development

Based on the mitochondrial dysfunction hypothesis, mitochondria-targeted drugs for bipolar disorder are being developed [58, 59]. Though a randomized controlled trial of *N*-acetylcysteine, one of the most promising agents targeting mitochondria, could not show a statistically significant effect for the primary outcome [60], further studies are needed to seek an effective treatment.

As discussed above, we have studied the possibility that mitochondrial dysfunction is related to bipolar disorder and have shown that mutant *Polg* transgenic mice, a mouse model of central nervous system (CNS) symptoms of mitochondrial disease, exhibit recurrent depressive episodes, which are reduced by the treatment with lithium. Based on the results of the gene expression analysis of the brains of the model mice and the postmortem brains of bipolar disorder patients, we found a commonly altered gene, *Ppif*, encoding cyclophilin D, a component of mitochondrial permeability transition pore (mPTP), a protein complex that penetrates the inner and outer mitochondrial membranes. Based on this finding, we hypothesized that mPTP would be a drug target. Since the opening of mPTP releases calcium ions (Ca^{2+}) from within mitochondria into the cytoplasm, the inhibition of mPTP can increase mitochondrial Ca^{2+} retention capacity and decrease cytosolic Ca^{2+} levels. Therefore, we investigated the possibility that the mPTP-inhibiting compound might become a new mood

stabilizer. We found that the parenteral administration of NIM811, a compound with mPTP inhibitory activity, improved behavioral changes in a mouse model [61]. Since this compound is derived from cyclosporin A, a cyclic polypeptide derived from fungi, it is difficult to improve its profile. Therefore, we have started a research project to explore mPTP inhibitors as candidates for mood stabilizers.

We screened 1,718 compounds using the mitochondria isolated from the mouse brain to find compounds that inhibit mPTP. As a result, we identified seco-cycline D (SCD) as an active compound. mPTP inhibition of SCD and its derivative was more potent than that of cyclosporine A, a known mPTP inhibitor. SCD was suggested to have a different mechanism of action than cyclosporine A. In the mouse middle cerebral artery occlusion model in which lithium has been reported to be effective, the repeated administration of SCD reduced ischemic area, suggesting that SCD may have a neuroprotective effect similar to that of lithium [62].

Further studies are needed to develop new mood stabilizers acting on the mitochondria.

15.11 Mode of Action of Current Anti-Bipolar Drugs

Based on recent findings in the neurobiology of bipolar disorder, the neurobiological mechanism of bipolar disorder may be summarized as shown in Fig. 15.1. Intracellular calcium signaling is altered by genetic factors related to calcium signaling pathways such as calcium channels and mitochondrial calcium regulation. This causes neuronal over-excitation and overexpression of emotion-related neural

Neurobiological mechanism of bipolar disorder

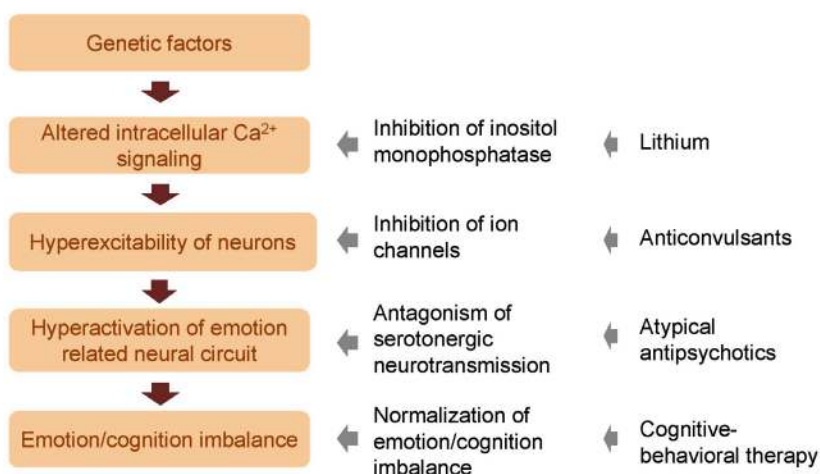


Fig. 15.1 Neurobiological mechanisms of bipolar disorder

circuits (serotonergic neurons → paraventricular nucleus of thalamus (PVT) → nucleus accumbens, amygdala, etc.).

Lithium improves intracellular calcium elevation via inositol monophosphatase (IMPase) inhibition, antiepileptic drugs decrease neuronal excitability by blocking ion channels, antipsychotic drugs inhibit serotonergic neurotransmission in emotion-related neural circuits, and cognitive behavioral therapy normalizes abnormally biased emotional/cognitive balance. These treatments exert their effect on different layers of the neurobiology of bipolar disorder. A recent revision of the treatment guidelines of bipolar disorder by the Japanese Society of Mood Disorders [63] recommends a combination therapy of drugs with different classes. According to the recent understanding of the neurobiology of bipolar disorder, there would be a good reason to validate combination therapy, in addition to the clinical evidence [64, 65]. In line with this, new compounds acting on mitochondria could be a new strategy of mood stabilization.

15.12 Clinical Considerations

- Clinicians should be aware that bipolar disorder can appear as a part of somatic diseases.
- About 20% of patients with mitochondrial diseases show bipolar disorder.
- Lithium, anticonvulsants, atypical antipsychotics, and cognitive behavioral therapy may act on the neurobiology of bipolar disorder at different levels, and thus, combined therapy may be effective.

15.13 Future Perspectives

We searched for brain regions where mtDNA deletions accumulated in mutant *Polg* transgenic mice and found that the highest levels of mtDNA deletions accumulated in the paraventricular thalamic nucleus (PVT) [66]. Point mutations also accumulated in this region [67]. Selective inhibition [66] or stimulation [68] of this region produced depressive-like episodes similar to those in mutant *Polg* transgenic mice.

PVT receives projections from serotonergic neurons and sends outputs to the nucleus accumbens which is involved in positive emotion; amygdala involved in negative emotion; and the anterior cingulate cortex involved in mood regulation and is activated by various stress and antidepressant treatments [69]. Recently, the role of PVT in the representation of salience was suggested [70]. Single-cell transcriptomic analysis classified PVT neurons into five types, with some continuity [71]. The anterior and posterior parts of PVT have opposing functions and projection patterns. The anatomical location and functional divergence of PVT in humans have not been well-elucidated. Our recent effort by postmortem brain analyses as well as

clinical studies using diffusion-weighted MRI has successfully identified human PVT [72]. Whether PVT is involved in the cause of bipolar disorder should be further investigated to understand the consequence of mitochondrial dysfunction in bipolar disorder.

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Chapter 16

Brain Imaging in Bipolar Disorders: From Averages to Heterogeneity, from Commonalities to Individual Characteristics



Tomas Hajek

16.1 Introduction

Brain imaging allows us to study the structure, function, and chemical composition of the brain in a completely non-invasive and safe manner. The introduction of brain imaging to psychiatry could have resulted in a similar revolution as the introduction of a microscope to histopathology. Yet, it did not. As a clinician, I am well aware that my favorite research tool has over-promised and underperformed. Brain imaging has had a limited impact on the everyday practice of clinical psychiatry. Why?

The largest studies to date report that effect sizes for differences between bipolar disorders (BD) and control individuals in cortical or subcortical volumes are small, i.e., Cohen's $d = 0.1$ – 0.3 [1, 2]. These studies recruited thousands of participants, so the between-group differences are highly statistically significant, but they are clinically meaningless. Even the largest effect size of 0.3 in these studies means an 88% overlap among the distributions of regional measures in BD and controls. This means that many BD participants would have the same values (i.e., volume or thickness of a region) as controls and any test based on this measure would have a very low sensitivity. Similarly, many controls could have the same values as BD participants and any test based on this measure would have a very low specificity. For diagnostic utility, the two distributions would need to be almost completely separate.

In keeping with this, studies applying machine learning (ML) in order to differentiate people with BD from controls, have not reached clinically relevant accuracies. The accuracies of correctly differentiating people with BD from controls have ranged from 59.50 to 73.00% [3, 4] based on raw MRI data and up to 60–65% based

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on automatically segmented regional volumes [5, 6]. In one of the largest and most generalizable studies including 3020 participants from 13 sites around the globe, the accuracy of correctly classifying individuals with BD from controls was 65.23% (95% CI = 63.47–67.00) [6]. This is well below the 80% threshold, which is deemed clinically relevant [7]. Why do conditions which cause such pronounced perturbation in the life of our clients have such seemingly limited manifestations in the brain?

A typical excuse is that even the best currently available technology may be insufficient to tackle the mysteries of the human brain, which is the most complicated matter in the known universe. I do not think this is a valid explanation. The technology even now is sufficient to make major advances in understanding how the brain works. My thesis is that the main reason why brain imaging has not sufficiently informed clinical psychiatry relates to the fact that clinical psychiatry has not sufficiently informed brain imaging. I am talking about clinical heterogeneity, which is obvious to any clinician, but mostly hidden to brain imaging researchers.

Clinicians quickly realize in their practice, that people with the same diagnosis can be very different in their symptoms, clinical course, impact of illness on their functioning, response to medications, etc. Some people with BD fully recover from their tenth episode and return to full functioning. Others are left with chronic symptoms and never return to work after the first episode. Some people with mood disorders end up homeless, others help win the Second World War or receive a Nobel Prize. Some people with BD continue to be unwell on multiple medications; others have a full cessation of all episodes on monotherapy with lithium (Li). This clinical heterogeneity is likely a reflection of neurobiological heterogeneity.

Yet, despite these obvious and marked differences among people with the same psychiatric diagnosis, brain imaging studies still typically search for the mythical average patient. Effectively, they are trying to identify a one-size-fits-all brain change, which characterizes most people with the same diagnosis. This approach leads to problems with interpretation. In our meta-analysis of amygdala volumes in BD [8], we found that some studies found larger, some studies reported comparable and some found smaller amygdala volumes in individuals with BD relative to controls. The negative effect sizes canceled the positive effect sizes and the combined effect size from all studies was essentially zero, demonstrating no overall difference between patients and controls in amygdala volumes. We could conclude that based on a meta-analysis of all studies to date, amygdala volumes are comparable in people with BD and healthy controls. Yet, this conclusion would ignore the significant differences reported in individual studies and even more importantly the fact that some studies found smaller, whereas others found larger amygdala volumes in patients compared to controls. Focusing on these interesting differences and linking the clinical heterogeneity with the biological heterogeneity would seem more interesting than reporting that on average amygdala volumes are comparable in patients and controls.

Similar arguments can be made about essentially any other brain imaging modality. There are usually marked differences between studies, i.e., marked statistical heterogeneity, which likely reflects the clinical heterogeneity and different composition of samples with regard to relevant variables. If people with the same diagnosis

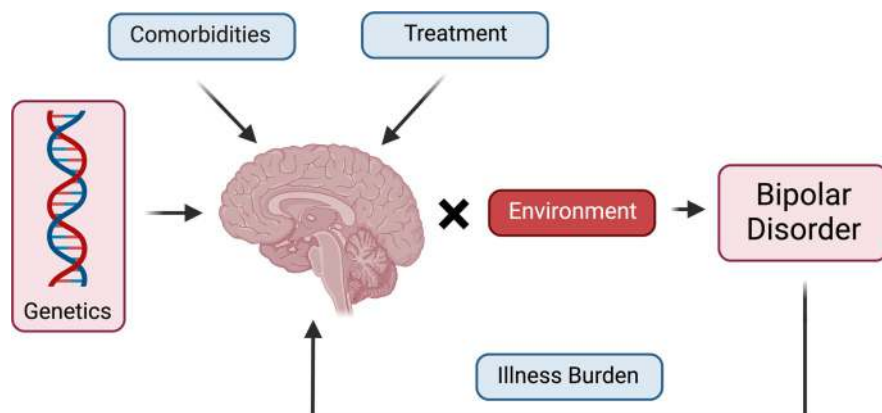


Fig. 16.1 Factors that contribute to brain alterations in bipolar disorders

of BD differ in their brain imaging findings, then the brain imaging findings cannot be purely related to the diagnosis. If they were, they would be consistent across people with the same diagnosis. Figure 16.1 shows some of the main factors that can contribute to brain changes in BD. Some brain alterations in BD likely reflect the genetic risk for the illness. But these genetically driven changes, which precede the onset of illness and could be used diagnostically are likely small and may be completely masked by other types of changes. These include changes related to broadly defined illness burden, which can be the number of episodes, time spent symptomatic, or duration of untreated depression [9–13]. Regardless of the causality, the brain of someone with multiple episodes would likely look different than the brain of someone who only had a few episodes. Comorbid conditions are a rule rather than an exception in BD and medical or psychiatric comorbidities leave their signatures on the brains of our patients [14–16]. We could for example imagine that certain brain changes in BD, are simply a reflection of certain comorbidity and would thus occur only in those with that specific comorbidity [17]. Last but not least any treatments, including both biological and psychological ones, likely modify the very structure of the brain, which is remarkably plastic [18–20]. The particular type and extent of changes observed would thus reflect a unique combination of the above-mentioned factors in the studied group of participants.

In a typical study, the individual factors from Fig. 16.1 are usually not quantified at all or are quantified with little precision. Studies may vastly differ in these relevant factors even if they all focus on people with the same diagnosis. It is impossible to replicate a recipe if you do not know the exact quantities of individual ingredients. Consequently, without the additional details, it becomes impossible to replicate the findings in brain imaging studies of BD participants. In this sense, the so-called crisis of replication in psychiatry is hardly surprising. Studies which broadly compare individuals with versus without BD, while ignoring many other relevant characteristics related to brain changes, are not going to show replicable results. What can we do about this?

It is my belief that the field needs a paradigm shift of sorts, where we move from looking at average differences across groups of patients to studying individual sources of those differences. In other words, we need studies which focus on the heterogeneity. Focusing on commonalities/averages and ignoring the differences, i.e., the heterogeneity, is not going to be helpful in multifactorial and complex illnesses, such as BD. Heterogeneity is not an annoying noise that we need to control for. It is something that can give us important insights into the illness. Focusing on heterogeneity provides a much more nuanced understanding of BD. Below, I outline some success stories that originated from this approach.

16.2 Brain Signatures of Genetic Risk for BD

Even if we were able to precisely quantify the effects of each relevant clinical dimension on the brain, it may not be enough, as there may be interactions among variables. For example, medications or comorbid conditions may mask or seemingly amplify changes related to the illness itself. Also, individual clinical factors do not exist in isolation. All BD individuals have a history of episodes; most BD individuals are now treated and most have comorbid conditions. However, what if we could identify people who are at high risk of developing the illness, but have not had episodes, treatment, or comorbid conditions? We could then study the biological risk for illness without confounding by illness-related variables. How could we do that?

The strongest risk factor for bipolar disorders is a family history of BD in first-degree relatives. Unaffected offspring of bipolar parents have a 10–15 times greater risk of developing BD than the general population. Brain alterations identified in these individuals are likely markers of risk for the illness, especially if we find similar alterations in the offspring of bipolar parents who already developed the illness. This, so-called genetic high-risk (HR) design is a particularly powerful way to identify endophenotypes or biological risk factors for BD. There is one caveat—the age of the studied individuals. The genetic susceptibility for BD in unaffected relatives of BD decreases with age. A person who was just born to parents with BD has his whole life in which he can develop the illness ahead of him. An 80-year-old offspring of parents with BD, who is still unaffected, likely did not inherit the susceptibility for BD. Therefore, the high-risk studies need to focus on people before or around the average age of illness onset; otherwise, they would be selecting for people who are free of genetic risk for BD. These genetic high-risk studies provided very interesting findings in terms of what they found, but also in terms of what they did not find.

What did these studies find? Genetic high-risk studies in BD provide remarkably consistent results. In a multisite, replication design HR study, we found replicated evidence that larger right inferior frontal gyrus (rIFG) volume was a marker of genetic risk for BD. Larger IFG was found among both Unaffected HR subjects and Affected Familial participants across two centers [21]. In a related study, we provided a proof of concept that using machine learning (ML) applied to structural

brain imaging can help identify subjects at genetic risk for BD, in part based on the larger rIFG [22]. At least four other independent research groups replicated this finding [23–27]. Increased IFG gray matter volume has previously been found in the early course of BD, in patients with first episode of mania [23]. Greater IFG volumes were also reported in both euthymic BD patients and healthy first-degree relatives when compared to healthy controls [25, 26]. Importantly, two meta-analyses found larger IFG gray matter (GM) volume in relatives of people with BD compared to healthy controls [28, 29]. In both meta-analyses, the larger IFG volumes were coupled with greater activation of the IFG during cognitive tasks and IFG was the only region that showed this convergence of findings. Furthermore, the IFG changes were specific to BD, as BD-relative showed a higher probability of convergent alterations in fMRI and VBM studies in the right VLPFC (BA 47) than relatives of people with schizophrenia [28].

In contrast to individuals at genetic risk, there is replicated evidence that IFG is smaller in people with fully developed BD, especially after a longer duration of illness [24, 30–32] and that there is a significant negative correlation between the duration of illness and gray matter volume in this region [21, 24]. In keeping with this, a meta-analysis found that right IFG is among the regions which are most consistently reported to have lower volume in adult individuals with fully developed BD relative to controls [33]. Several longitudinal studies reported accelerated loss of frontal GM in people with BD relative to controls [34], and cortical thinning in inferior frontal cortices in relation to manic/hypomanic episodes [12]. All in all, aside from the fact that IFG structural change is found in unaffected relatives, it is also associated with the illness and is heritable [35, 36]. Thus, volumetric alterations of IFG meet the criteria for a brain imaging endophenotype of BD [37].

It is very interesting that the patterns of IFG alterations differ between relatives of people with BD, where IFG is larger, and people with full illness, where IFG is smaller, especially in those with longer duration of illness. The larger rIFG volume may be a marker of an early stage of BD, which manifests already in the absence of any diagnosable behavioral alterations among unaffected offspring of bipolar parents. At the same time, the longer a person suffers from BD, the smaller his IFG becomes. The fact that neuroanatomical markers of vulnerability for BD may be dynamically affected by illness-related variables further complicates the use of MRI for diagnostic purposes. It also suggests some novel mechanisms, which may determine brain structure in BD. To understand these, we need to look at structure–function links.

The larger rIFG volume does not seem to be a marker of resilience because the rIFG volumes were also larger among affected subjects. Alternatively, this could be an example of illness-related plasticity. Perhaps BD patients need to “over-exercise” the rIFG to compensate for some cognitive or executive deficits or to maintain euthymia. Over time, the increased functional demands on this region may render it more vulnerable, eventually resulting in atrophy. Indeed, a longitudinal study found that compared to controls, HR participants showed accelerated cortical thinning and volume reduction in right lateralized frontal regions, including the inferior frontal gyrus IFG (pars triangularis and pars opercularis) [38]. In an expanded sample and using a different method of analyses (automated segmentation), we replicated the

finding of larger IFG volume in relatives of BD probands and also located maximum differences in the pars triangularis subdivision [39]. What could be the functions involved in this?

Studies in healthy individuals and lesion studies have shown that the pars triangularis of the IFG is not only associated with but also necessary for successful response inhibition [40–42]. Impaired response inhibition is central to many symptoms of mania, such as increased risk-taking, impulsive behavior, talkativeness, and excessive spending. Interestingly, previous studies suggested that an impaired response inhibition is the most likely candidate for a neurocognitive endophenotype for BD [43–45]. In keeping with this, two meta-analyses reported increased activation of IFG during cognitive tasks in relatives of individuals with BD [28, 29]. In contrast, BD is marked by diminished activity in the IFG, particularly during response inhibition to emotional stimuli [46] and during reward processing [47]. So IFG structure, activation, and cognitive functions subserved by this region, i.e., response inhibition, meet the criteria for an endophenotype in BD. This conclusion has excellent face validity vis-à-vis symptoms of illness and is very robust as evidence for each of these facts is replicated and congruent across different studies.

So the findings are highly replicated between studies as well as between modalities and point toward key cognitive concepts. They also show some interesting differences between people at risk and those with fully developed BD. Consequently, it is interesting to look at what these studies did not find. Individual HR studies [21, 28, 29] and the largest investigation to date, a mega-analysis of 852 first-degree relatives of BD probands (FDR-BD) [48], showed that many of the neuroimaging changes previously reported in BD are absent in those at risk for the illness. Also, in contrast to smaller brain volumes generally reported in BD, de Zwarte et al. found larger brain volumes and larger intracranial volume (ICV) in first-degree relatives among FDR-BD. When controlling for ICV, there were no significant differences in brain measures between FDRs-BD and control subjects, including regions such as basal ganglia, amygdala, hippocampus [48]. This is a striking finding, which does not receive enough attention. The fact that relatives of BD probands if anything have larger brain volumes, whereas individuals with fully developed BD show a range of volumetric decreases has important implications. It may suggest that most of the alterations we see in people with fully developed BD are actually a consequence of BD, not its cause. Even more importantly, if many of the brain changes in BD are not pre-existing, perhaps we may be able to prevent them. In order to do that, we need to identify risk and protective factors for brain changes in BD.

16.3 Risk Factors for Brain Changes in BD

Identifying risk factors for brain alterations is critical not only for research but also for clinical care. Some of the risk factors for brain alterations in BD may be preventable or at least modifiable. Focus on the prevention or treatment of these risk factors could create opportunities for the prevention or treatment of brain alterations and

related adverse clinical/cognitive outcomes. As these risk factors may not be found in all individuals with BD, targeting them would allow for more rational, personalized treatment approaches. Also, identifying risk factors for brain changes in BD could help us better understand the pathophysiological mechanisms underlying these alterations. Understanding the mechanisms could help identify new biological targets, which could lead to the development of new treatments [49].

The traditionally studied risk factors for brain alterations include a broadly defined burden of psychiatric illness. This generally means the cumulative impact of illness, including the duration, time spent ill, number of episodes, duration of untreated depression, etc. [9–13]. The hypothesis that there is a pathological reorganization of the brain during the course of illness [12, 13, 50], which may contribute to cognitive and clinical deterioration is termed neuroprogression [51, 52]. However, the illness burden is difficult to measure. It is virtually impossible to retrospectively quantify the number of days spent symptomatic. Even quantifying the exact number of episodes may be difficult, especially in people with chronic, residual symptoms. Lastly, there is the issue of reverse causality, where more pronounced brain alterations may actually be a cause of a more severe/recurrent illness, not a consequence of it [53]. A progressive course of illness may apply only to some individuals with BD [52]. While it is clearly wrong to state that neuroprogression applies to all people with BD, it is equally wrong to discard this hypothesis on the grounds that it may not apply to all BD participants [52]. This is precisely the same error which I discuss in the introduction. In a complex disorder such as BD, one size clearly does not fit all. In any case, the illness burden is already targeted by available treatments, which generally try to treat or prevent episodes of illness. Therefore, focusing on illness burden does not give us new ways to improve the prognosis of psychiatric disorders. Consequently, we should look for predictors of brain alterations, which are frequent in BD, preventable, modifiable, easy to quantify, and targeted by specific treatments other than psychiatric medications. One such target is obesity.

Obesity is the fifth leading cause of death globally and one of the leading causes of disability [54–56]. Obesity is disproportionately frequent in individuals with BD. Between one-half and two-thirds of individuals with BD are overweight or obese, yielding three times higher odds of obesity in BD relative to the general population [57–62]. High rates of obesity in severe mental illnesses (SMIs) may be related to shared genetics, pathophysiology, and risk factors, including effects of medications or lifestyle factors [16, 63]. Regardless of the reasons for the comorbidity, we need to better understand the brain, cognitive, and psychiatric correlates of obesity in SMI.

Shorter life expectancy, high cardiovascular morbidity/mortality, and high rates of dementia in SMI can all be tracked to comorbidity with obesity [64–68]. There is another hidden problem, which receives even less attention, but at a great cost. We and others have shown that SMIs complicated by obesity or related metabolic alterations are associated with greater psychiatric morbidity, chronicity, disability, functional deterioration, and worse response to psychiatric medications [69–77]. These psychiatric correlates of a peripheral disorder, such as obesity, are likely related to the associations between obesity and brain structure/cognitive functioning [78, 79].

Indeed, it is becoming clear that the brain is one of the target organs for obesity-related damage. Obesity is commonly associated with structural and functional brain alterations [80–84], accelerated brain aging [85–88] and with an increased risk of cognitive impairment and dementia [89–92]. This link was long ignored, on the assumption that brain changes seen in obesity were related to cardiovascular sequelae of obesity. But this is not always the case. Obesity remains associated with cognitive or brain changes even when we control for vascular risk factors and these links appear causal [85, 93–96]. Also of note, obesity is associated with increased risk not only of vascular dementia but also of Alzheimer dementia [89, 97, 98]. In fact, in the USA, the proportion of Alzheimer's dementia that is attributable to obesity is 21% [89]. As individuals and as a society we should not ignore these numbers.

Obesity is associated with some of the same brain [80–83] and cognitive alterations [99–101] as BD [1, 2, 15, 102]. Yet, we cannot extrapolate from studies that separately studied BD or obesity as there can be interactions between the two. In other words, the presence of BD, may for example amplify alterations associated with obesity. Indeed, previous findings have suggested that the combination of obesity and psychiatric illness on diverse outcomes, including brain volume, may be worse than the sum of them [103–105]. Also, we can only quantify the contribution of BD or obesity to specific brain alterations in studies that represent both predictors. In addition, when synthesizing the brain imaging literature across SMIs, we can make the following statements. The brain imaging alterations partially overlap across MDD, BD, and schizophrenia [106, 107] and markedly differ among people with the same diagnosis [108–110]. These facts could be explained by shared comorbidity with obesity, but only if we study the conditions jointly. Therefore, we need studies specifically on people with obesity and SMI.

In collaboration with the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) consortium, we performed the largest studies mapping the brain correlates of both obesity and BD [17, 108, 111, 112]. These studies have documented (a) negative associations between obesity and gray matter cortical thickness or fractional anisotropy of white matter, (b) regions where these obesity-related alterations occur overlap with regions associated with BD, (c) the effects of obesity and BD are additive, i.e., will be most pronounced in individuals with both BD and obesity, (d) obesity plays a role in associations between obesitogenic medications and brain structure, and (e) obesity was associated with similar cortical alterations as both BD and schizophrenia [108, 112].

These results have replicated the negative associations between obesity and cortical thickness, especially in the caudal and rostral anterior cingulate, entorhinal cortex, and several frontal lobe regions [81, 112, 113], but with much fewer correlates in surface area [112, 113]. When initiating these studies, we expected to find interactions between BD and obesity, such that the statistical effects of obesity on brain structure would be more pronounced in BD than in controls. We did not find that. What we did find was that BD and obesity each independently contributed to brain alterations in a given person [17, 111]. The effects of obesity and BD are additive, i.e., will be most pronounced in individuals with both BD and obesity, relative to people with only one or none of these conditions. In other words, BMI may be an

easy-to-acquire method to gauge the extent of brain alterations in BD. Also, this means that the extent of brain alterations in people with BD will vary based on their BMI, thus resulting in differences in brain imaging findings between people with the same diagnosis. The varying presence of obesity-related brain alterations in people with SMIs could also explain variations in clinical outcomes, as brain imaging changes tend to be associated with cognitive alterations, which are among the strongest determinants of functioning [114–117].

The overlap between regions associated with obesity and those linked with BD is quite striking. While there are unique regions associated only with BD, most of the regions associated with obesity overlap with regions associated with BD. Specifically, 90% of cortical brain regions, which are associated with obesity were also associated with BD [111]. Furthermore, obesity significantly contributed to brain changes in BD. Specifically, we demonstrated that ventriculomegaly in BD was to a large degree (up to 47%) mediated by obesity [17]. It is surprising that ventriculomegaly, which is perhaps the most replicated finding in BD is in fact to a large degree related to high rates of obesity in BD. Differences in ventricular volumes between individuals with BD and controls may in fact be smaller and less consistent than previously reported and may in part depend on factors other than the diagnosis of BD. Any explanations of ventriculomegaly in BD need to take into account the comorbidity with obesity.

People often puzzle about the overlaps across MDD, BD, and schizophrenia [106, 107]. The traditional explanations look for shared pathology, but these findings could also be explained based on shared comorbidities. Indeed, in one of our studies, we saw that 11/12 regions where obesity was associated with lower cortical thickness were also associated with lower cortical thickness in schizophrenia [112]. Many of these regions, including the anterior cingulate, fusiform gyrus, and several frontal lobe regions, were the same regions that were associated with both BD and obesity in a separate study [111]. These were also the same regions reported to be associated with obesity in another large study of participants with MDD and controls [113]. Furthermore, the effect sizes across cortical regions for differences between people with versus without obesity are highly correlated with effect sizes for differences between people with versus without MDD ($r = 0.452$) or BD ($r = 0.513$) [113]. These findings could help explain the marked overlap among major psychiatric disorders in brain imaging alterations [107, 118]. Perhaps this overlap is related to the high rates of obesity, which are present across SMIs.

The brain correlates of obesity also provided insights into the effects of obesitogenic medications on the brain. There is a growing body of literature showing that many psychiatric medications, including antipsychotics [119–121] and anticonvulsants [2, 122, 123] are in fact negatively associated with brain structure. Many of these medications are also obesitogenic. If obesity is associated with brain alterations and some medications are associated with obesity, it is also likely that the obesitogenic effects could explain some of the negative effects of these medications on the brain. Indeed, in the fusiform gyrus, 34.6% of the medications versus cortical thickness association was mediated by BMI. However, this was not the dominant pattern. In general, the number of medication classes used jointly (including

anticonvulsants, antipsychotics, and antidepressants), was significantly associated with lower cortical thickness in 22/34 ROIs (64.7%) even when controlling for BMI [111]. So the negative effects of BMI on cortical thickness did not fully explain the negative effects of medications on the brain. In contrast, Li was significantly associated with greater cortical thickness in 9/34 ROIs (26.5%) even when controlling for BMI. In other words, the negative effects of BMI on cortical thickness did not cancel the positive effects of Li. In fact, a significant negative association between BMI and cortical thickness became non-significant in the isthmus cingulate and rostral anterior cingulate when modeled jointly with the significant positive effect of Li on cortical thickness [111].

When interpreting these results, we need to keep in mind the cross-sectional nature of these studies. The association is not causation, so we cannot infer the causality or temporal direction of these effects. It is possible that obesity causes brain changes or that brain changes cause obesity. Neurostructural/functional alterations in the reward system [124], conditioning to hedonic stimuli [125], or in appetitive behavior [126, 127] could predispose people to obesity. On the other hand, obesity could cause brain alterations via systemic inflammation, oxidative stress, insulin resistance/diabetes, atherosclerosis, hypertension, or dyslipidemia [16, 78, 80, 128–131]. While both directions may be at play simultaneously, obesity as a cause of brain alterations appears to be the more prominent link for the following reasons. Previous studies investigating associations between genetic risk for obesity and brain structure reported involvement of a much smaller set of regions, i.e., surface area of the lateral occipital lobe [113] or medial prefrontal volume [132] than those found to be linked with obesity by us and others [81, 112, 113]. Also, prospective studies show that obesity is a predictor of future brain alterations [86, 133]. Treatment of obesity leads to alleviation of brain changes [134] and Mendelian randomization studies suggested a causal link between obesity and brain alterations [95, 96].

The effects of obesity on a wide range of neurostructural measures, which are additive and similar to the effects of BD are frankly concerning and more pronounced, diffuse, and replicated than we initially anticipated. This could explain both the neuroanatomical overlap across SMIs, which share comorbidity with obesity, as well as the differences between people with the same diagnosis, due to the additive effects of varying rates of obesity across people with the same diagnosis. If obesity contributes to brain changes, we have a modifiable and treatable risk factor for brain alterations. Consequently, targeting obesity could lower the extent of neurostructural alterations in BD. This could also ameliorate currently intractable outcomes, such as cognitive impairments, residual symptoms, and poor functioning, which have also been associated with obesity or neurostructural alterations [114–117]. In addition, this line of research could help identify novel treatment targets and mechanisms of action. Perhaps some novel pharmacological approaches to the treatment of obesity and related metabolic alterations such as the GLP1 agonists could also aid in the treatment of brain changes and related psychiatric outcomes [135]. Aside from pursuing this line of research, we should also look for other options for neuroprotection in BD.

16.4 Neuroprotective Factors in BD

One of the most replicated brain imaging findings in unipolar depression (UD) is smaller hippocampal volume [136, 137]. In contrast, most meta-analyses in BD reported comparable hippocampal volumes between BD participants and controls and greater hippocampal volume alterations in unipolar depression versus bipolar disorders [136, 138]. This is truly puzzling. There are no biological markers or symptoms found in unipolar depression, which are also not manifest in BD. In addition, depression in BD is typically the main manifestation of the illness [42], is more likely to recur [43], and may start earlier [44] than unipolar depression. Perhaps the reasons for this discrepancy between UD and BD are not related to the illnesses *per se* but rather to differences in treatment. Perhaps the reason for this discrepancy lies in the greater use of putatively neuroprotective medications in BD.

Lithium is the gold standard for the treatment of BD. While it has antidepressant properties, it is rarely used in UD. Li is one of the most bioactive elements and has one of the most replicated preclinical evidence for neuroprotective properties. Neurons pre-treated with Li are protected from a range of toxic stimuli in a range of disease models. Among 28 psychiatric medications, including antipsychotics, anti-convulsants, and antidepressants, Li demonstrated the most replicated evidence for neuroprotection in the widest range of models [139]. The neuroprotective valence of Li, determined by the sum of its valence score for neuroprotective actions minus its valence score for neurodegenerative actions, was +36. Antipsychotics did not get scores above five, antidepressants did not get above 13 [139]. Could the neuroprotective properties of Li and the fact that it is more frequently used in BD explain why hippocampal volumes appear to be preserved in BD?

We tested this in a meta-analysis, where we separated the studies based on the presence or absence of Li treatment [20]. We expected that hippocampal volumes would be smaller among BD individuals with no current exposure to Li, relative to Li-treated individuals who would show comparable hippocampal volumes to controls. As expected, BD participants who were not treated with Li had significantly smaller hippocampal volumes than controls (Cohen's $d = -0.36$ to -0.38) or Li-treated BD individuals (Cohen's $d = -0.93$ to -1.07), who had significantly larger hippocampal volumes than controls (Cohen's $d = 0.51$ – 0.53). If the data were analyzed jointly in the Li and non-Li groups, the negative effect sizes in the non-Li to controls comparisons would be canceled by the positive effect sizes in the Li versus controls comparisons, resulting in seemingly no difference between patients and controls. Consequently, the preserved hippocampal volumes among BD subjects in previous meta-analyses which included both Li-treated and Li-untreated individuals could have been related to the inclusion of Li-treated participants.

The meta-analysis also demonstrated that individuals with BD do have smaller hippocampal volumes, of similar extent as in people with UD, but only once exposure to Li is controlled for. The meta-analysis did not fully explain why individuals on Li had larger hippocampal volumes than controls or people with BD who are not treated with Li. This is because Li treatment in the included studies was defined

only by often self-reported presence or absence of Li treatment at the time of scanning, without any information about the dose, duration, or compliance.

To counter this shortcoming, the International Group for Study of Li Treated Patients (IGSLi) designed and ran a series of studies with a unique design. Studying the effects of Li on the brain early in the course of illness, where brain changes secondary to the illness may be small or non-existent, would not be optimal. Therefore, in order to maximize the effect of BD on the brain, we recruited only BD participants with substantial illness burden, i.e., at least 10 years duration of illness and at least five major affective episodes. By setting stringent criteria for the presence or absence of Li treatment, we ensured a sufficient contrast between the groups in exposure to Li and minimized any effect of past history of Li treatment on the brain. Specifically, Li-treated participants had to have a documented history of Li treatment for at least 2 years, including compliance verified by repeated Li levels. This was made easier by recruiting participants from specialized Li clinics. The non-Li group had to have less than 3 months of Li more than 2 years ago, to minimize any carry-over effect of previous Li treatment.

These studies showed a remarkably consistent picture across different sites included in IGSLi and across different brain imaging modalities. In all sites and all measures, Li-treated individuals had comparable hippocampal volumes, prefrontal NAA levels relative to controls, despite the fact that the Li-treated individuals had a substantial burden of illness [140–142], an average of 27.1 years of highly recurrent illness and 11 episodes of BD [141]. In addition, BD individuals not treated with Li had smaller hippocampal volumes and NAA levels than Li-treated participants, despite the fact that both clinical groups had comparable illness burden.

We were particularly interested in the association between the effects of Li on the brain and treatment response. It is possible that Li acts on brain structure indirectly by treating or preventing episodes of illness. If that was the case, the positive effects of Li on brain structure would only be seen in responders to treatment and the putative neuroprotective effects of Li would not be of benefit to people without BD. It is also possible that the effects of Li on the brain are independent of mood-stabilizing properties of Li. In the IGSLi studies, the positive association between long-term Li treatment and hippocampal volumes was independent of treatment response and occurred even in participants with episodes of illness while on Li [142]. This suggests that the effects of Li on GM may be related to some of its biochemical properties and are not just an epiphenomenon of treatment response. This in turn suggests that even individuals without BD could benefit from neuroprotective effects of Li.

One relevant criticism of these studies was the generalizability of the findings. After all, individuals treated in specialized clinics may not represent the broad picture of BD treated in outpatient settings. In this sense, it is remarkable that Li treatment is positively associated with GM thickness, subcortical volumes and even fractional anisotropy measures in the largest and most generalizable mega-analyses performed by the ENIGMA consortium, including thousands of BD individuals [1, 2, 143]. These studies compile data from legacy datasets across studies with different exclusion and inclusion criteria performed around the world and are thus as generalizable as can be.

Perhaps most importantly, association is not causation, so we cannot infer causality or temporal direction of changes from cross-sectional studies and need longitudinal study designs. The first longitudinal study showed total brain gray matter increases of ~3% (24 cm³) after 4 weeks of Li treatment [144]. Gray matter increases after 4 weeks of treatment were replicated in another study in BD [145] and one in controls [146]. Three additional prospective controlled studies demonstrated a greater increase in GM in BD participants treated with Li relative to prospectively followed controls or individuals with BD receiving valproate [147–149]. One of these studies was a randomized controlled trial (RCT), thus eliminating prescriber-related bias. Participants randomly assigned to Li treatment showed GM increases relative to individuals randomly assigned to valproate [148]. Across the studies, the Li-related changes occurred in total GM, hippocampus, prefrontal cortex, subgenual cingulate, and dorsolateral prefrontal cortex. They were detectable after 4 weeks, peaked after 10–12 weeks, and were still present after 2–4 years of Li treatment.

We can conclude that there is in fact level I evidence for the positive association between Li treatment and brain gray matter volume, which has been repeatedly demonstrated in cross-sectional studies, meta-analyses, mega-analyses, and replicated longitudinal studies including a randomized controlled trial. For a more detailed discussion of these studies and their limitations, see [150]. This still leaves a lot of questions. If Li alleviates GM alterations, could it also lower the risk of neurodegenerative disorders, which are elevated in BD? Could it also do the same even in people without BD?

A more detailed discussion of the topic of Li treatment in neurodegenerative disorders is beyond the scope of this paper. Briefly, population studies, showed that repeated Li prescriptions are associated with lowering the risk of dementia, whereas repeated prescriptions of valproate are linked with increasing dementia risk [151]. Similarly, continuous prescriptions of Li for 301–365 days reduced the risk of alzheimer's dementia (AD), whereas continuous prescription of anticonvulsants increased it [152]. Overall 4/6 studies found that lithium reduced the risk of dementia in individuals with BD, cumulatively showing 49% (OR: 0.51 [95% CI: 0.36–0.72], $P < 0.0001$) risk reduction of dementia in Li-treated individuals [153]. These population or cohort studies are an interesting natural experiment, but they do not protect from prescriber or patient-related biases. A multisite RCT in AD did not show an overall impact of Li on symptoms of dementia [154], but there was a positive effect of Li on cognition and Brain derived neurotrophic factor in one site [155]. This trial however was performed in individuals with fully developed AD, when it can be too late to interfere. Perhaps even more importantly, the duration of Li treatment in this trial was very short—6 weeks titration, 4 weeks maintenance phase. Surely, 10 weeks of treatment is unlikely to make a difference in fully manifest AD, where biological changes may occur decades before the onset of symptoms [156]. Trials in amnesic mild cognitive impairment aMCI, which are also generally longer, showed a positive impact of Li on progression of cognitive impairment and on AD-related biomarkers [157–159]. Some concerns about the safety of use in the elderly and of the dosing have been expressed as the main reason for not pursuing research into Li as a neuroprotective treatment [160]. Recent studies document that

Li can be safely used in the elderly and in fact, is associated with positive health outcomes [161]. Also, doses used for the treatment of mood disorders may not be required for the neuroprotective indication. Levels/doses of Li below the therapeutic range for the treatment of mood disorders prevented cognitive loss in aMCI [158, 162], even when microdoses of Li (300 µg) were used [162]. In fact, even trace levels of Li in drinking water, presumably consumed over the lifespan of the individual, were associated with a lower risk of AD [163, 164] or AD-related mortality [165, 166].

So among psychiatric medications that were considered for repurposing as neuroprotective agents, Li shows the most replicated evidence across the largest range of different studies, from tissue cultures, and animal models, through population studies on Li and lower risk of dementia, including level 1 evidence for the association between Li and GM in human participants and even some signal in RCTs targeting mild cognitive impairment. In the absence of disease-modifying treatments for any neurodegenerative disorders, we cannot afford to ignore this robust and replicated evidence base [167]. Yet, continuing research into the effects of Li is minimal. This is likely related to the fact that as a natural element, Li cannot be patented. The future of research into neuroprotective effects of Li is unlikely to come from big pharma and it lies on the shoulders of academics. All I am saying is “give Li a chance.” For more detailed review of these studies, see <https://hajeklab.com/presentations/>

16.5 Novel Trends

As of the early 2000s, typical brain imaging studies included tens of participants. I remember how excited I was when in 2011 I read the first mega-analysis which contained 321 individuals with BD [168]. Five years later I was fortunate enough to contribute to a study with over 1700 BD participants [1]. Large-scale, multisite brain imaging datasets are becoming more common through initiatives such as ENIGMA [111], ADNI [169], ABCD [170], the human connectome project [171] and others. One of the first attempts to do this was the ENIGMA consortium, which was established by Dr. Thompson and has since become one of the most successful initiatives in the field of brain imaging. ENIGMA works with legacy datasets and provides a platform for interested researchers to combine their fully anonymized data across studies by facilitating sharing and standardizing analytical procedures. This has allowed the group to publish some of the largest and most cited brain imaging studies in MDD, BD, and schizophrenia [2, 113, 119].

A common misconception is that large studies are needed to increase statistical power. Yet, this may not be particularly beneficial. The greater statistical power means that even smaller differences become statistically significant. However, such small differences are typically clinically insignificant and of little use in translating brain imaging findings to individual persons with SMI. There are other reasons why large studies are beneficial. These reasons include: (1) studying interactions, (2)

obtaining representative samples of people with a given disorder, and (3) applying cutting-edge multivariate machine learning (ML) techniques.

Analyzing interactions is statistically power-hungry. If we want to accurately model the unique and combined statistical effects of several conditions (i.e., obesity and SMI) we need large samples. Second of all, individual smaller studies with stringent inclusion criteria typically do not provide generalizable findings. This is one of the underappreciated advantages of large, multisite datasets—they provide a generalizable snapshot of the illness across multiple geographic locations.

Thirdly, and this is a key consideration, the traditional mass univariate analyses, which analyze individual brain regions as separate dependent variables may not adequately capture the network characteristics of complex disorders. It is clear that there is not going to be a single brain lesion that is necessary and sufficient to cause BD, so the focus needs to shift from individual regions to networks, from mass univariate to multivariate analyses. Multivariate techniques, such as machine learning, increase predictive power by targeting alterations distributed throughout the whole brain, which may better characterize patterns of brain changes in SMIs or obesity. These approaches require large samples to optimize the performance of the classifier, provide a generalizable snapshot of the studied disorder, and allow for rigorous cross-validation in left-out datasets. Results of the ML methods can be difficult to interpret and translate into practice, which still leaves room for other types of multivariate analyses including clustering [108] or principal component analyses [172].

These novel ways of analyzing large datasets yield very interesting results, which could not be uncovered by traditional mass univariate techniques. For example, in our recent study, we applied clustering to brain imaging data in a large sample of 2436 individuals. The algorithm detected two clusters which however were not clearly separated and essentially divided the distribution of similarities in cortical thickness among participants into two almost equal parts. One cluster/part of the distribution had generally lower cortical thickness than the other. More importantly, individuals in the low-thickness cluster were more likely to be diagnosed with BD, have higher BMI, and be older. At the same time and perhaps most remarkably, 45% of BD individuals were categorized into the higher-thickness cluster, together with most of the controls (57%). The BD individuals in this cluster were more likely to have bipolar II disorder or be treated with Li. This shows that the boundaries between BD and controls in terms of brain imaging findings are not particularly well defined and depend on the stacking up of additional neuroprotective (Li) and neuroprogressive factors (obesity) [108].

This is in keeping with another finding, which consistently emerges from applying multivariate analyses to large datasets. Multivariate brain patterns often lack specificity and tend to be associated with a wide range of system-level variables. There seems to be a nonspecific background of brain alterations, which is shared across many different disorders [107, 173–175]. For example, PCA detected a profile of cortical thickness alterations, which explained 48% of the variance in brain imaging data and was shared across six major psychiatric disorders [176]. Data from ENIGMA consortium also confirm marked neuroanatomical overlap across adult psychiatric disorders [118]. This general dimension derived from

neuroimaging data is sometimes termed “neural P-factor” [177] and it poses a significant challenge when we try to uncover disorder-specific signatures in the brain. Some have argued that there may be more cause-specific alterations after removing this nonspecific pattern of the first component [175]. However, the lesser principal components usually explain less than 5% of variance in the data. All in all, many different variables, including age, obesity, and psychiatric diagnoses may be negatively associated with overlapping patterns of cortical thickness across a wide range of cortical regions.

16.6 Future Directions

Increasing the sample size of future studies is not going to be sufficient to resolve key issues as the quality and depth of phenotyping in large, legacy datasets is limited. We cannot correctly name the phenomena we observe through the lens of MRI scanners without having much more information about the participants, beyond just the diagnosis. Future studies would benefit from better quality clinical data, i.e., clinical psychiatry needs to better inform brain imaging. Measures such as medications at the time of scanning, which are frequently used in studies, are not a sufficient proxy for medication exposure. Similarly, while studies may exclude individuals with certain comorbidities, many of the comorbid conditions that are frequent in BD, such as anxiety disorders or substance use/abuse are usually permitted, but not quantified or included in analyses. In addition, cardiovascular risk factors such as obesity, diabetes, and hypertension, which are rampant in BD, are usually not the basis for exclusion and are usually not accounted for in the analyses.

Obviously, novel biomarkers that are beyond everyday clinical practice are important, but a lot of key insights can be gained from collecting everyday clinical data. Ideally, research should be integrated with clinical services, where regular follow-ups provide a wealth of information as a part of clinical practice. It is much easier to add research visits to people who have regular clinical follow-ups than to obtain high-quality/high-density clinical data from research participants who are recruited by advertisement and seen once.

Brain imaging could provide objective and precisely quantifiable outcome measures in clinical trials. Outcomes based on reductions of symptoms or symptomatic thresholds are not sufficient. For example, a 50% reduction in symptoms does not guarantee a return to premorbid functioning and does not guarantee a favorable prognosis with regard to the risk of recurrence. Perhaps specific brain alterations could be the outcome measures in future treatment trials, especially if we chose measures that are closely associated with cognitive functioning or favorable prognosis. The treatment goals should be expanded from reductions of symptoms to maintaining the premorbid state of the brain.

We should also by now be awakening to the fact that we are unlikely to be dealing with static lesions. Brain is incredibly plastic and continuously sculpted by among others episodes of BD, medications, psychotherapy, and comorbid

conditions. So the focus should switch from static, cross-sectional studies to dynamic, longitudinal observations. Prospective studies continue to be rare but will be necessary to address many of the most interesting and clinically relevant research questions. For example, we cannot identify predictors of future brain, cognitive alterations, or poor clinical outcomes in cross-sectional studies. Answering many of the most interesting and clinically relevant research questions will ultimately require a prospective design. Cross-sectional studies cannot determine whether observed brain/cognitive/biochemical abnormalities result from the progression of pathological changes over time or represent static and/or pre-existing conditions. As clinicians, we want to prognosticate the future trajectory of the illness based on current symptoms/clinical factors. Only a longitudinal study can give us such information and help us identify which baseline factors predict future worsening of brain/cognitive and clinical outcomes. Identifying risk factors for adverse neurobiological outcomes could inform new preventive or treatment strategies for currently intractable clinical problems and is a key area of research.

16.7 Conclusions

The picture that is starting to emerge from brain imaging studies in BD is one of marked structural plasticity, where brain structure in BD is not static, but may dynamically reflect the changing balance between neuroprogressive and neuroprotective factors. Many of the brain changes found in adults with BD are not pre-existing and emerge only later in the course of illness. In addition, the alterations may be made worse by medical comorbidities such as obesity, or they can be made better by for example treatment with Li. It is a combination of factors that create a particular set of alterations in a given individual with BD. Considering this, it is not surprising that brain imaging findings across individuals and across studies are so heterogeneous. It is also not surprising that the boundaries between neurotypical and atypical phenotypes may be less clear than we thought, as many of the risk factors for brain alterations can also be found in people without BD. One size fits all approach based on averaging across many people and ignoring relevant sources of heterogeneity will not get us much further. These findings emphasize an individualized approach focusing on unique clinical, anthropometric, and demographic characteristics of each individual.

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Chapter 17

Neuropathology of Bipolar Disorder



Camila Nascimento, Paula Villela Nunes, and Beny Lafer

Bipolar disorder (BD), like other psychiatric disorders, still lacks a specific neuropathologic substrate or a defined neuropathological diagnostic criterion, as can be observed in Alzheimer's disease (AD) and other neurodegenerative disorders. Underpowered studies and substantial clinical and methodological heterogeneity across experiments potentially hinder the identification of BD's consistent neural biomarkers [1, 2]. Moreover, findings from neural biomarkers of BD frequently lack specificity. Challenges remain in identifying robust and reproducible biomarkers to better understand the neurobiology, nosology, diagnosis, and targeted treatments needed to improve patient outcomes in BD [1]. However, despite these limitations, neuroimaging, morphological, and molecular correlates have been associated with BD neuropathology and major findings will be presented in this chapter [2].

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17.1 Brain Imaging

Measures of brain structure and function can work as a link between phenomenology, course, outcome, treatment response, genetics, and behavior [1]. Macroscopic alterations can help us understand which brain structures and their changes are reliably associated with BD, its subtypes, and other clinical measures such as illness duration, severity, genetic risk, and relationship with common medications [1]. Overall, these studies point to a diffuse pattern of brain alterations, including smaller subcortical volumes, lower cortical thickness [3] and altered white matter integrity in groups of individuals with BD [1].

On average, higher bilateral ventricular volumes and lower hippocampal, amygdala, and thalamic volumes were detected in BD with small to moderate effect sizes with some degree of variation. The group differences may reflect either accelerated atrophy in BD with potential disease-related neuroprogression, chronic effects of the illness, and/or effects of long-term use of medication. Alternatively, smaller volumes may represent a potential risk factor for BD arising in the early stages of development [1]. Overall, no structural brain differences were detected between BD subtypes (BD-I, BD-II, and BD-NOS).

Common medications such as lithium appear to have a normalizing effect on gray and white matter structures, whereas other treatments such as anticonvulsants appear to have the opposite effect [1]. These results should be interpreted cautiously as medication status is confounded to some extent with illness characteristics (such as symptom severity and limited response to medication). Furthermore, a simple binary coding (prescribed/ not prescribed) was used to determine medication status at the time of scan. Current studies are investigating such medication factors as treatment history, dose, and serum level, to better model interactions between different pharmacological agents—polypharmacy is common in BD—and their associated effects on brain structure [1].

Diffusion tensor imaging studies of BD implicate widespread white matter alterations within and beyond the fronto-limbic regions that appear to precede emotional instability. Limbic and non-limbic tract disruptions have been reported, but inconsistencies exist in the literature. Fractional anisotropy—a measure of white matter directionality, coherence, and integrity—was lower, on average, in participants with BD with the strongest effects in the corpus callosum and cingulate. Higher fractional anisotropy was associated with later disorder onset and shorter illness duration. Lithium treatment was associated with higher fractional anisotropy [1].

A key question in psychiatric neuroimaging is the extent to which brain variations are shared or differentiate major psychiatric disorders. Many mental illnesses overlap in symptomatology, response to medication, and underlying genetic risk. Examples include known intersections between BD, major depressive disorder, and schizophrenia. Whether shared clinical features reflect similar underlying brain structure and function is poorly understood [1]. Initial results point to more widespread and greater cortical effects in schizophrenia than those found in BD and major depressive disorder. In line with prior hypotheses regarding underlying

biological correlates of BD versus major depressive disorder, frontal lobe systems showed greater deficits in BD cases, whereas limbic regions tended to show greater deficits in major depressive disorder cases [1].

Regarding functional studies, meta-analyses point to significant differences in the right ventral posterior cingulate cortex from both cognitive experiments and emotional experiments, demonstrating that connectivity in this region distinguishing BD from controls is unique to resting-state experiments [2]. The posterior cingulate cortex is a core default mode network node implicated in mood disorders. Altered functions of the posterior cingulate cortex in BD may reflect in rumination and/or attention dysregulation [2]. Other areas that revealed differences in activation in BD were the left amygdala—specific to emotional experiments—orbitofrontal cortex, right ventrolateral prefrontal cortex, and the right striatum [2].

17.2 Microscopic and Molecular Alterations

Microscopic neuropathological studies have been extensively conducted in the brains of subjects with a history of neurodegenerative diseases. Studies from autopsied brains of individuals presenting with cognitive decline and dementia have yielded important knowledge on the pathways that underlie neurodegeneration. To date, neuronal loss, gliosis [4]—characterized by a reduction in the density, number, and size of glial cells, particularly astrocytes—and the abnormal, stereotypical aggregation of specific proteins across brain regions [5] are recognized as hallmarks of neurodegeneration in neurodegenerative diseases. Thus, similar strategies have been applied to study neuropathological changes in psychiatric disorders.

Microscopic neuropathological studies are usually conducted in postmortem brain samples of subjects with a clinical history of BD and age-matched controls. Specific brain regions are dissected, embedded in paraffin or other preservation reagents. Microscopic slides are prepared from these tissue blocks as thin layers of the brain samples. Alterations can be investigated by staining the microscopic slides with either broad reagents to highlight the morphology of the cells and evaluate cell number/density of neural cell types (including neurons, microglia, and astrocytes) or with specific markers to investigate changes in specific cell types (e.g., interneurons, active microglia, calcium-binding proteins calbindin positive neurons parvalbumin-immunoreactive neurons, and parvalbumin-immunoreactive neurons) and molecular pathways (e.g., neurodegenerative related proteins and inflammation).

Regarding alterations in cell number and density (of glia and neurons), modifications in cortical layer structure (which is probably related to cell loss) have been observed in specific brain regions. A meta-analysis of microscopic neuropathological changes in BD included multiple brain regions, dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, amygdala, entorhinal cortex, white matter, and thalamus [6]. Findings point to a limited number of brain collections and small sample sizes. Furthermore, few studies attempted to replicate a previous one, somewhat limiting the potential of meta-analyses in this field. Nevertheless, this

meta-analysis was able to find significant results. Glial deficits and thinning gray matter were found in the subgenual cingulate, with the latter being the most robust finding since it was observed by two independent studies. Reduced density of calcium-binding proteins calbindin positive neurons in the dorsolateral prefrontal cortex was significant after meta-analysis. Although this finding was not replicated, and all cortical layers have been included together, decreased interneuron density or number has been found in several brain regions in different studies [7–12]. Decreased neuronal density has been identified in the three nuclei of the amygdala (lateral, basal, and accessory basal). Findings in the amygdala were sourced from two independent studies that used different methodologies. In the case of the hippocampus, although several neuropathological studies have found reductions in neuronal density, there is inconclusive evidence of a reduction of non-pyramidal neurons. Neuropathological investigation of the entorhinal cortex showed a reduction in density of parvalbumin-immunoreactive neurons. Investigation of other neocortical regions was essentially negative. Another important conclusion of this meta-analysis is that it does not seem to be a single and specific neuropathological characteristic of BD.

Regarding protein aggregation, in AD, abnormal aggregates of tau protein are found in the form of neurofibrillary tangles, while extracellular aggregates of β -amyloid are present as neuritic plaques. In Parkinson's disease, the protein that is found abnormally aggregated is the alpha-synuclein protein. In frontotemporal dementia, besides aggregates of tau protein, three other malformed proteins are present, including TAR DNA-binding protein 43 (TDP-43), fused in sarcoma DNA-binding protein, and in rare cases, Ewing's sarcoma and TATA-binding protein-associated factor 15 [13]. Few studies have investigated the presence of some (but not all) of these malformed proteins in the brains of BD subjects. The most complete analysis involved the investigation of phosphorylated tau, phosphorylated α -synuclein, and amyloid- β of 11 BD subjects [14]. The presence of argyrophilic grains (a kind of morphological presentation of phosphorylated tau protein) was found in all BD subjects in this specific study. Although the distribution between cases and controls did not differ, the argyrophilic grains staging was higher in BD specifically in the amygdala, thalamus, and locus coeruleus. Additionally, Lewy body pathology (i.e., presence of phosphorylated α -synuclein) was observed in two BD cases. Interestingly, one case report suggested a diagnosis of Lewy body dementia in an elderly BD patient who had her first manic episode at the age of 24 years old [15]. However, neuropathological evaluations were not performed to confirm the Lewy body disease [16]. Neuropathological abnormalities of the TDP-43 protein were found in the hippocampus of one out of three BD patients included in one study [17]. Interestingly, higher levels of TDP-43 were found in the same brain region of BD in another study [18]. Taken together, further investigation in larger sample sizes is needed for a better understanding of the eventual role of proteins related to neurodegeneration in BD. Furthermore, it is not possible to rule out the possibility of shared molecular substrates between BD neurodegenerative diseases since mental disorder patients are at higher risk of developing dementia later in life [19]. The fact that associations have been found points to potential shared

mechanisms and deserves further investigation on molecular factors associated with neurodegeneration, such as neuroinflammation and oxidative stress.

Inflammation is a biological pathway associated with neurodegeneration [20] and has been suggested to underlie BD pathophysiology. Systemic low-grade inflammation has been consistently demonstrated in the bloodstream, mainly seen as an elevation of cytokines and C-reactive protein (CRP) with specific pro-inflammatory factors during mood episodes [21]. Neuroinflammation in BD has been found in imaging and molecular studies. Measure of translocator protein, a marker of microglial activation, have been found using brain positron emission tomography (PET) [22]. A systematic review was published involving neuroinflammatory molecular data on 51 studies conducted in postmortem brain samples from 14 brain regions [23]. Among the inflammatory factors evaluated are microglia- and astrocytes-related factors, cytokines, chemokines, adhesion molecules, and others. Alterations in cell density, protein expression, and gene expression of glial cells have been found in addition to modifications in astrocyte cell number and proteins, as well as in the expression of inflammatory proteins and genes. The main conclusion of this article is the high variability across studies (in terms of brain region, inflammatory factor, postmortem interval, undergoing treatment) making it difficult to establish causation. Another study compared the levels of cytokines, CRP, and cortisol in two different brains involved in emotional regulation (hippocampus and anterior cingulate) [24] regions and found that brain regions show different immune responses [25]. This could explain the high heterogeneity found in the meta-analysis and suggests the field can benefit from postmortem brain studies focused on the same brain regions and inflammatory factors to make the data comparable and establish more robust causal relationships. Taken together, given the fact that BD is a complex disorder in which genetic and environmental play a role, the heterogeneity reported in the results of neuropathological studies could be expected.

17.3 Mechanisms

Genetic and environmental factors may underlie the microscopic and molecular alterations. Microscopic and molecular changes may be the source of macroscopic and clinical alterations.

Neuroimaging studies indicate alterations in the frontal cortex, cingulate, corpus callosum, amygdala, hippocampus, thalamus, and bilateral ventricular volumes. Among the structural alterations are smaller subcortical volumes, lower cortical thickness, and altered white matter integrity (Fig. 17.1, Macroscopic). These alterations may be associated with microscopic modifications in brain structure (cortical layers, as an example), which, in turn, could be sourced from brain cells (neurons and glia) number and density modifications (Fig. 17.1, Microscopic). The fact that macroscopic and microscopic alterations are found in the same brain regions suggests the associations between these abnormalities. Molecularly, alterations in brain cell number may be associated with increased inflammation, alteration in protein

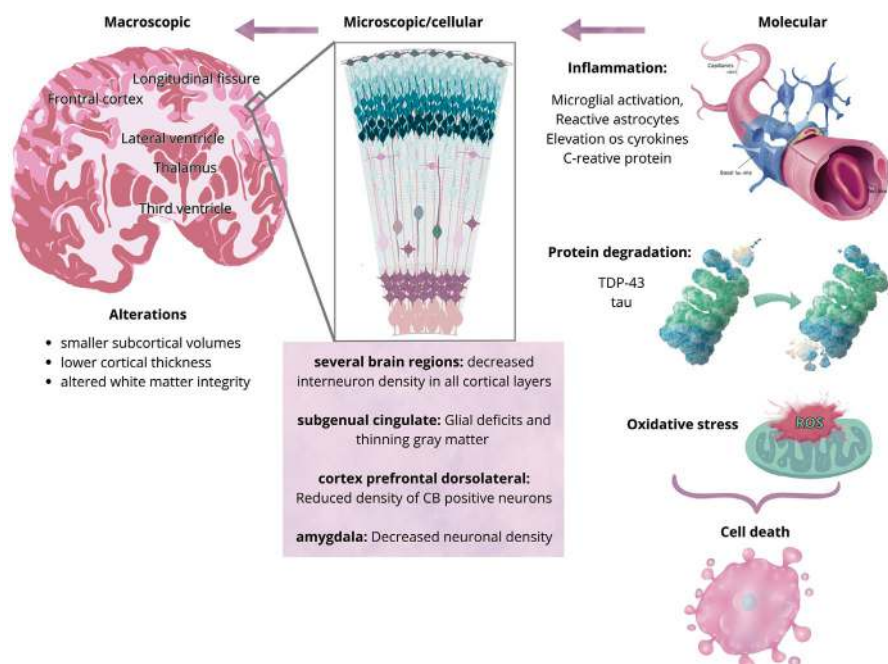


Fig. 17.1 Relationship between macroscopic, microscopic, and molecular neuropathological changes in bipolar disorder. Macroscopic and microscopic alterations seen in the brain of bipolar disorders individuals may originate from molecular alterations, including inflammation, altered protein degradation pathways, oxidative stress, and cell death

degradation pathways (including endo-lysosomal and autophagy pathway, and ubiquitin-proteasome system [26]), and oxidative stress, which could culminate in cell death (Fig. 17.1). This proposal of mechanism may explain the progression of the disorder, high rates of relapses, and the frequent difficulty to fully recover after acute episodes. However, it is still not completely clear what the mechanism of switching on/off the mood episodes along the disease course would be.

17.4 Clinical Aspects

In the intricate landscape of bipolar disorder (BD), characterized by a multifactorial etiology and inherent clinical complexity, the limited pool of available data on its neuropathology confronts significant challenges. The amalgamation of heterogeneity and small sample sizes has, unsurprisingly, yielded no definitive insights into the neurobiology associated with the clinical course of BD, aligning it with other conditions like schizophrenia and major depressive disorder. The absence of specific biomarkers or anomalous proteins further complicates the narrative, emphasizing the elusive nature of BD's neuropathological fingerprint.

Notably, neuropathological findings suggest a disturbance in brain homeostasis, pointing toward a potential breakdown in the self-regulation of BD's neurobiology. In the presence of heightened inflammation, this disturbed homeostasis may allow for the manifestation of manic symptoms and depressive episodes. While the biological system appears adept at maintaining homeostasis during euthymic periods, underlying and not fully comprehended biological aberrations disrupt this delicate balance, manifesting as mood episodes, psychosis, and, in some cases, cognitive decline.

Consistently, the prefrontal cortex, hippocampus, thalamus, and limbic system-associated regions emerge as focal points of disruption in BD. Impulsivity finds potential roots in prefrontal cortex dysfunction, cognitive symptoms in the hippocampus, and anxiety and depression in the amygdala, anterior cingulate, and the broader limbic system. However, attributing symptoms to specific brain areas remains an evolving narrative with inherent limitations, necessitating continued exploration for a deeper understanding of bipolar disorder's intricate neural underpinnings.

17.5 Conclusions and Future Perspectives

In summary, studies reveal structural changes in various brain regions in BD patients. The coexistence of macroscopic and microscopic changes in several brain regions suggests interconnected abnormalities. Molecularly, alterations in brain cell number may be associated with increased inflammation, and disruptions in protein degradation pathways, potentially leading to cell death. This proposed mechanism provides insight into the progression of BD, relapses, and the increased challenge of recovery after acute episodes. However, the data published up to date evidence the high heterogeneity between studies regarding brain regions analyzed and the technologies applied to evaluate neuropathological alterations in BD. The most advanced field is neuroimaging and, still, we lack specific findings that could point to definitive brain alterations. Therefore, at present, no BD imaging or neuropathological correlates have been identified to hold clinical or diagnostic significance. Collaborative efforts (such as the ones made for neuroimaging findings) focusing on the analysis of the same brain cells, molecular alterations, and brain regions across different cohorts will be crucial to provide more robust findings and insights into the physiopathology of BD.

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Chapter 18

Cognitive Functioning in Bipolar Disorder



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18.1 What Cognitive Profile Presents Patients with Bipolar Disorder?

Cognitive dysfunction is prevalent in bipolar disorder (BD), resembling schizophrenia but typically less severe. Impairments encompass attention, processing speed, verbal learning, memory, and executive function. Moreover, social cognition affects the ability to perceive, interpret, and respond to others' intentions and behaviors [1]. Theory of mind entails understanding and predicting others' thoughts, intentions, and emotions, recognizing that these mental states differ from one's own is crucial for social interactions [2]. The theory of mind deficits persists beyond mood episodes and stability, impacting work and relationships.

Cognitive impairment in BD varies widely, with widely scientifically reproduced three-cluster model suggesting differing levels of cognitive function across individuals. This variability underscores challenges in assessing and treating cognitive deficits effectively in BD. Although there is no consensus on the prevalence of cognitive impairment in BD, recent evidence suggests a three-cluster model to describe

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cognitive heterogeneity: 30% of individuals with BD have normal cognitive function, 30% present with selective impairments in specific domains, and 40% exhibit significant deficits across multiple domains [3]. While many individuals with milder forms of BD face challenges, some individuals and their family members achieve remarkable success and creativity, even surpassing the general population [4]. This variability highlights the need to explore factors influencing different outcomes in BD. The cognitive heterogeneity poses significant methodological and clinical challenges in assessing the efficacy of interventions targeting cognitive impairment.

Residual depressive symptoms, poor clinical course, and a higher number of previous manic episodes may negatively impact cognitive performance in patients with BD. Other recent published studies suggest that a history of childhood maltreatment can also negatively affect cognitive functioning in BD [5]. Cognitive impairments in BD are not alleviated by antipsychotic, antidepressant, or mood-stabilizing treatments and persist during clinical remission for many patients. These impairments are often exacerbated by substance misuse and medical comorbidities, contributing to socio-occupational disability and representing a substantial socio-economic burden. The connection between illness progression and cognitive dysfunction in BD is unclear; impairments may stem from neurodevelopmental factors like genetic susceptibility, as well as the neurotoxic effects of recurring mood episodes. It appears that some degree of cognitive impairment is evident in unaffected first-degree relatives of patients with BD and in the premorbid stage at least in a subgroup of patients with BD. However, the most significant decline in cognitive functioning may occur around the time of the first BD episode [6]. These cognitive deficits are crucial as novel treatment targets due to their impact on psychosocial functioning and may have more impact than other clinical factors such as symptom severity.

18.2 How Neuropsychological Assessment Should Be Conducted in BD?

As discussed in this chapter, cognitive impairments are prevalent in BD and encompass a wide range of cognitive domains. Some recommendations have been established for carrying out an accurate neuropsychological assessment. Among the main ones, the following are worth mentioning: selection of tests with appropriate validity, sensitivity, specificity, and reliability, specifically adapted and validated for BD. It is recommended to include tests assessing all cognitive domains that may be affected in BD. Additionally, these tests should effectively track changes over time, including in test-retest designs and during interventions. In addition, the selection should be carried on according to the patient's life stage. With the demographic shift toward an aging population, there are increasingly more patients with BD reaching old age. Since BD carries a higher risk of developing dementia, instruments for older adults should be appropriately selected to detect cognitive decline. These

should include the specific cognitive domains most affected by aging, with a particular emphasis on executive function, learning and memory, and verbal ability [7].

To date, there is no standardized battery for the neuropsychological evaluation in BD, although there are some recommendations based on the aforementioned points. Thus, some years ago, a task force from the International Society of Bipolar Disorders (ISBD) focused on identifying the existing limitations in neuropsychological assessment in BD, developed a consensus in the cognitive assessment. This working group also highlighted the importance of harmonizing cognitive evaluation in BD to enhance the interpretation of results across sites and studies. This battery, called the ISBD Battery for Assessment of Neurocognition (ISBD-BANC), includes the test listed in Table 18.1. The selection was based on a systematic review that analyzed, at that time, the most commonly used instruments with higher validity and reliability for BD [8].

Years later, the ISBD Targeting Cognition Task Force established clinical guidelines and recommendations for cognitive assessment in BD in terms of whether, when, and how to assess and address cognitive performance [9]. The main recommendations are as follows:

1. An objective screening assessment should be conducted as the first step to determine the presence of cognitive impairment. In case of detecting any impairment, a comprehensive neuropsychological assessment should be also performed. Additionally, screening tests are useful for monitoring changes over time. Despite the Screen for Cognitive Impairment in Psychiatry test (SCIP) [10] is recommended for young and middle-aged patients with BD, and for older patients or those suspected of dementia, the Montreal Cognitive Assessment (MOCA) [11] would be the best option.

Table 18.1 The ISBD-BANC neuropsychological battery for BD

Cognitive domain	Specific neuropsychological test
Processing speed	Symbol coding from the Brief Assessment of Cognition in Schizophrenia (BACS)
	Trail Making Test-Part A (TMT-A)
	Animal Naming
Attention	Continuous Performance Test (CPT)
Working memory	Letter Number Sequencing (WAIS-III)
	Spatial Span (WAIS-III)
Verbal memory	Hopkins Verbal Learning Test
	California Verbal Learning Test
Visual memory	Brief Visuospatial Memory test
	Stroop Color Word Test (SCWT)
	Wisconsin Card Sorting Test (WCST)
Executive function	TMT-B

Adapted from ref. [8]

2. A comprehensive assessment is only recommended in specific cases, such as when an impairment in screening measures is detected, if a differential diagnosis with organic disease should be done, the presence of suspected cognitive decline over time, or the need to evaluate each domain in greater detail.
3. The evaluation should be conducted during full or partial remission.
4. Regarding the frequency of evaluations, it is advisable to perform a follow-up assessment, at least, every 5 years.
5. Evaluations must be conducted by a well-trained clinical specialist.
6. The subjective cognitive impairment should also be addressed, but this should be contrasted with an objective assessment to avoid false positives. The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) [12] is recommended for this purpose.
7. The impact of cognitive deficits on various areas of daily life (work, relationships, etc.) should be considered.

Another widely used neuropsychological battery is the Matrices Consensus Cognitive Battery (MCCB). Although this battery was initially developed for assessing patients with schizophrenia, there is a consensus that it is a valid tool to assess cognitive impairment in BD, especially, when including the TMT-B and the Stroop Color Word Test (SCWT) [13]. The MCCB evaluates processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social. It takes approximately 60–90 min to be administered and must be conducted by a trained clinician.

In addition to the MCCB, there is another battery, the Brief Assessment of Cognition in Affective Disorders (BAC-A) [14], first designed for schizophrenia but validated after for affective disorders. It assesses visuomotor abilities, working memory, learning and verbal memory, attention, processing speed, verbal fluency, and executive function (problem-solving). Moreover, it includes the assessment of social cognition by affective interference and inhibition. Its administration takes roughly 35 min. It has demonstrated efficacy in detecting cognitive deficits in patients with BD [14], even in distinguishing between unipolar depression and BD [15]. Overall, evidence indicates that both the MCCB and the BAC-A are sensitive tools for the detection of cognitive impairments in BD and can be used for diagnostic purposes.

Due to the integration of new technologies into our society, computerized cognitive assessment is becoming increasingly frequent. However, their use is still not widespread due to their limitations, despite their advantages. On one hand, this modality has the advantage of being fast, providing immediate results, and not requiring an expert clinician as they are usually patient-administered. On the other hand, these limitations could be related in part due to the high cost of some programs, the complexity of implementation since a computer is usually required, the lack of awareness and training among potential users, and, mostly, concerning the issues that patient's performance is not necessarily directly observed by the clinician, resulting in losing important information [16].

Among these computerized tools, two screening instruments have been created so far: THINC-Integrated Tool (THINC-it) and Internet-Based Cognitive Assessment Tool (ICAT) [17]. The ICAT is the computerized version of the SCIP and has not only demonstrated a high concurrent validity with the SCIP but also a good sensitivity to cognitive impairment of patients with BD [18]. Another web-based, patient-administered cognitive screening tool is the THINC-IT. It was originally designed for unipolar depression [19], but it is already validated only for BD type II showing accurate results in the assessment of cognitive impairment [20]. However, an assessment of verbal learning and memory, two relevant cognitive domains in cognition in BD, are not included. Lastly, an immersive virtual reality cognition assessment tool, the Cognition Assessment in Virtual Reality (CAVIR) was developed. The CAVIR could represent a sensitive and valid instrument for measuring real-life cognitive impairments in mood and psychotic disorders [21].

18.3 Which Are the Factors Associated with Cognitive Impairment?

Different factors may influence directly or indirectly cognitive functioning in BD (see Fig. 18.1). The most studied factors associated with cognitive impairment in this group of patients have been some illness characteristics, such as the illness duration (chronicity), number of affective episodes and hospitalizations, lifetime history of psychotic symptoms, and subthreshold clinical symptomatology. Even though, some conflict results appear with some of the abovementioned factors such as, for instance, the psychotic symptoms. Data coming from meta-analysis reported significant associations between cognitive impairment and the number of manic episodes and total hospital admissions [22]. Manic episodes may exert a neurotoxic effect mainly in the hippocampus and prefrontal cortex, leading to poorer performance in measures of verbal memory and executive function with a greater number of manic episodes. Beyond acute episodes, even with appropriate pharmacological treatment, a substantial proportion of patients experience subthreshold symptoms. This subclinical symptomatology may further contribute to cognitive difficulties in addition to a negative impact on psychosocial functioning. Overall, it could be assumed that a more severe illness is associated with greater cognitive impairment.

Beyond clinical factors, childhood maltreatment, which includes physical or emotional abuse, neglect, sexual abuse, and witnessing violence or household dysfunction [23], has gained significant research attention. Childhood trauma is linked to changes in the structure, function, and connectivity of brain areas vital for cognition, such as the prefrontal cortex, hippocampus, amygdala, and white matter tracts [24]. A systematic review by Barczyk et al. [25] analyzed the relationship between childhood trauma and cognitive function in mood disorders, finding a consistent negative impact of childhood trauma on global cognitive function and specific cognitive domains such as executive function and attention in euthymic patients, and

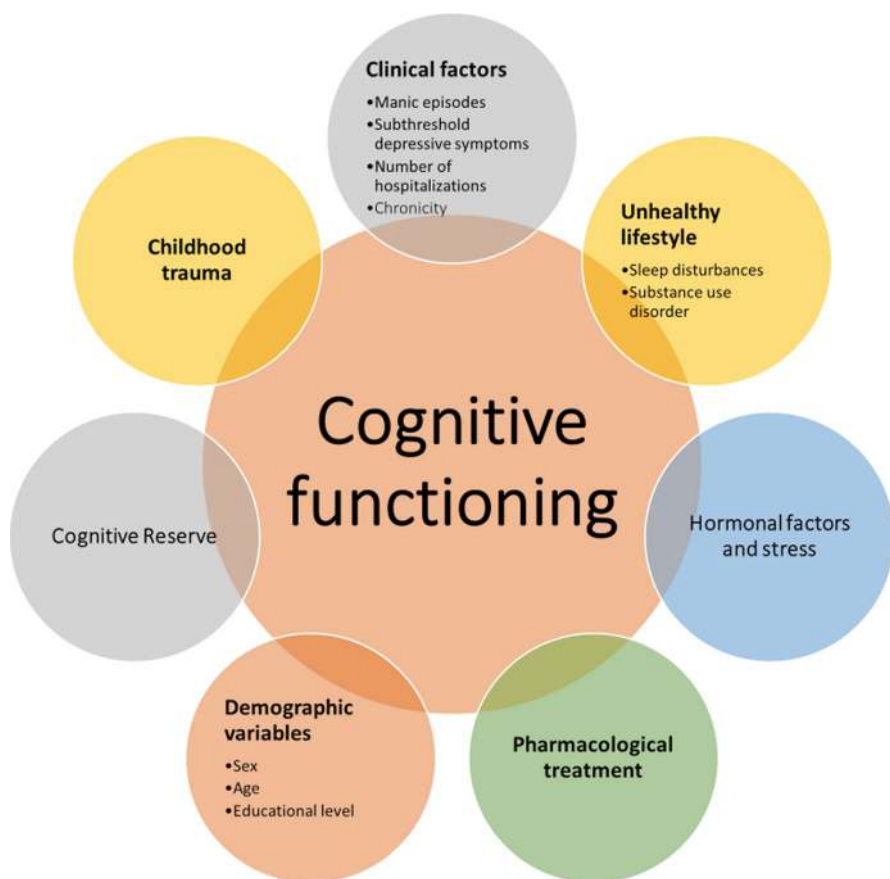


Fig. 18.1 Factors influencing cognition in BD

psychomotor speed in in-episode patients. Physical and sexual abuse and physical neglect were consistently associated with poorer cognitive performance.

Unhealthy lifestyle habits such as poor diet, sleep disturbances, physical inactivity, smoking, and substance misuse may also contribute to cognitive impairment in BD, though many of these factors are understudied [26]. Substance use disorders (SUD), prevalent in nearly 40% of patients with BD [27], have been more closely examined. This comorbidity not only worsens the illness and quality of life but also intensifies cognitive impairment. The cognitive profile of SUD is generally similar to what is observed in BD and other mental disorders, although different cognitive patterns may emerge depending on the primary drug used. Most studies indicate a worsened cognitive impairment with both disorders present, especially in memory and executive function [28, 29], due to significant neurobiological overlap between both disorders. However, findings on attention and processing speed are inconsistent. Many studies lack detailed analysis of specific SUD variables, such as early onset, duration, usage patterns, and type of substance, contributing to heterogeneous

results. For example, most studies associate comorbid alcohol use with worse cognition, while findings on cannabis use are contradictory. Future research should carefully consider specific substances, consumption patterns, and resulting cognitive profiles for a better understanding of this population [28].

Abnormal sleep is common in BD and can produce cognitive deficits in attention, memory, and executive functions, even in healthy individuals. Limited research suggests that sleep disturbances in BD worsen cognitive performance, particularly working memory, and may negatively impact social relationships and occupational performance. Other unhealthy lifestyle factors, such as poor diet quality and physical inactivity, are less investigated in relation to cognitive impairment in BD [30], despite there is clear evidence indicating that people with BD often have poor dietary habits [31] and tend to be more sedentary [32]. These habits may predispose individuals to metabolic dysfunction, which is prevalent in this population and linked to cognitive impairment. A recent meta-analysis in mood disorders found that comorbidity with metabolic dysfunction is associated with significantly lower global cognition [33]. Lower performance was observed in working memory, followed by attention, executive functions, and processing speed. Type 2 diabetes was most associated with cognitive deficits, followed by peripheral insulin resistance, Body Mass Index ≥ 25 , and metabolic syndrome (MetS) or multiple cardiometabolic risk factors. Bora et al. [34] specifically analyzed obesity and MetS components in BD, finding the strongest association between obesity and executive functions. A recent study by Sánchez-Ortí et al. [35] provided evidence on the cumulative effect of MetS components in predicting cognition and social functioning in euthymic patients with BD, as well as identifying those with worse outcomes. These findings suggest that early detection of individuals with MetS components is crucial, highlighting the need to promote healthy lifestyle behaviors and/or therapeutic interventions that can positively impact both symptom severity and neurocognitive function.

Comorbidity with other mental conditions may affect cognitive functioning. Particularly, anxiety disorders may significantly contribute to the magnitude of cognitive dysfunction. Moreover, a cortisol level rising is usually common in both depressive and manic episodes. Therefore, hypercortisolemia maintained for prolonged periods could damage structures related to memory, such as the hippocampus. Another common comorbid mental condition is the attention-deficit hyperactivity disorder (ADHD) [36]. The co-occurrence of BD and ADHD could theoretically result in additive or even synergistic cognitive impairments, but empirical findings have been inconsistent [37–39].

Concerning the effect of pharmacological treatment, also mixed findings have been observed. Some studies indicated an association between poorer performance in cognition and treatment with antipsychotics [22], although negative findings have also been reported. Antipsychotics may be deleterious to cognition; however, this might be also related to the patient population receiving them, with more frequent psychotic symptoms, manic episodes, and hospitalizations, that is, the association could be explained by a greater illness severity. Therefore, the literature on the impact of antipsychotics on cognition still remains unclear. Lithium and other mood

stabilizers or antidepressants have been less associated with cognitive impairment compared with antipsychotics [22, 40], except for sodium valproate, which has also been associated with worse cognitive outcomes when compared to other anticonvulsants. Lastly, it is also well-known that a prolonged administration of benzodiazepines may affect memory, attention, and motor speed. However, the effect of treatment is difficult to assess in patients with BD, since they are usually prescribed drugs combinations at varying doses, and few studies accounted for illness heterogeneity or severity, past medications, and treatment adherence. As Xu et al. [40] suggested, medication is generally associated with improvements in cognition secondary to symptom reduction in the treatment of an acute episode. In contrast, in euthymic patients, this is a complex factor to analyze, and there are only a few studies that can distinguish these effects from the natural course of the disorder. Finally, the impact of cognitive reserve, a complex concept defined as the ability to cope with brain damage to delay the onset of clinical and cognitive manifestations of the pathology and minimize their expression [41], was systematically reviewed in BD [42]. Several environmental factors determine cognitive reserve, such as education, lifestyle, and mental and physical activity, some of them reviewed above.

18.4 How Is the Evolution of Cognitive Performance Throughout the Illness?

Patients with BD experience cognitive impairments which could range from mild to severe deficits, even remission periods [43]. The evolution of cognitive performance in BD over the course of the illness shows inconsistent results in the literature. Therefore, progression and overall course of cognitive deficits in BD still remain unclear. Some patients may experience partial or total recovery of cognitive function after each episode while other patients could worsen after relapses.

There is a scientific trend that supports the idea that, given the intrinsic progressive nature of the disease—expressed through subsequent relapses, episodes, increased severity, and the emergence of medical and psychiatric comorbidities—it would have an effect on cognition, which progressively worsens as these events occur. Thus, the neuroprogression hypothesis postulates that there would be a progressive worsening over the course of the disease, with negative cognitive and functional impacts. Therefore, following this statement, the cognitive impairment in BD would result from certain factors that favor disease progression, particularly those related to the number of episodes, psychotic symptoms, hospitalizations, and illness duration [44, 45] resulting in a longitudinal progressive worsening of the disease, with more marked cognitive dysfunction as the disease progresses. Older patients represent an opportunity to study the long-term effects of the disease on neurocognition, as they are in a more chronic stage due to its long duration. In this regard, a meta-analysis has described several cognitive impairments compared to healthy controls, affecting many cognitive domains, especially verbal memory [46]. Despite

this higher prevalence of cognitive dysfunction in older adults with BD, it seems that there is no progressive cognitive decline with the long-term effects of the illness. Another meta-analysis identified a similar evolution in cognitive performance between recent-onset patients with BD and late-life patients who have long-term exposure to the disease (more than 30 years) [47].

Nevertheless, evidence from longitudinal data indicates that the disease is not irremediable progressive but remains stable over time. Several meta-analyses conducted with longitudinal studies identify stability in cognitive performance over a short and relatively long period (between 1.5 and 5 years of follow-up), indicating no steeper cognitive decline compared to a healthy control group. Noteworthy, the follow-up period in these cited studies is relatively short, preventing characterization the long-term course of cognitive performance. Altogether, these findings do not support the notion of progressive cognitive decline in most patients with BD, suggesting that neurodevelopmental factors may play a significant role [48–50].

Contrary to what was aforementioned, dementia has been linked with BD, as a higher risk of developing dementia has been identified in people suffering from this illness condition. Thus, some meta-analyses have found that a diagnosis of BD constitutes a risk factor for developing dementia, identifying the number of affective episodes as a risk factor and lithium treatment as a protective factor [51]. In this regard, it is suggested that the increased risk of dementia is not only due to the direct impact of age but also to specific clinical factors related to the disorder that may accelerate brain aging and favor certain neuroprogression processes [52]. It has also been suggested that those who develop dementia may already have a predisposition to it, as a severe phenotype of the disease is underpinning (such as psychosis, early onset, greater tendency to relapse and new episodes, etc.), which predisposes to neuroprogression, ultimately resulting in dementia. Additionally, it remains unclear whether dementia occurs as a direct effect of repeated episodes due to cumulative toxicity, or if those with a higher risk of dementia simply have a greater tendency toward relapse [3].

In light of these findings, the idea of the existence of distinct trajectories that would correlate with cognitive performance has also been postulated. Thus, heterogeneous trajectories of the disease have been described, while the cognitive performance of one group of patients remains relatively stable over time, another group shows a greater decline [53–55]. In that sense, differential cognitive trajectories in BD have been proposed, indicating discrete cognitive subtypes that could be represented in three subgroups: (1) subjects who remain stable over time, achieving recovery after each mood episode; (2) another group of patients who experience a decline with each new episode without achieving recovery, thus deteriorating over time; (3) a trajectory that would already begin with a low premorbid level, experiencing a decline after the onset of the disease. The differences between these subgroups are influenced by multiple factors, including clinical, medical or psychiatric comorbidities, premorbid intellectual capacity, cognitive reserve [56], sociodemographic factors, as well as lifestyle habits such as diet, physical exercise, stress, or sleep quality.

Regarding cognitive impairment according to the clinical stage of the disease, cognitive dysfunction is also present from the early stages of the disease. For

instance, it has been found that individuals at high risk of developing BD, that is, in unaffected first-degree relatives of individuals with BD, exhibit poorer cognitive performance in several cognitive domains (visual memory, verbal memory, processing speed, sustained attention, and executive function) compared to healthy controls [57–59]. These differences observed among relatives would have a mild effect, with these impairments distributed at an intermediate level between BD and healthy controls. Similarly, cognitive deficits are also detected in recent-onset patients, as shown in the first episodes of mania [60, 61]. After illness onset, patients with BD, although less severe than schizophrenia, seem to experience a further decline in cognitive function [62]. These results would indicate that neurodevelopmental factors could play a role in cognitive function in BD.

18.5 Association Between Cognitive Performance and Functional Outcome

BD is considered one of the most impairing mental health disorders worldwide, impacting multiple areas of functioning including work, family, and social life [63, 64]. A large collaborative study including over 5800 patients from multiple cohorts detected high rates of functional impairment, ranging from 42 to 75% across different sites [65]. A meta-analytic study found that more than 65% of euthymic patients experience work-related impairment and over 40% also have difficulties with autonomy and maintaining interpersonal relationships [66]. Patients report much higher unemployment rates when compared with healthy controls [67]. Similar to cognitive dysfunction, functional deficits persist even after symptomatic remission in a significant subset of patients, indicating a substantial gap between achieving clinical remission and regaining full functioning. Even though, functional impairment in euthymia varies greatly between patients [68]. This variability may be captured by at least two dimensions representing the clinical severity and cognitive impairment [69, 70]. On one hand, among clinical factors, we found affective symptomatology, psychiatric and medical comorbidities, and SUD. The persistence of subsyndromal symptoms, especially depressive ones, has been identified as one of the strongest correlates of psychosocial dysfunction in BD [65, 71, 72]. This residual symptomatology affects multiple domains, including occupational outcomes [73] and quality of life [71]. On the other hand, there is a strong association between cognition and psychosocial functioning in BD. Indeed, evidence suggests that cognitive functioning may be a better predictor of future general functioning than the severity of affective symptoms [74]. The cognitive deficits experienced by patients may translate into real-world difficulties; they may struggle with work, academic performance, social interactions, and maintaining relationships. The relationship between cognition and general functioning has been detected in cross-sectional studies in both symptomatic and euthymic patients (Baune and Malhi, 2015), and in longitudinal studies. In fact, this association is

more consistent in longitudinal studies when functioning is assessed more specifically (e.g., occupational functioning) or using instruments with different functional domains (e.g., the Functioning Assessment Short Test (FAST) scale) instead of general measures. Specifically, verbal memory and executive functioning are considered important determinants of everyday functioning, although performance in attention and processing speed has also been linked [75]. Available evidence also underscores that cognitive dysfunction is a predictor of unfavorable employment outcomes [76–78]. Therefore, addressing cognitive dysfunction and treating sub-syndromal symptoms, especially subdepressive ones, seems to be crucial to minimize its impact on everyday functioning and quality of life in patients suffering from BD.

18.6 Which Are the Interventions Proved to Be Efficacious for Enhancing Cognitive Impairment in BD?

Cognitive interventions and pharmacological compounds have emerged as a new treatment option to promote cognitive enhancement and functional recovery of patients with BD.

18.6.1 Candidate Pharmacological Compounds

Several small-scale randomized pilot studies have explored different pharmacological interventions for cognitive improvement in euthymic patients with BD, showing varying results:

- Lurasidone: An atypical antipsychotic acting on dopamine and serotonin receptors, shown to significantly improve verbal memory and executive function [79].
- Intranasal Insulin: Enhances neuroplasticity and neurotransmitter activity, with one study reporting improved cognitive performance [80].
- *Withania somnifera* (Ashwagandha): Known for neuroprotective and anti-inflammatory properties, showed improvements in attention, executive function, and immediate memory, although these results did not hold after multiple comparison adjustments [81].
- Erythropoietin (EPO): Enhances neuroplasticity and neuron survival, showing significant and lasting improvements in verbal memory, attention, and executive function [82]. However, in a recent randomized clinical trial (RCT) there were no effects of EPO over saline on any cognitive or functional outcomes and neural activity [83].
- Creatine monohydrate: An oral supplement that increases fat-free mass and improves physical activity performance. In one study with a small sample size

($N = 18$), the creatine monohydrate group demonstrated an improvement in verbal fluency.

- Tianeptine: An antidepressant agent that modulates glutamatergic synaptic neurotransmission. Preliminary results suggest that tianeptine has a pro-cognitive effect on working memory [84].

Other compounds had mixed or no significant cognitive benefits:

- Galantamine: Improved attention and verbal memory in an open-label study but showed no cognitive effects in a randomized controlled trial [85, 86].
- Donepezil: Showed no cognitive improvement in a small open-label study [87].
- N-acetyl cysteine: Is reported to be an efficacious adjunctive treatment for schizophrenia and BD. No cognitive benefits were found in an RCT between the compound and placebo [88].
- Pramipexol: Is a D2/D3 agonist that has demonstrated precognitive effects in preliminary trials. No significant cognitive improvements in an RCT [89].
- Pregnenolone: No improvement in memory and executive function in an RCT [90].
- Citicoline: Mixed results, with some improvement in verbal memory but no overall cognitive benefits in follow-up studies [91, 92].
- Modafinil and Armodafinil: Mixed results, with modafinil showing some cognitive benefits in mood disorders [93].
- Methylene Blue: Is a pharmacological agent with diverse pharmacologic mechanisms. No significant cognitive improvements despite some beneficial effects on depression and anxiety symptoms [94].
- Docosahexaenoic Acid (DHA): Is an Omega 3 fatty acid. No significant cognitive or functional improvements in patients with BD [95].

Some compounds showed promise in bipolar and unipolar depression:

- Mifepristone: A glucocorticoid receptor antagonist, demonstrated significant improvements in verbal and spatial working memory [96, 97].
- Creatine Monohydrate: Showed significant improvements in verbal memory and executive function, although findings were not corrected for multiple comparisons [98].
- Vortioxetine: Showed some cognitive benefits in major depressive disorder (MDD), though effects varied and were limited [99].

Overall, while there is some evidence for cognitive benefits from certain pharmacological interventions in BD, further research is needed to confirm these findings and better understand their efficacy [100].

18.6.2 Neurostimulation on Cognitive Function

Three studies investigated the effects of neurostimulation on cognitive function in patients with BD. These included two studies on repetitive Transcranial Magnetic Stimulation (rTMS) and one on transcranial Direct Current Stimulation (tDCS), all utilizing a randomized double-blind sham-controlled design. One rTMS study ($N = 43$) targeting the left dorsolateral prefrontal cortex did not show cognitive benefits compared to sham [101]. Conversely, another rTMS study ($N = 52$) reported significant improvements in 2 out of 10 cognitive measures after 10 consecutive days of DLPFC rTMS, although not corrected for multiple comparisons. The tDCS study ($N = 42$) demonstrated significantly greater improvements in TMT-B and Rey-Osterrieth Complex Figure Test delayed recall for active versus sham tDCS [102]. A recent pilot RCT [103] also revealed significant improvements in verbal learning in the active rTMS group ($N = 16$) compared to the sham group ($N = 20$).

Additionally, Theta-burst stimulation (TBS) is a type of TMS that induces short-term facilitation and inhibition using brief stimulation procedures. While cognitive enhancements were not linked to intermittent TBS (iTBS), the discovery that increases in hippocampal volume correlated with improved memory implies potential prefrontal-temporal neuroplasticity. This could underpin cognitive improvements in future investigations of iTBS in BD [104]

18.6.3 Non-pharmacological Interventions

Potential psychological treatments for cognitive and psychosocial impairments have been investigated in a small number of studies inspired by the robust effects of cognitive remediation (CR) on cognitive and psychosocial function in schizophrenia [105]. Ten studies examined the effect of CR as an add-on to pharmacotherapy in partially remitted MDD or patients with BD. Of these, some studies included computerized CR tasks.

Cognitive Remediation

The first non-randomized CR trial was a proof-of-concept study involving a mixed sample of 2 BD and 14 unipolar depression (UD) patients in partial remission. Participants were allocated to either 10 weeks of twice-weekly group-based CR or a waitlist control group [106]. The study demonstrated CR-related improvements in memory encoding and retention (primary outcomes) but no improvements in attention, psychomotor speed, and executive function (secondary outcomes).

Another study investigated the effects of 3 months of CR on residual depressive symptoms and cognition in 18 partially remitted patients with BD [107]. The treatment included 14 sessions targeting mood monitoring and residual symptoms, organization, planning, time management, attention, and memory training. Improvements were noted in one of three observer-based measures of executive function.

An RCT by Bernabei et al. [108] showed that patients undergoing active intervention improved significantly more in executive functions, attention, memory, functioning, and impulsivity compared to patients in the control group. The Copenhagen group conducted the first RCT of 12 weeks of group-based CR ($N = 18$) versus standard treatment ($N = 22$) in partially remitted patients with BD [109]. This program included education on cognitive function and dysfunction in BD, and modules focusing on compensation techniques and computerized training of attention, memory, and executive functions. The results indicated no beneficial effects of CR on primary and secondary cognitive outcomes, but improvements were observed in subjective mental sharpness, quality of life, and measures of executive function as tertiary outcomes.

Some studies involved computerized training combined with group-based CR sessions to aid the transfer of acquired skills to daily life. The largest CR trial to date ($N = 75$) reported significant improvements in global cognition, visual-spatial learning, and processing speed [110]. A non-randomized trial investigated the effects of 8 weeks of computerized cognitive treatment versus treatment as usual (TAU) on psychological distress, daily function, and cognition in a mixed sample of UD and patients with BD with current depression [111]. Results showed training-related improvements in attentional and executive functions.

A 10-week computer-assisted CR was examined in a mixed sample of BD and UD patients in partial remission ($N = 38$; 13 BD) in an open-label trial [112]. Improvements were observed in working memory but not in attention, processing speed, verbal memory, or executive functioning. fMRI assessments before and after CR indicated increased task-related dorsolateral prefrontal and hippocampal activity in CR-treated patients [112]. The study involved no control treatment.

Another study evaluated 20–30 hours of computerized, metacognition-informed, therapist-led CR over 12 weeks in patients with BD, comparing it to TAU [113]. The study involved 29 patients in the CR group and 31 in the TAU group. The CR group showed moderate improvements in working memory, IQ, and executive function, which persisted at a 3-month follow-up, along with significant improvements in psychosocial functions and functional capacity. A study by Gomes et al. [114] investigated the effects of 12 sessions of group-based CR in BD ($N = 20$) versus TAU ($N = 19$), with cognition as a secondary outcome. CR improved response times, visual memory, and some aspects of facial expression recognition. A group from Frankfurt developed a new CR intervention and tested it in a naturalistic controlled trial [115]. Twenty-six patients with BD and 10 matched controls completed the program, which involved software training and group sessions. After 12 weeks, the CR group showed improvements in working memory, problem-solving, and divided attention, along with reduced depressive symptomatology.

Finally, a study examined the effects of group-based action-based cognitive remediation (ABCR) in twice-weekly sessions over 10 weeks, compared to 10 weekly structured control meetings supervised by a therapist. The study involved 32 participants with BD in the ABCR group and 29 in the control group. The primary outcome was global cognition, with executive function and psychosocial function

as secondary outcomes, and additional cognitive measures, functional capacity, and subjective cognitive difficulties as tertiary outcomes [116]. No significant improvements were found in global cognition. However, the ABCR group showed significantly greater improvement in executive function with a large effect size, and moderate-to-large improvements in verbal learning and memory were also observed in the ABCR group. ABCR-treated patients reported improved subjective cognitive functioning in daily life but showed no changes in psychosocial function or functional capacity compared to the control group.

The increasing volume of studies with CR for BD shares some similarities. Most studies involve short-term follow-ups with medium to small sample sizes. Therefore, new CR intervention proposals for BD are still needed.

Functional Remediation (FR)

FR was investigated in a multicenter RCT of 239 euthymic patients with BD [117]. Patients were allocated to 21 weeks of functional remediation ($N = 77$), psychoeducation ($N = 82$), or treatment as usual ($N = 80$). The FR intervention involves 21 weekly sessions addressing attention, memory, and executive function with emphasis on patients' functioning in their daily life settings. Although FR improved psychosocial function compared with treatment as usual (primary outcome), there were no cognitive benefits of FR over psychoeducation or treatment as usual (secondary outcome). Interestingly, post-hoc analyses in a subgroup of patients with cognitive deficits revealed FR-associated improvement of verbal memory [118]. Overall, five out of six FR studies reported significant improvements in psychosocial functioning with a moderate mean effect, whereas only two out of them demonstrated cognitive benefits [119].

In summary, cognitive interventions offer promising avenues for addressing cognitive deficits associated with BD. The diverse range of studies reviewed underscores the potential efficacy of CR, both in traditional and computerized forms, as well as other neurostimulation techniques. Future research should continue to explore the mechanisms underlying cognitive improvements. Long-term studies with larger sample sizes and rigorous controls are essential to validate the efficacy and durability of these interventions.

18.7 Final Clinical Perspective Aspects and Conclusions

- A substantial group of patients with BD will develop cognitive impairment even during remission. Research supports a three-cluster model of cognitive profiles in BD: (1) an intact group, with preserved neuropsychological performance; (2) a selectively impaired group, whose neurocognitive performance is only significantly affected in a few cognitive domains; and (3) a globally impaired group.
- Although there is no standardized battery specially designed for patients with BD, recommendations exist for proper assessment. For a quick screening, SCIP and MOCA are highly recommended tools while ISBD-BANC suggests enhanc-

ing the Matrices battery by including TMT-B and SCWT tests, for a more comprehensive assessment of cognitive performance in BD.

- Cognitive dysfunction in BD likely results from multiple factors. Variables such as chronicity, number of hospital admissions and affective episodes (especially manic ones), presence of psychotic features, as well as subthreshold depressive symptoms are known to negatively impact cognitive performance. Additionally, childhood trauma, inadequate lifestyle habits, medication, and some medical and psychiatric comorbidities like metabolic syndrome, anxiety, and substance misuse can further compromise cognition among this population.
- The longitudinal evolution of cognitive performance in BD is heterogeneous and different trajectories have been described: (1) a group of patients maintain stable cognitive performance recovering fully after episodes, (2) another group experiences cumulative decline with each new episode, and (3) a group of patients show continuous decline from a low premorbid cognitive level.
- Cognitive dysfunction significantly contributes to the burden of BD, since it is associated with a poor functional outcome. Deficits on verbal memory and executive function, as well as attention, mostly affected in a substantial part of patients, are usually correlated to unfavorable functional indicators, such as low levels of autonomy and employment.
- Both pharmacological and non-pharmacological interventions, particularly cognitive remediation, show promise in improving cognitive dysfunction in BD. However, further research is needed to expand reliable treatment options.

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Chapter 19

Biomarkers of Neuroprogression



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19.1 Introduction

Bipolar disorder (BD) is a chronic psychiatric illness, often presenting high heterogeneity among patients regarding the symptoms presented and the progression of the disease. Patients with bipolar disorder can have a reduced life expectancy of about 8–12 years [1]. Studies have shown that individuals with mood disorders present function impairment [2], and cognitive function was shown to be negatively associated with features of the disorder's progression, such as the number of mood episodes, duration of illness, and number of hospitalizations [3]. In addition, changes in peripheral biological markers and structural changes in the brain have been associated with illness progression in BD [4, 5].

The trajectory of bipolar disorder varies, and a subgroup of patients may undergo clinical progression. A systematic review showed that an increase in the number of mood episodes is associated with: (a) an elevated risk of episode recurrence, (b) prolonged episode duration, (c) an increase in the symptomatic severity of episodes, (d) a reduced threshold for developing mood episodes, and (e) an increased risk of developing dementia [6].

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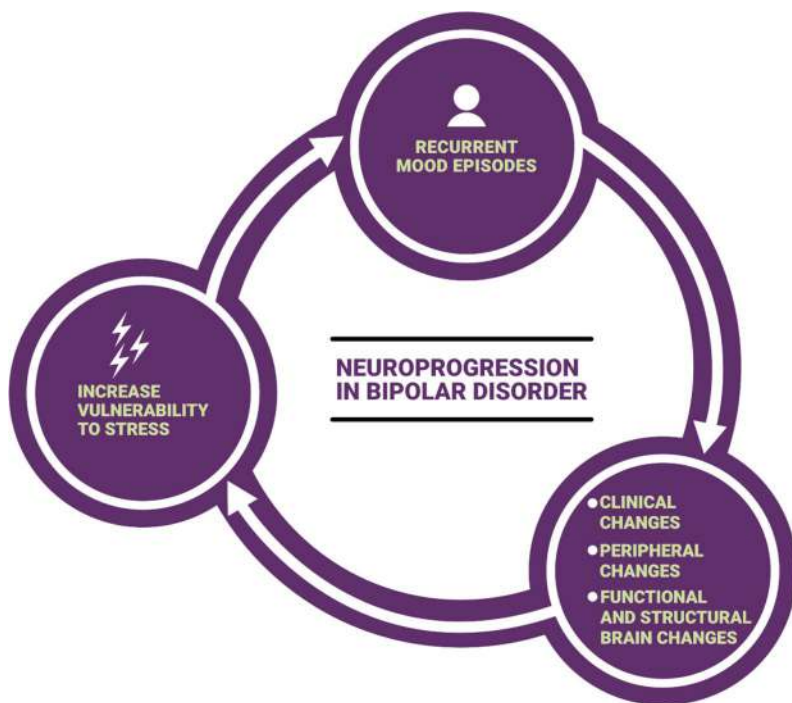


Fig. 19.1 Neuroprogression in bipolar disorder. Mood episodes are associated with clinical and biological changes as well as functional and structural brain changes. These changes can lead to increased vulnerability to stress and recurrence of mood episodes, reinforcing the cycle of neuroprogression in bipolar disorder

The impact of repeated mood episodes on clinical outcomes is known as clinical progression [6]. The biological basis of the clinical progression of bipolar disorder is called neuroprogression [7, 8]. As the illness progresses, the clinical and biological changes associated with mood episodes become more pronounced, increasing the vulnerability to stress and new episodes, which in turn reinforces the cycle of neuroprogression in BD (Fig. 19.1).

Studies have supported the notion that the progression of bipolar disorder is associated with changes in brain structures [9], as well as inflammation, oxidative stress, cellular dysfunctions involving the endoplasmic reticulum (ER), and impairments in neuroplasticity and resilience [8]. Although there has been a substantial increase in understanding of disease progression, the associated mechanisms are complex and heterogeneous and involve diverse signaling systems and pathways. The present chapter aims to review these changes in biological markers associated with neuroprogression in bipolar disorder.

19.2 Central Changes and Neuroprogression

19.2.1 *Structural Brain Changes*

The goal of accurately diagnosing individuals through changes in brain structures due to psychiatric disorders has traditionally fallen short in psychiatry. As technology and imaging methods have evolved, we are closer to achieving this aim as there is an accumulation of evidence suggesting several changes that could serve as potential markers for neuroprogression in BD. Several authors have linked distinct alterations in brain structure, functionality, and white and gray matter volumes to neuroprogression. Initially, studies have focused on specific structures in brain pathways hypothesized to modulate mood, which were shown to be altered in individuals with multiple episodes [10]. As functionality and memory are markedly impaired in late-stage individuals, further studies sought to investigate structures related to executive functioning, culminating in studies of overall brain gyrification that demonstrated gradual changes in brain structure compatible with neuroprogression [11].

A noteworthy aspect linked to BD and its progression is an overall reduction in brain volume, as highlighted in a recent meta-analysis. This comprehensive study identified an augmented ventricle-to-brain ratio as one of the most frequently reported structural changes in BD literature [4]. Notably, individuals with multiple bipolar episodes tend to exhibit significantly larger lateral ventricles compared to those in their first episode or healthy controls [10, 12]. The largest longitudinal MRI study on BD to date, conducted by the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) and the BD Working Group, supported this prior evidence of brain matter reduction. Involving 307 BD patients and 925 healthy controls, this study revealed a faster enlargement of ventricular volumes in BD patients, and a significant association between a higher frequency of (hypo)manic episodes and faster volume reduction, primarily in the prefrontal cortex [13].

In addition to observations concerning the reduction in brain volumes, some authors have specifically concentrated on evaluating absolute numbers of white matter and its involvement in bipolar disorder (BD). These patients exhibit an overall decrease in white matter volumes, even during the early stages of the disorder when compared to control subjects, underscoring the impact of BD on the brain's white matter even in its initial phases [14]. These alterations in neural networks have also been linked to the cognitive symptoms in early-stage BD patients, suggesting that changes in white matter might manifest as an initial neuropathological process underlying the evident cognitive decline seen in BD [15].

Gray matter loss is also linked regarding the context of brain atrophy and the progression of BD. Indeed, this aspect stands as the most commonly reported observation among studies in this field [4]. Late-stage BD patients appear to experience decreases in gray matter [14], which are intricately associated with declines in cognitive functions, and have been strongly linked to the frequency of depressive and manic episodes [16, 17]. However, this area of research remains characterized by conflicting results. For instance, Lisy et al. discovered a positive correlation between

gray matter volume and illness duration, as well as the number of depressive episodes [18]. In addition, other studies have presented divergent findings, such as Nery et al., for instance. They were not able to identify differences in gray matter volumes between BD patients and healthy controls and failed to establish a correlation between gray matter and the number of episodes [19]. This discrepancy underscores the ongoing complexity in understanding the nuanced relationship between gray matter alterations and various parameters associated with bipolar disorder.

In addition to examining the differences in gray and white matter, some authors have also delved into assessing the gyrification of individuals with BD. Gyrification refers to the brain's process of remodeling its surface morphology to form sulci and gyri, thereby expanding the cortical surface area [20]. It is hypothesized that altered gyrification patterns in BD could encompass various brain networks, potentially leading to impaired cognitive functioning, disruptions in emotional regulation, and clinical symptoms. Even though a recent systematic review revealed mixed results when comparing BD patients to controls [21], other authors found that gyrification tends to be less pronounced in late-stage BD patients compared to those in the early stages [11]. These findings suggest the existence of progressive alterations in brain gyrification across different stages of bipolar disorder, indicating its potential role as a marker delineating various stages of the condition.

Another relevant biomarker explored in recent studies is cortical thickness (CT), calculated as the shortest distance between the pial surface and the gray matter/white matter limit [22]. This measure can be utilized as an approximation to brain integrity, as it encompasses multiple factors regarding neurons and glia and can signalize neuropathological processes [23]. As shown in a recent meta-analysis, BD patients have significantly lower CT scores in the frontal cortex, as well as in the insula and the cingulate cortex compared to controls [24]. In addition, CT reduction in the frontal lobes has been linked to illness duration in BD [25], while other longitudinal studies have related BD to an accelerated cortical thinning rate [26]. This reduction in CT has further been linked to high-risk groups for BD, particularly in prefrontal and sensorimotor regions, according to a longitudinal study conducted by Roberts et al. [27]. Interestingly, this effect was seen even in those without incidence of psychopathology [27]. Further supporting the connection between CT and neuroprogression, one longitudinal study found that patients using lithium had a significant increase in medial occipital thickness, while patients who underwent hypomanic or manic episodes presented with an abnormal thinning in inferior frontal cortices. [9]. This study also provides further evidence of previously reported protective effects associated with lithium use in relation to dementia and neuroprogression in BD [28].

Numerous structural changes within specific brain regions have been associated with neuroprogression. One pivotal structure undergoing alterations is the corpus callosum (CC), a bundle of white matter fibers that connects the two cerebral hemispheres and plays a crucial role in brain connectivity, constituting a significant portion of the brain's white matter [12]. It is involved in the integration of processes related to language, attention, arousal, memory, emotion, and sensory-motor functions [29]. The CC has been shown to be particularly affected by stressful events and

trauma [30, 31] and the recurring episodes characteristic of BD induce a cumulative adaptive response, which has been correlated to the neuroprogression [32]. Evidence of this process has been found in multiple studies that correlate CC thinning and impairments related to abnormalities in inter-hemispheric connectivity in BD [33, 34]. Moreover, these structural changes have been further linked to neuroprogression by Lavagnino et al. [35], who studied the images of 41 bipolar female patients and 25 healthy controls, and were able to demonstrate that late-stage BD I patients had reduced posterior CC volumes compared to early-stage and control groups [35].

In addition, BD neuroprogression notably affects the hippocampus, a key component of networks associated with emotional responses [17]. Not only is the hippocampus crucial for memory acquisition, retrieval, and consolidation [36], but it also plays a fundamental role in various forms of learning [37]. Numerous studies have delved into assessing the impact of this structure in BD patients [13, 38], yet the literature presents somewhat conflicting findings regarding the specific influence of the hippocampus in BD neuroprogression [10, 39]. Nevertheless, there is compelling evidence that late-stage BD patients exhibit reduced hippocampal volume compared to healthy controls. This reduction was correlated with a decline in functionality, notably manifesting as poorer verbal memory recall among affected individuals [11]. This is compatible with another study that was able to show a negative correlate between the hippocampal volume to the duration of depressive ($r = -0.636$; $p = 0.035$) and manic ($r = -0.659$; $p = 0.027$) episodes in a geriatric sample of BD individuals [40]. Therefore, In spite of divergent outcomes, there is substantial evidence linking this region to neuroprogression in bipolar disorder.

Recurrent episodes in patients with BD have been found to impact the cerebellum as well. In a comprehensive examination of progressive gray matter loss, Moorhead et al. demonstrated that individuals with BD experience an accelerated decline in gray matter in the cerebellum, compared to age- and sex-matched controls [17]. This aligns with the concept of neuroprogression and is corroborated by other studies, such as DelBello et al. that found smaller cerebellar vermal volumes in BD patients undergoing multiple mood episodes in contrast to those in their first episode or healthy control subjects [41]. Additionally, Mills et al. (2005) illustrated that patients with multiple manic episodes have smaller hippocampus volumes than healthy subjects, and Brambilla et al. (2001) observed a trend ($p = 0.075$) for an inverse correlation between the number of episodes and vermis area V3. These findings collectively support the notion that the cerebellum is notably affected by the neuroprogression associated with BD.

The amygdala, a brain structure extensively examined for its role in mood and emotional reactivity brain circuits, has also been associated with several anomalies in BD. Adolescents and young adults with BD exhibited significantly smaller amygdala volumes compared to healthy controls [42]. This pattern extended to older adults with BD, showing reduced right amygdala volumes in euthymic patients compared to controls [40]. Although a consistent reduction in amygdala neuron density has been observed in BD [24], there are conflicting results in this area. Some authors report amygdala enlargement in high-risk individuals for BD compared to controls and that BD patients would have larger amygdala volumes than both the

controls and the high-risk group [43]. This inconsistency may stem from a lack of consideration of the amygdala's distinct subnuclei, which can also vary in BD [44]. Moreover, a generalized age-related reduction in amygdala volume in BD patients has also been established in a recent review article, emphasizing how individuals with BD undergo a neurodegenerative process that appears to be implicated in the brain's maturation and accelerated aging in BD [45].

19.2.2 Functional Brain Changes

Advancements in functional neuroimaging are reshaping the focus from structural changes to connectivity and activation as early markers of bipolar disorder (BD) progression. Borgelt et al. [46] demonstrated bilateral decreased activation in the prefrontal and cingulate cortices, alongside multiple subcortical structures, in late-stage compared to early-stage patients [46]. Altered activation patterns in limbic regions, encompassing the VLPFC, orbitofrontal cortex, subthalamic regions, and cingulate, have been linked to compromised modulatory control over brain regions associated with emotion. This observation suggests a possible neuroprogression mechanism that heightens vulnerability, indicating that the deficiency in effective modulatory control may contribute to the increased susceptibility observed in the process of neuroprogression [46].

Moreover, recent research linked BD clinical staging to mild neurological and cerebellar symptoms, highlighting the subtle decline patients undergo during neuroprogression [47]. These early manifestations may signify the onset of cognitive decline, supported by evidence indicating that individuals with BD are three times more likely to develop dementia [28]. Additionally, neurochemical associations were found by Deicken et al. [48], revealing a negative correlation between illness duration and N-acetylaspartate, a neuronal marker indicating potential neuronal loss and dysfunction, in the right hippocampus of BD patients [48]. Borgelt et al. [46] supported these findings, reporting a reduction in the same marker in the anterior cingulate cortex of multiple-episode patients [46]. These combined neurochemical and structural insights contribute to a comprehensive understanding of BD progression beyond functional and connectivity dimensions.

19.2.3 Neuroinflammation in BD

Glial cells play a pivotal role in the intricate landscape of brain development, function, and illness. Through a complex network of interactions, these cells communicate with neurons, releasing a diverse array of signals, including neurotransmitters, growth factors, and cytokines [49]. This intricate communication modulates

neuronal activity and ensures the maintenance of brain homeostasis. Remarkably, glial cells are instrumental in various critical processes within the nervous system, such as myelination, synaptic pruning, immune defense, and metabolic support [49].

Post-mortem brain studies in individuals with bipolar disorder have shown evidence of neuroinflammation, which would be associated with illness progression and mood episodes. The findings point to the role of the immune system in the cellular and molecular mechanisms underlying BD, with a focus on the glial cells, the microglia, astrocytes and oligodendrocytes, and inflammatory cytokines [50].

One hypothesis is that this immunological response can be triggered by damage-associated molecular patterns (DAMPs). DAMPs are intracellular molecules released into the extracellular environment from dying cells and can be detected by the innate immune system, leading to an inflammatory response. Previous studies showed significantly increased levels of DAMPs in the periphery in individuals with bipolar disorder [51]. More specifically, individuals with BD showed increased levels of circulating cell-free (ccf) nuclear (n)DNA, heat-shock protein (HSP) 70, and HSP90 alpha when compared to controls [51]. Research has demonstrated that mood episodes are associated with neuronal injury, prompting the release of DAMPs, which, in turn, activate microglia [52]. Taken together, these findings support the notion that peripheral inflammation and neuroinflammation in BD are mediated by DAMPs.

Microglia are known as the macrophages of the central nervous system (CNS) with a key role of supporting neuroplasticity through synaptic pruning [53]. Acute activation of microglia under physiological conditions is considered an innate and adaptive mechanism to reduce tissue damage and restore homeostasis in the CNS. However, chronic activation of microglia is associated with increased release of inflammatory markers [54]. This activation of microglia sets in motion a positive feed-forward loop, releasing more cytokines and increasing inflammation, thereby sustaining microglial activation. Notably, microglial activation is also associated with an increased production of reactive oxygen species (ROS), leading to elevated oxidative stress. This exacerbates damage to the CNS, culminating in cell death and impacting cognitive function [55]. Previous studies corroborate these findings, indicating microglial and astroglial activation in bipolar disorder [52, 56, 57]. One of the first studies to show *in vivo* neuroinflammation found focal microglial activation in the right hippocampus of individuals with bipolar disorder [58].

Increased permeability of the blood–brain barrier (BBB) is proposed to be associated with the infiltration of peripheral cytokines into the CNS, inducing microglial activation through transport channels and permeable regions of the BBB [59]. Once these pro-inflammatory cytokines gain access to the brain they can further damage the BBB and lead to a reduction in neurotransmitters such as dopamine, norepinephrine, and serotonin, which ultimately can lead to changes in mood regulation and cognitive function [60]. Taken together, these changes indicate a potential link between neuroinflammation and peripheral inflammation in BD.

19.3 Peripheral Biological Changes and Neuroprogression

19.3.1 *Inflammatory Biomarkers and Neuroprogression*

There is growing evidence associating inflammation with the pathophysiology of bipolar disorder [60]. Cytokines, essential cell signaling proteins, play a crucial role in coordinating inflammatory processes and can consequently serve as peripheral inflammatory biomarkers [61]. Studies have shown that patients with bipolar disorder in advanced stages of illness progression exhibit elevated levels of inflammatory markers, such as tumor necrosis factor alpha (TNF- α) [62, 63] and interleukin (IL)-6 [64], as well as the chemokine CCL11/eotaxin-1 [65]. Several meta-analyses also support the presence of changes in peripheral biomarkers in bipolar disorder [66–68].

Among inflammatory markers, original studies, reviews, and meta-analyses highlight changes in the levels of pro-inflammatory cytokines, for example, interleukin (IL)-6, tumor necrosis factor (TNF) α , interferon (IFN) γ , and other soluble factors such as C-reactive protein (CRP), the soluble interleukin (IL)-2 receptor, soluble TNF-1 and IL-4 receptor [4, 8, 69, 70]. The findings of a recent systematic review, assessing the levels of various biomarkers in patients with bipolar disorder based on illness progression, highlighted a predominant focus on inflammatory markers among the included studies. In particular, studies revealed increased levels of the pro-inflammatory cytokine TNF- α in the later stages of BD compared to their respective control groups [4].

A recent review discussed the biological basis of neuroprogression and how it may underlie pathological brain reconfiguration in bipolar disorder, contributing to the systemic impairments observed among these patients. Given this, it was proposed that the following biological pathways would be interconnected, contributing to neuroprogression in bipolar disorder: inflammation, oxidative stress, cellular dysfunctions involving the endoplasmic reticulum, mitochondria, and calcium signaling, and impairment in neuroplasticity and resilience. Throughout the course of the illness, these biological changes can worsen clinical outcomes, including cognition and functioning, and then lead to more pronounced changes in peripheral and central biomarkers [8].

19.3.2 *Oxidative Stress and Neuroprogression*

Oxidative stress is defined as an imbalance between the cellular production of reactive oxygen species (ROS) and the counteracting antioxidant mechanisms [71]. The mitochondria serve as one of the main sources of ROS and free radicals. These are produced during the energy production process involving glucose and oxygen, and could lead to the generation of oxidative stress. Oxidative stress can lead to structural damage in cellular proteins, fats, carbohydrates, and nucleic acids (DNA and

RNA) [71]. Due to its high oxygen consumption and vulnerability to ischemia, the brain is especially susceptible to oxidative stress [72]. Peripheral levels of biological products associated with oxidative stress have been found to be elevated in individuals with late-stage bipolar disorder. In particular thiobarbituric acid reactive substances (TBARS), catalase [5], and 3-nitrotyrosine [73]. In studies that were able to analyze staging in bipolar patients, it was found that glutathione reductase and glutathione S-transferase were significantly elevated in late-stage patients [73] when compared to their early-stage counterparts. Correspondingly, levels of nitric oxide [74] and 8-hydroxy-2'-deoxyguanosine (a DNA adduct created through oxidative damage) [75] have been positively correlated with the number of manic episodes experienced by individuals with bipolar disorder. Interestingly, a study by Siwek et al. [76] examined TBARS in euthymic and depressive mood states for early and late-stage bipolar patients [76]. They found TBARS to be elevated in both early and late-stage patients in the depressive state when compared to controls. However, only late-stage BD patients also had increased TBARS in euthymia when compared to controls, further supporting the connection between increased oxidative stress and bipolar illness progression. Total oxidant status, which estimates the overall oxidation state of the body, has also been found elevated in late-stage bipolar individuals [77]. Although there is a strong literature base supporting the relationship between oxidative stress and late-stage Bipolar disorder, it is important to note some oxidative stress markers did not yield significant elevation such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in both early and late-stage euthymic BD patients. Notably, this finding is aligned with previous literature which associates SOD and GSH-Px levels with mood episodes as they are often increased in BD patients experiencing manic and depressive episodes. There was a lack of correlation between the number of manic episodes and 5-hydroxymethylcytosine levels in individuals with BD [75]. 8-Hydroxy-2'-deoxyguanosine's positive correlation with the number of manic episodes suggests that oxidative damage observed with guanosine and not cytosine may be associated with bipolar illness progression and disease severity.

19.3.3 Endoplasmic Reticulum Stress and Neuroprogression

The endoplasmic reticulum (ER) is a complex cellular organelle that is responsible for the synthesis, folding, and post-translational modification of proteins [78]. ER stress occurs when its function becomes compromised leading to the accumulation of unfolded proteins [79, 80]. This stress activates protective mechanisms such as the unfolded protein response (UPR) consisting of ER chaperones which function to enhance protein folding capacity and degrade misfolded ER proteins [81]. However, if ER is under intense and persistent stress a signaling cascade that activates programmed cell death is initiated [82, 83]. Genetic and in vitro studies in psychiatric literature have revealed an association between ER stress and UPR with bipolar disorder. Using in vitro ER stress inducers lymphoblastoid cells from BD

patients had decreased responses in XBP1, a transcription factor that regulates genes coding for ER chaperones and C/EBP homologous protein (CHOP), a protein that mediates cell death [84]. To further demonstrate the possibility that individuals with BD have impaired responses to ER stress, studies have shown reductions in glucose-regulated protein 94 (GRP94) [85], an ER chaperone, and decreased total XBP1 gene expression [86] when comparing BD patients to healthy controls. When examining lymphocytes from late-stage BD patients a significant impairment in ER stress response, evidenced by decreased levels of glucose-regulated protein 78 (GRP78), was observed when compared to early-stage BD patients and healthy controls [87]. There was also a pronounced increase in ER stress-induced cell death when comparing late-stage BD patients to both early-stage BD patients and healthy controls [87]. These findings suggest an increase in ER stress response impairment and greater susceptibility to cell death as bipolar disorder progresses.

19.3.4 Impaired Calcium Signaling and Neuroprogression

Hypercalcemia is known to cause neuropsychiatric dysfunction, manifesting in both the central and peripheral nervous systems, ultimately impacting an individual's mood and cognition. Calcium's relationship with Bipolar disorder has been studied for over a century, with prevalent research predominantly focusing on intracellular calcium ion concentrations. The most recent meta-analysis displayed a robust elevation in basal and stimulated free intracellular calcium in both platelets and lymphocytes from bipolar patients [88]. The mechanisms that regulate calcium levels in the human body are complex with genetic, cellular, and hormonal underlyings. The CAC1NAC and CAC1NAD belong to a family of genes that encode for the alpha subunit in calcium channels; this subunit forms pores through which calcium ions can cross cell membranes, and therefore have a direct effect on calcium ion concentration. There has been a strong association between CAC1NAC [89] and bipolar disorder and increased expression of CAC1NAD in BD patients when compared to controls [90]. Intracellularly, the mitochondria and endoplasmic reticulum are interconnected through calcium concentration, with both organelles having high calcium concentration in comparison to other intracellular components [91]. Literature has been proposed attributing the impaired calcium homeostasis observed in BD individuals to mitochondrial and endoplasmic reticulum deficits [92, 93]. In particular mitochondrial DNA mutations seen in BD individuals have been hypothesized to affect intracellular calcium signaling and homeostasis [94]. Lithium, BD's most established mood stabilizer acts on both intracellular calcium signaling and mitochondrial B-cell lymphoma-2 (BCL-2) proteins, which are known to affect mitochondrial permeability and apoptosis susceptibility [92]. Calcium homeostasis is also predominantly regulated by an integrated hormonal system that acts on skeletal and gastrointestinal systems through the involvement of parathyroid hormone. A recent study involving bipolar individuals found that the number of acute episodes experienced were positively correlated with elevated parathyroid hormone (PTH)

levels, thus providing insight into PTH levels' influence on the long-term outcome of bipolar disorder and its positive correlation with clinical progression. This study suggests a relationship between chronic calcium imbalance and bipolar disorder's illness progression [95].

19.4 Clinical Considerations

- It is important for clinicians to know that a subset of patients with bipolar disorder can present neuroprogression.
- Studies have shown changes in central and peripheral biomarkers according to the progression of the illness in individuals with BD.
- Morpho-functional alterations in fronto-limbic networks constitute fundamental aspects of BD and align with the disorder's progression and clinical presentation.
- Peripheral biological changes with inflammation, oxidative stress, endoplasmic reticulum impairment, and calcium signaling observed in late-stage bipolar disorder individuals show potential for interrelation and can be amalgamated to interpret the prospective underlying biological mechanisms during illness progression.

19.5 Future Perspectives

As discussed in this chapter, there are several markers that have been associated with neuroprogression in bipolar disorder, including brain and peripheral biomarkers. A summary of these findings is described in Fig. 19.2. However, it is important to note that the study of neuroprogression is highly complex, and there is still much to be learned about the biological changes that occur in relation to this. The interaction among molecular pathways responsible for the clinical outcomes remains unclear. Moreover, the reasons why only a subset of patients undergo a progressive course leading to more severe clinical outcomes, such as reduced treatment response, recurrent mood episodes, and impaired cognition and functioning, remain unknown. Gaining insights into this biological heterogeneity can offer valuable perspectives and ultimately advance our comprehension of the diverse clinical presentations observed in individuals with bipolar disorder.

To gain a more comprehensive understanding of these changes, it is essential that detailed and rigorous studies evaluating the progression of the illness over time are conducted. By doing so, we can observe the associated biological changes and identify potential factors that contribute to neuroprogression. Longitudinal studies that follow patients over an extended period of time are particularly valuable in this regard. These studies allow us to observe changes in the brain and other biological systems as the illness progresses, providing valuable insights into the underlying

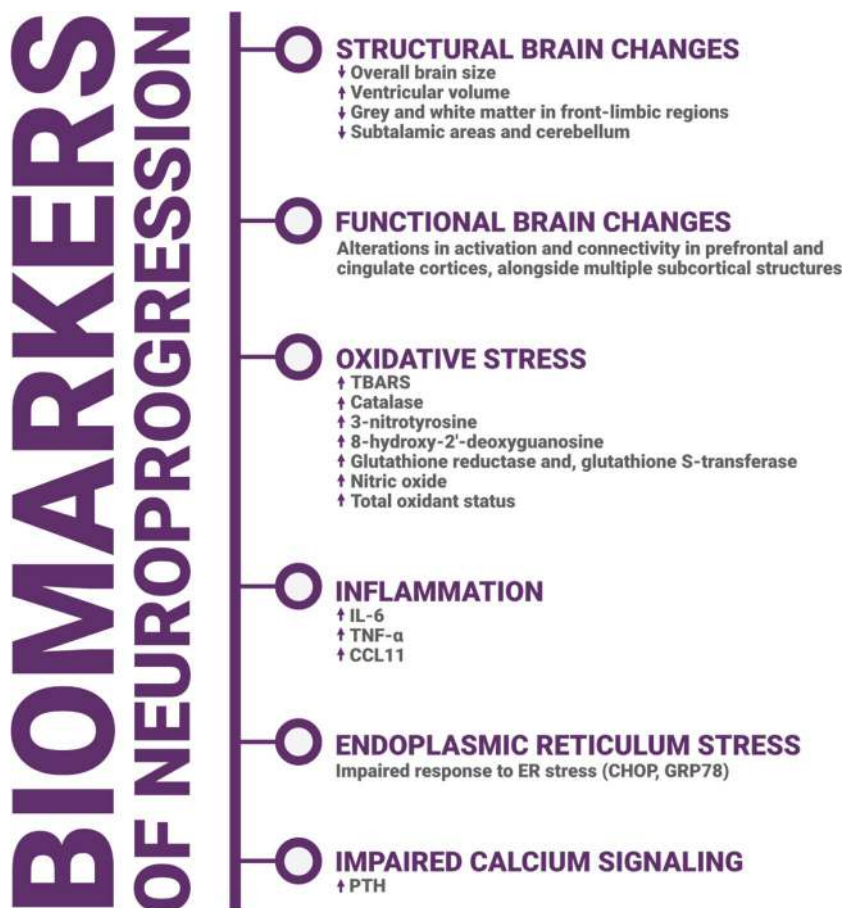


Fig. 19.2 Biomarkers associated with neuroprogression in bipolar disorder. A summary of the biological, neuroanatomical, and functional changes that have been discussed regarding the illness progression in bipolar disorder is presented. TBARS = thiobarbituric acid reactive substances, IL = interleukin, TNF = tumor necrosis factor, CCL11 = C-C motif ligand 11, DAMPs = damage-associated molecular patterns, ccF = circulating cell-free, HSP70 = 70 kilodalton heat shock proteins, HSP90α = heat shock 90 kDa protein alpha, BBB = blood–brain barrier, ER = endoplasmic reticulum, XBP1 = X-box binding protein 1, CHOP = C/EBP homologous protein, GRP94 = glucose-regulated protein 94, eIF2α = eukaryotic initiation factor 2α, GRP78 = glucose-regulated protein 78, PTH = parathyroid hormone

mechanisms of neuroprogression. Moreover, recent advancements in technology are affording us the capability to discern subtle changes during the disorder's progression. Innovative techniques are expanding the literature by identifying alterations in function and connectivity within brain structures. This is especially promising as it may allow us to intervene in these regions before irreversible structural changes occur. Additionally, artificial intelligence is emerging as a powerful

tool that aggregates our knowledge, aiding in the prediction of individuals more at risk. By identifying these mechanisms, we can develop more targeted interventions, leading to improved outcomes for individuals with bipolar disorder, paving the way for more effective interventions in the future.

19.6 Conclusions

Research on biomarkers in bipolar disorder has led to the development of the concept of neuroprogression. This concept has contributed to shifting the focus from symptom management to illness trajectory management. Understanding the biological underpinnings of neuroprogression can provide vital insights into the disorders' complex mechanisms and guide the development of more effective treatments, ultimately leading to a better prognosis for individuals with bipolar disorder. By identifying specific biomarkers associated with neuroprogression, clinicians may be able to monitor illness progression and tailor interventions to the individual's unique needs.

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Part III

Pharmacological Treatment

Chapter 20

Treatment of Mania and Hypomania



Kamyar Keramatian, M. Ishrat Husain, and Lakshmi N. Yatham

20.1 Introduction

Bipolar disorder is characterized by recurring episodes of depression and (hypo) mania. Although individuals with bipolar disorder tend to spend most of their time in depressive episodes, manic or hypomanic episodes are the defining features of bipolar disorder. Mania is a mood state that involves extreme mood elevation and heightened energy level accompanied by a lack of insight and impaired judgment, which commonly lead to marked functional impairment, and the need for hospitalization. Hypomania, on the other hand, is a milder form of mood and energy elevation that although associated with a departure from person's usual level of functioning, does not lead to marked functional impairment. Both mania and hypomania can manifest in various ways, exhibiting a spectrum of symptoms and severity. While some affected individuals may present with a predominantly euphoric mood, others primarily display irritability. Also, about a third of manic symptoms are intermixed with depressive features [1]. Finally, mood-congruent or mood-incongruent psychotic symptoms are common in manic episodes with more than half of the episodes manifesting these symptoms [2]. Such clinical heterogeneity may have implications for assessment as well as the development of tailored treatment strategies.

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This chapter focuses on treatment strategies for mania and hypomania. We begin the chapter by providing a brief historical overview of the treatment of mania. We then provide an updated summary of the recommendations by the 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines [3] for the pharmacological treatment of acute mania as well as relapse prevention. We end the chapter by reviewing some of the unmet needs in the treatment of mania and hypomania and suggestions for future research.

20.2 Historical Perspective

The word “mania” derives from the ancient Greek word *μανία*, which means “madness,” or “frenzy” [4]. An ancient Greek philosopher and physician, Hippocrates (460–370 B.C.), was among the first to systematically outline the characteristics of mania and, along with melancholia and paranoia, regarded it as a disorder of the brain [5]. In modern times, Philippe Pinel (1745–1826), a pioneering French physician, categorized pathological mental states into four groups including dementia, melancholia, “mania without delirium,” and “mania with delirium” [6], with the latter roughly corresponding to what is now called mania with psychotic features. In the nineteenth century, Emil Kraepelin (1856–1926), a German psychiatrist and the father of modern psychiatry, introduced a unifying diagnostic construct for mood disorders called “manic-depressive insanity,” and differentiated it from the non-affective psychosis “dementia praecox,” which later became known as schizophrenia [7]. It was not until 1980, with the release of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), that bipolar disorder was formally recognized as a diagnostic entity, requiring the presence of a manic episode for establishing the diagnosis.

The first medication widely recognized for its anti-manic properties was lithium. In a noteworthy development, an Australian psychiatrist, John Cade (1912–1980), published an article describing the effectiveness of lithium carbonate in 10 patients with “psychotic excitement” [8]. The results from this non-controlled study were later confirmed by a placebo-controlled trial led by a Danish psychiatrist, Morgan Schou [9]. This study sparked interest among other scholars leading to several other international trials and a subsequent increase in clinical use of lithium to treat acute mania [10]. The first North American publication on the use of lithium for the treatment of mania was published in 1960 [11], leading to a decade-long underground prescription of lithium among North American physicians, until it was finally approved by the United States Food and Drug Administration (FDA) for treatment of acute mania in 1970. Another milestone came in 1975, two years after the publication of the first positive placebo-control relapse-prevention trial [12], when lithium was approved by the FDA as the first medication for prophylaxis of mania.

Valproate was first approved as an antiepileptic medication in 1967 in France and became available in the United States in 1983 [6]. However, the anti-manic

properties of valproate became evident a decade later after the publication of a landmark placebo-controlled trial that showed comparable efficacy of valproate and lithium to treat symptoms of mania [13]. A year later, in 1995, valproate (divalproex sodium) received FDA approval for the treatment of acute mania. This led to a decrease in prescription of lithium in the United States while prescription of valproate experienced a steady rise, which continued until the 2000s when the prescription pattern shifted toward using second-generation antipsychotics to treat mania [6]. Of note, neither valproate nor carbamazepine (a tricyclic antiepileptic that received FDA approval for acute mania in 2004) ever received regulatory approvals for manic relapse prevention.

The 2000s witnessed a surge in new medication approvals for acute mania. Apart from carbamazepine, all these medications were atypical antipsychotics that were originally developed for the treatment of schizophrenia. Olanzapine was the first atypical antipsychotic medication to receive FDA approval for treating acute mania (2000) after a placebo-controlled trial suggested significant improvement in manic symptoms in patients who received olanzapine, compared to placebo [14]. This study was the first in a series of atypical antipsychotic trials suggesting that these medications as a class may have anti-manic properties. Subsequently, risperidone (2003), quetiapine (2003), ziprasidone (2004), aripiprazole (2004), quetiapine extended release (2008), and asenapine (2009) received FDA approvals for the treatment of acute mania. In more recent years, cariprazine was approved by the FDA for the anti-manic indication in 2015. As for relapse prevention, olanzapine (2004), aripiprazole (2005) risperidone long-acting injection (2009), quetiapine (2007; as an adjunct to lithium or valproate), ziprasidone (2009; as an adjunct to lithium or valproate), and aripiprazole long-acting injection (2017) have received FDA approvals.

20.3 Treatment of Mania

Treatment of mania usually includes three specific goals, i.e., addressing acute agitation, treating manic symptoms, and preventing relapses.

20.3.1 Management of Agitation

Agitation is a common feature of mania, which can manifest as restlessness or verbal and physical aggression. However, it is important to rule out alternative causes of agitation including other medical conditions, substance intoxication, or substance withdrawal [3]. Agitation should also be distinguished from akathisia, an extrapyramidal symptom caused by dopamine antagonists. Failure to identify akathisia can lead to prescription of more dopamine antagonist agents, inadvertently exacerbating agitation. When agitation is deemed a symptom of mania, the first step in

management is to initiate treatment for the manic episode, as outlined in the following sections. If agitation continues, the use of a rapid-acting pharmacological agent may be indicated. This would include a loading dose of divalproex (DVP), a typical or atypical antipsychotic, and/or benzodiazepines. In case of ineffectiveness of oral formulations or non-compliance, intramuscular formulations need to be considered.

20.3.2 Principles of Pharmacological Treatment of Acute Mania in Adults

We provide below a stepwise approach to treating acute mania according to the 2018 CANMAT guidelines.

Step 1: Review General Principles and Assess Medication Status: The first step in the management of acute mania is to establish the most appropriate treatment setting by conducting a thorough assessment that would include risks of violence and self-harm, the patient's level of insight and their ability to adhere to treatment, as well as physical and mental health comorbidities. Medications and substances that can contribute to the worsening of manic symptoms (e.g., antidepressants, psychostimulants, caffeine, and alcohol) should be discontinued. History of previous responses to and tolerability of medications should be obtained to direct therapeutic choices.

Step 2: Initiate or Optimize Therapy and Check Adherence: The CANMAT guidelines recommend both monotherapy and the combination of a mood stabilizer and an atypical antipsychotic as appropriate first-line treatments for acute mania. In about half of patients with acute mania, symptoms will respond to monotherapy within 3–4 weeks [15]. However, clinicians should consider recent meta-analytic evidence [16] suggesting that augmentation therapy with antipsychotics and mood stabilizers tends to be more effective than monotherapy in treating manic symptoms with no significant difference in tolerability at weeks 3 and 6. First-line monotherapy options are lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine while first-line combination options include a combination of quetiapine, aripiprazole, risperidone, or asenapine, with lithium or divalproex.

The 2018 CANMAT guidelines list the first- and second-line recommendations hierarchically based on the efficacy of each agent in treating acute mania as well as considerations for efficacy in treating bipolar depression, relapse prevention, safety and tolerability, and risk of a treatment-emergent affective switch. According to this approach, treatments that have demonstrated efficacy across the spectrum of acute episodes (i.e., both mania and depression) and prophylaxis are ranked higher than those that have demonstrated efficacy for mania only. In cases where two agents have demonstrated comparable efficacy across the phases, factors related to tolerability and safety determine the hierarchical ranking. Clinicians are encouraged to consider treatments listed higher up first, unless other factors such as history of previous nonresponse or patient preferences dictate otherwise.

If manic symptoms are not controlled within the initial 2 weeks of receiving therapeutic doses of a first-line agent, it is important to consider additional factors contributing to nonresponse such as possible non-adherence and ongoing substance use before deciding on adding or switching medications. The CANMAT recommended first-line, second-line, and third-line treatments for acute mania are listed in Table 20.1.

Step 3: Add on or Switch Therapy (Alternate First-Line Agents): If treatment with one or a combination of first-line agents at optimal doses is inadequate or intolerable, the recommendation is either to switch to or (in case of monotherapy) add on an alternate first-line treatment. It should be noted that despite level 1 evidence for monotherapy with paliperidone and ziprasidone, the CANMAT guidelines do not recommend combination therapy with these two agents due to lack of evidence for additional efficacy with combination therapy.

Step 4: Add on or Switch Therapy (Second-Line Agents): If the expected outcome is not achieved after trying all first-line recommendations, one of the second-line choices—including monotherapy with olanzapine, carbamazepine, ziprasidone, and haloperidol; or combination therapy with olanzapine and lithium or divalproex or with lithium and divalproex; or electroconvulsive therapy (ECT)—should be considered.

Table 20.1 Pharmacological treatment of acute mania—adapted from 2018 CANMAT guidelines

First-line (hierarchical ranking)	Second-line (hierarchical ranking)	Third-line	Not recommended
Monotherapy Lithium Quetiapine Divalproex Asenapine Aripiprazole Paliperidone (>6 mg) Risperidone Cariprazine	Olanzapine Carbamazepine Olanzapine + Li/DVP Lithium + DVP Ziprasidone Haloperidol ECT	Carbamazepine / oxcarbazepine + Li/DVP Chlorpromazine Clozapine Haloperidol + Li/DVP rTMS Tamoxifen Tamoxifen + Li/DVP	Allopurinol Eslicarbazepine / licarbazepine Gabapentin Lamotrigine Omega-3 fatty acids Topiramate Valnoctamide Zonisamide Brexpiprazole
Combination therapy Quetiapine + Li/ DVP Aripiprazole + Li/ DVP Risperidone + Li/ DVP Asenapine + Li/ DVP			

The first- and second-line agents are listed hierarchically. Third-line agents are in alphabetical order

DVP divalproex, *ECT* electroconvulsive therapy, *Li* lithium, *rTMS* repetitive transcranial magnetic stimulation

Step 5: Add on or Switch Therapy (Third-Line Agents): Exploring third-line treatment options is warranted only after adequate trials with all first- and second-line options (alone and in combination) have been unsuccessful.

20.3.3 Treatment of Acute Mania in Children and Adolescents

Up to two-thirds of individuals with bipolar disorder experience their first mood episode during childhood or adolescence. However, it is imperative for clinicians to distinguish between distinct periods of elevated or irritable mood that are characteristic of manic or hypomanic episodes and chronic irritability and explosive outbursts seen in other conditions such as emerging personality disorders, substance use disorder, and attention-deficit/hyperactivity disorder (ADHD) [3].

While the data are limited, the CANMAT guidelines indicate that the general principles for managing adults with bipolar disorder described earlier also apply to youth [3]. Additional considerations for this demographic include the higher likelihood of having more comorbid psychiatric conditions and more susceptibility to adverse effects of psychotropic medications compared to adults. The CANMAT guidelines recommend lithium, risperidone, aripiprazole, asenapine, and quetiapine as first-line options. Olanzapine, ziprasidone monotherapy, and quetiapine adjunctive therapy are recommended as second-line options while divalproex is recommended as a third-line option for the treatment of acute mania in youth.

20.3.4 Treatment of Acute Mania in Older Adults

In 2005, nearly a quarter of the patients with bipolar disorder in the United States were over 60 years old [17]. This proportion is projected to increase in the coming years due to ongoing demographic aging. It has been estimated that over half of all patients with bipolar disorder are older than 60 years old [18]. The data for the management of acute mania in older adults is limited. CANMAT guidelines recommend monotherapy with lithium or divalproex as first-line treatments while quetiapine is regarded as second-line. Asenapine, aripiprazole, risperidone, or carbamazepine are considered as third-line treatments whereas clozapine and ECT are reserved for treatment-resistant episodes.

20.3.5 Clinical Features that Help Direct Treatment Choices

Bipolar disorder is a complex and clinically heterogeneous condition, and variations in clinical features may help direct treatment choices. For individuals who present with euphoric grandiose mania, few previous mood episodes, a

mania-depression-euthymia course, as well as those with a family history of bipolar disorder, lithium is recommended as a preferred treatment choice over divalproex or atypical antipsychotics [3]. In contrast, for patients with a history of several previous mood episodes, predominantly irritable or dysphoric mood as well as those with comorbid substance use disorder or with a history of traumatic brain injury, divalproex is considered a preferred treatment choice. Finally, in patients with a previous history of partial response to monotherapy as well as in those presenting with severe manic episodes or mood-incongruent psychotic features combination therapy with lithium or divalproex plus an atypical antipsychotic is recommended.

20.3.6 Treatment of Acute Mania with Mixed Features

It has been estimated that more than one-third of manic episodes meet DSM-5 criteria for mixed features, defined as having three or more non-overlapping depressive signs or symptoms [1]. Mixed features are associated with an earlier age of onset, increased comorbid anxiety or substance use, elevated risk of hospitalization, and suicidal behaviors [1, 19–21]. The CANMAT and ISBD groups have recently published their specific recommendations for the management of individuals presenting with acute mania with mixed features [21]. Since no medication had sufficient evidence to be recommended as first-line, CANMAT guidelines recommended using second-line agents for the initial treatment of acute mania with mixed features. These second-line agents include asenapine, cariprazine, divalproex, and aripiprazole while ziprasidone, olanzapine (either as monotherapy or in combination with lithium/divalproex), quetiapine, carbamazepine extended release, and ECT are recommended as third-line options [21].

20.3.7 Prophylaxis of Mania

Bipolar disorder is a chronic and relapsing condition and therefore, almost all affected individuals require maintenance pharmacological treatment to prevent relapse and restore day-to-day functioning. A recently published meta-analysis showed that maintenance treatment is associated with a reduced annual risk of relapse into manic/hypomanic/mixed episodes from 39.7% (discontinuation group) to 19.2% (maintenance group) [22]. Moreover, there is increasing evidence to suggest that in some affected individuals, bipolar disorder may be a neuroprogressive condition in which recurrent manic episodes are linked to reductions in brain volumes, neurocognitive impairment, and poor clinical outcomes [23].

About half of the patients with bipolar disorder fail to adhere to the maintenance treatment [24, 25]. As such, ongoing efforts in providing psychoeducation as well as rapport building and collaborative engagement with patients and their families are highly recommended to improve the acceptability of maintenance treatment in

order to minimize the risk of relapse. In fact, there is meta-analytic evidence suggesting that implementing such measures can boost adherence to treatment twofold compared to treatment as usual [26].

Step 1: Review General Principles and Assess Medication Status: Most medications that are recommended for the treatment of acute mania have relapse-prevention efficacy. Therefore, it is recommended that medications that have been effective in treating acute mania should be continued to reduce the risk of relapse. If the patient is not receiving or responding to pharmacological treatment, a detailed history of clinical course (including the predominant mood polarity, and the polarity of the most recent mood episode), response to previous trials, comorbidity, and family history should be obtained and taken into account to determine the selection of a most appropriate agent for maintenance treatment.

Step 2: Initiate or Optimize Therapy and Check Adherence: In the same manner as a treatment for acute mania, the 2018 CANMAT guideline recommends that maintenance treatment should follow the hierarchy (as listed in Table 20.2), unless additional considerations such as patient preference, previous response and tolerability, or predominant polarity warrant alternative choices. Moreover, if a patient has been successfully treated for acute mania with a first-line maintenance treatment, the guidelines recommend continuing that treatment even if it is lower down in the hierarchy. It is sometimes necessary to adjust the dose during maintenance treatment to minimize the adverse effects and help with treatment adherence.

There is growing evidence to suggest that the risk of relapse is decreased when an atypical antipsychotic is combined with a mood stabilizer during the maintenance phase. In a recently published meta-analysis [27], combination therapy was associated with lower rates for recurrence at 1, 2, 3, 9, and 12 months when compared with placebo and mood stabilizers. It is therefore reasonable to continue the combination therapy for the first 12 months after response in order to reduce the risk of relapse.

Table 20.2 Pharmacological treatment for maintenance therapy in bipolar I disorder—adapted from 2018 CANMAT guidelines

First-line (hierarchical)	Second-line (hierarchical)	Third-line	Not recommended
Lithium Quetiapine Divalproex Lamotrigine Asenapine Quetiapine + Li/ DVP Aripiprazole + Li/ DVP Aripiprazole Aripiprazole OM	Olanzapine Risperidone LAI Risperidone LAI (adj) Carbamazepine Paliperidone (>6 mg) Lurasidone + Li/DVP Ziprasidone + Li/DVP	Aripiprazole + Lamotrigine Clozapine (adj) Gabapentin (adj) Olanzapine + fluoxetine	Perphenazine Tricyclic antidepressants

The first- and second-line agents are listed hierarchically. Third-line agents are in alphabetical order

Adj adjunctive, *DVP* divalproex, *LAI* long-acting injection, *Li* lithium, *OM* once monthly

Step 3: Add on or Switch Therapy (Alternate First-Line Agents): If the initial treatment is proven to be ineffective or intolerable, consider switching to or adding on an alternate first-line agent.

Step 4: Add on or Switch Therapy (Second-Line Agents): The CANMAT guidelines recommend using second-line treatments only after unsuccessful trials of multiple first-line options. Olanzapine, long-acting injectable risperidone monotherapy or adjunctive therapy, carbamazepine, paliperidone, adjunctive ziprasidone, and adjunctive lurasidone are recommended as second-line options for maintenance treatment of bipolar disorder by the CANMAT guidelines.

Step 5: Add on or Switch Therapy (Third-Line Agents): Third-line options for maintenance treatment of bipolar disorder include aripiprazole and lamotrigine, clozapine (adjunctive), gabapentin (adjunctive) and olanzapine and fluoxetine combination.

20.4 Treatment of Hypomania

For many individuals with bipolar disorder, hypomanic episodes tend to be associated with minimal functional impairment or even periods of greater productivity and creativity. However, some patients may experience frequent and relatively severe irritable or mixed hypomanic episodes that may require clinical attention [3]. Although most anti-manic agents have not been studied in hypomania, clinical experience suggests that all anti-manic medications including lithium or divalproex, and/or atypical antipsychotics, can also be effective for the treatment of hypomania [3].

20.5 Safety and Monitoring

Clinicians should obtain a complete medical history and order laboratory investigations prior to initiating pharmacological treatment for mania or once the patient is cooperative. Recommended laboratory investigations include complete blood count, electrolytes (including calcium), liver enzymes, serum bilirubin, prothrombin time and partial thromboplastin time, urinalysis, urine toxicology screening for substance use, estimated glomerular filtration rate and serum creatinine, thyroid-stimulating hormone, fasting glucose, fasting lipid profile, electrocardiogram (for patients over 40 years of age or if otherwise indicated), pregnancy test, and serum prolactin [3].

For patients who are taking lithium, thyroid and renal function, as well as plasma calcium, should be assessed at baseline, after 6 months, and at least annually thereafter. Lithium has a narrow therapeutic index (i.e., relatively small difference between toxic and therapeutic doses). The CANMAT guidelines recommend establishing two consecutive serum levels in the therapeutic range after the initiation of

lithium. Subsequent measurements should be done every 3–6 months. Serum levels should be measured at least 5 days after the most recent dose titration. The target serum level at the trough point (i.e., 12 h after the last dose) is 0.8–1.2 mEq/L in the acute phase and 0.6–1 mEq/L during maintenance. Recommended serum level in older adults is between 0.4 and 0.8 mEq/L.

In patients who are taking divalproex, clinicians are advised to obtain menstrual history to assess for polycystic ovary syndrome, as well as hematology profile and liver function tests at 3- to 6-month intervals during the first year and yearly thereafter. Divalproex serum levels should be measured during treatment initiation and repeated every 6 months. The recommended serum level for divalproex is 350–700 mM/L (50–100 µg/mL) and needs to be measured at least 3–5 days after the most recent dose titration.

Patients who are initiated on carbamazepine should receive education regarding the risks of skin rashes and be monitored for Stevens-Johnson syndrome and toxic epidermal necrolysis. They should also have their serum sodium levels measured at least annually due to the risk of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and hyponatremia. Carbamazepine serum levels should be measured every 6–12 months or more frequently if clinically indicated.

Patients who are initiated on atypical antipsychotics should be monitored for metabolic side effects and movement disorders. As such, clinicians should assess body weight monthly in the first 3 months and every 3 months thereafter. In addition, blood pressure, fasting glucose, and lipid profile should be assessed at 3 months and annually thereafter or as clinically indicated. Regular monitoring for extrapyramidal symptoms including conducting validated scales for tardive dyskinesia such as the Abnormal Involuntary Movement Scale (AIMS) is also recommended.

20.6 Future Perspectives

Manic episodes in bipolar disorder present a complex and challenging clinical scenario, often requiring swift resolution to prevent prolonged hospitalizations and functional impairments. Current treatment often involves high doses and combinations of psychotropic medications, leading to adverse effects and compromised physical health outcomes. Addressing these challenges requires a paradigm shift toward the identification of biomarkers for treatment response to personalize treatment strategies, and the integration of innovative technologies to enhance the prevention of mania.

20.6.1 Personalized Treatment Approaches

The current one-size-fits-all approach to treating manic episodes often results in suboptimal outcomes and adverse effects. To minimize the burden on individuals with bipolar disorder, future research should focus on personalizing treatment

approaches. Tailoring interventions to the specific needs of each patient can optimize outcomes and reduce the risk of adverse effects associated with high-dose and combination pharmacotherapy.

One promising avenue involves the identification of biomarkers that can predict treatment response to established pharmacotherapies such as lithium, valproic acid, and atypical antipsychotics [28]. Despite ongoing research, consensus on validated biomarkers remains elusive. Neuroimaging, molecular, and physiological markers have been explored, but limitations in sample sizes and study designs hinder progress [29–31]. Recent studies suggest potential benefits in targeting reward neural network markers using neuromodulation techniques like transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) [32, 33]. However, further large-scale, longitudinal studies are needed to establish reliable biomarkers of mood state and treatment response in bipolar disorder. Recruiting diverse and large naturalistic samples, especially focusing on younger patients in the early stages of the illness, could provide valuable insights into individual trajectories of treatment response and the neuroprogressive nature of bipolar disorder, particularly in the context of recurrent manic episodes.

20.6.2 Innovative Technologies in Manic Episode Prevention and Management

The integration of technology into the management of manic episodes represents a promising avenue for future developments. Smartphone apps and wearables have shown preliminary evidence in predicting outcomes in bipolar disorders, particularly in episode prediction [34]. These digital tools can facilitate the assessment and monitoring of symptoms, enhancing self-management strategies and potentially preventing manic recurrence.

Ongoing studies are investigating the utility and cost-effectiveness of digital tools in predicting manic episodes. Implementing these technologies on a larger scale could revolutionize the way clinicians and individuals manage bipolar disorder, providing real-time insights into mood fluctuations and treatment response. The use of technology in this context aligns with the broader trend of digital mental health interventions, offering scalable solutions that can reach diverse populations.

20.6.3 Prevention Strategies and Psychosocial Interventions

Preventing manic episodes remains a challenging but crucial goal. Maintenance pharmacotherapy, particularly with atypical antipsychotics and lithium, has shown efficacy [35, 36]. However, there is a need for head-to-head comparisons to determine the relative effectiveness and tolerability of specific agents and drug

classes. Further, treatment adherence is a significant challenge in patients with bipolar disorder, with poor adherence leading to frequent relapses. Discovery of novel agents with longer half-lives or novel drug delivery mechanisms that ensure sustained release of drug for a prolonged period of time may help to address this issue.

In addition to pharmacotherapies, the implementation of evidence-based psychosocial interventions, such as family therapy and psychoeducation, can significantly enhance treatment adherence and lifestyle approaches to disease management. These interventions play a crucial role in addressing the broader psychosocial aspects of bipolar disorder, fostering a comprehensive approach to treatment.

20.6.4 Global Implications and Resource-Limited Settings

The burden of bipolar disorder extends globally, with substantial treatment and research gaps, especially in low and middle-income countries. Harnessing technology and scalable interventions can address these disparities, providing cost-effective solutions for individuals in resource-limited settings. The integration of evidence-based psychosocial interventions on a broader scale, facilitated by technology, holds the potential to bridge the gap in the global burden of bipolar disorder.

20.7 Conclusion

Manic and hypomanic episodes are the core features of bipolar disorder. This chapter provided a historical perspective of the pharmacological treatment of manic episodes as well as a summary of CANMAT guidelines and treatment recommendations. The future directions for the treatment of manic episodes in bipolar disorder emphasize biomarker identification and validation, personalized approaches, the discovery of novel drugs with prolonged half-lives or novel drug delivery mechanisms to address poor treatment adherence, and the integration of innovative technologies to move toward prevention. By advancing our understanding of biomarkers, tailoring interventions to individual patients, and leveraging technology for real-time monitoring and support, we can improve outcomes and reduce the overall burden of bipolar disorder. Adopting a global perspective that considers the unique challenges of resource-limited settings will contribute to more inclusive and effective strategies for managing manic episodes in bipolar disorder across populations and settings.

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Chapter 21

Mixed Features and Rapid Cycling



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21.1 Definition

21.1.1 Mixed Features

There was a major change in mixed states definition from Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) to DSM-V [1]. DSM-IV used the term *mixed episode* as a unique entity, where both manic/hypomanic episode and depressive episode criteria had to be satisfied for a proper diagnosis. In DSM-V, the term *mixed features* emerged, where a full episode (manic/hypomanic or

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depressive) is required, accompanied by at least three symptoms of the opposite pole. This change resulted in two main outcomes: an increase in the prevalence and consequences of mixed states, and the need for new treatment studies that consider the new criteria in their analyses. Considering the new terminology, we will primarily use the term *mixed features* in this chapter. We will use the term *mixed states* when describing this phenomenon more comprehensively.

21.1.2 Rapid Cycling

Rapid cycling is a specifier of bipolar disorder (BD) diagnosis where the patient presents at least four mood episodes meeting the criteria for manic, hypomanic, or depressive episodes within 12 months.

21.2 Epidemiology

21.2.1 Mixed Features

While there has been extensive research into factors associated with mixed states, the data available regarding the clinical heterogeneity of these features is still limited [2]. The numbers were also affected by changes in diagnostic criteria from DSM-IV to DSM-V, which became wider [3]. The prevalence rates of mixed episodes were around 6% when using DSM-IV [3]. However, the *mixed features* specifier presented a threefold greater risk for mixed features in patients with BD according to the DSM-V definition (15.7% were manic/hypomanic episodes with mixed features, and 3.9% were depressive episodes with mixed features) [3]. Currently, the occurrence of mixed features during depressive and manic/hypomanic episodes among bipolar patients is estimated to be between 24% and 35% [4, 5]. A systematic review of 17 studies found that the prevalence of mixed features was 11.6% in depressive episodes. Meanwhile, the presence of mixed features in manic or hypomanic episodes was 26.8% [6]. Hence, mixed states are assumed to be more prevalent in cases where manic symptoms are predominant.

Mixed presentations are related to higher rates of suicide attempts and greater suicidal ideation compared to non-mixed states [2, 7–10]. Studies indicate that mixed features are a significant risk factor associated with suicidality in BD, potentially increasing the likelihood of a suicide attempt by up to 65 times [11]. Patients with mixed features present longer periods of mood instability. These individuals also have more lifetime mood episodes than those without mixed presentations [7]. Furthermore, alcohol and substance abuse or dependence is more prevalent in mixed bipolar patients [2, 7–9]. Regarding gender, mixed features are more common in females [9, 12]. Patients presenting mixed states are at higher risk of developing comorbid anxiety disorders [7, 8]. They are also more likely to experience early-life stressors and present stress-related disorders [7].

21.2.2 Rapid Cycling

The prevalence of 12-month rapid cycling was 0.3% in the general population, according to a cross-national community study that evaluated 54,000 individuals in 10 countries [13]. A review of 12 clinical studies evaluated 8000 bipolar patients and found that the one-year prevalence of rapid cycling was 18% in this population [14]. Moreover, it is estimated that the lifetime prevalence of rapid cycling is around 30% among patients diagnosed with BD [13, 14].

There is some evidence that patients diagnosed with rapid cycling tend to develop symptoms earlier in life than non-rapid-cycling bipolar individuals [15]. According to a cross-national study, individuals with rapid cycling endured onset at a younger age (16,7 years old) compared to non-rapid-cycling individuals (20 years old) [13]. Regarding gender, a meta-analysis that evaluated 16 clinical studies associated rapid cycling predominantly with women [16], a finding that was confirmed by other studies in subsequent years [17, 18], and by the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) [12].

Rapid-cycling BD is significantly more frequent in BD type II (BDII) [12, 16–18]. It is also known that rapid-cycling individuals demonstrated higher rates of comorbidity with lifetime anxiety disorders, such as social phobia, generalized anxiety disorder (GAD), and specific phobia. Most patients in this condition shared severe manic or hypomanic symptoms (63.2%), which is higher than non-rapid-cycling patients (54.1%) [12, 13]. A history of child abuse, parental negligence, parental divorce, and parental depression appears to be more prevalent among individuals with rapid-cycling BD compared to those with non-rapid-cycling BD [13]. Hypothyroidism is a clinical abnormality often found in BD patients, and it is likely to have a higher incidence in rapid-cycling individuals [18, 19].

Moreover, rapid-cycling BD individuals are more likely to attempt suicide [13, 20]. A study with 305 bipolar patients found that individuals diagnosed with rapid-cycling BD (18% of the sample) exhibited a significant rise in their lifetime history of suicidal ideation [20]. In addition, suicide attempts were significantly higher in rapid-cycling individuals [12, 20].

21.3 Clinical Features

21.3.1 Mixed Features

According to the DSM-5-TR, mixed features are defined as major depression, mania, or hypomania with at least three symptoms of the opposite polarity. Regarding manic and hypomanic episodes, symptoms of the opposite pole must be present on most days of the current or recent mood episode and consist of dysphoric or depressed mood, decreased interest or pleasure in activities, psychomotor retardation, decreased energy or fatigue, guiltiness and feelings of worthlessness, and

recurrent thoughts of death, suicide, or suicide attempts. Concerning depressive episodes, symptoms of the opposite pole are elevated or expansive mood, inflated self-esteem or feelings of grandiosity, pressured speech, flight of ideas or racing thoughts, increased energy or goal-directed activity, decreased need for sleep, and involvement in activities with a high risk of painful consequences, such as risky sexual behavior, buying sprees, and foolish business investments [12].

Manic episodes with mixed features commonly manifest emotional lability, irritability, anhedonia, less euphoria, and reduced grandiosity. Additionally, there is often a less pronounced reduction in the need for sleep, and greater anxiety, dysphoria, and feelings of guilt [21–24]. During depressive episodes with mixed features, studies indicate that patients may exhibit irritability, emotional lability, increased cognitive activity such as racing thoughts and distractibility, and heightened psychomotor activity characterized by increased talkativeness, impulsivity, and restlessness [23, 25–27]. These symptoms can bring significant distress to the patient, notably increasing the risk of suicide [28, 29].

Rapid Cycling.

This specifier consists of the presence of at least four mood episodes meeting the criteria for mania, hypomania, or major depressive episode within the past 12 months [12]. Clinical features associated with each polarity are appropriately described in the designated chapters.

21.4 Assessment and Diagnosis

21.4.1 Mixed Features and Rapid Cycling

Accurately diagnosing and treating mood disorders requires careful adherence to established clinical guidelines, particularly when dealing with complex symptoms like mixed features and rapid cycling [12, 30]. Guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT) emphasize the importance of comprehensive evaluations. This detailed approach is crucial because mixed features significantly increase the risks of suicide, rapid mood changes, difficulty functioning, and resistance to treatment [31].

Recognizing and accurately diagnosing mixed features is crucial as they necessitate different treatment approaches to manage the disorder effectively [32]. Considering that the risk of suicide is an important characteristic of bipolar patients, especially in mixed presentations, it is essential to assess it during consultations [31]. If suicide risk is identified, interventions such as self-care strategies, psychological support, and safety planning should be incorporated [33].

The DSM-4 established strict criteria for diagnosing mixed episodes, requiring the simultaneous presentation of full criteria for both manic and depressive episodes [34]. However, the transition to DSM-5 refined this approach by introducing mixed features as specifiers for manic or depressive episodes in BD, as well as in major

depressive disorder (MDD), aligning more closely with the complexities seen in clinical practice [35]. This adjustment underscores the importance of recognizing the presence of symptoms from the opposite polarity, even when full criteria for a mixed episode are not met, in shaping the therapeutic plan.

Rapid cycling is highlighted as a specifier for the clinical course of BD, associated with a worse prognosis [36]. The genesis of this phenomenon can be multifactorial, involving substance use, pharmacological interventions, and hormonal fluctuations, emphasizing the need for careful assessment for appropriate identification and management [7]. Nonetheless, a decreased interval between episodes may indicate severity, disease progression, or poor treatment response.

The diagnostic assessment process for identifying mixed features and rapid cycling in patients with BD involves a systematic approach. Initially, it is crucial to investigate patients displaying concurrent depressive/anxious symptoms alongside signs of impulsivity, substance abuse, irritability, or elevated mood (potential manic/hypomanic symptoms) [37, 38]. It is also vital to consider an underlying mood disorder in cases of vague/nonspecific somatic symptoms or reverse vegetative symptomatology [39]. The diagnostic assessment should include a detailed history, covering the history of affective episodes, comorbidities, and pharmacological history; a thorough mental state examination; assessment of suicide and self-harm risks; consideration of collateral reports from family or caregivers; and investigation of potential organic etiologies through laboratory and imaging tests, when indicated [39].

For evaluating mixed features, a detailed examination of opposite-pole symptoms is involved [30]. It is necessary to determine if these symptoms are clinically significant and predominant during the episode [40]. Identifying possible triggers or precipitating factors, such as psychosocial stress, medications, or substance use, is also crucial [40]. Furthermore, it is essential to differentiate mixed features from similar conditions, such as pure mixed episodes, agitated depression, or dysphoric mania [40]. The use of standardized scales, like the Young Mania Rating Scale (YMRS) and the Beck Depression Inventory, can help to quantify symptoms [41]. Evaluating rapid cycling requires detailed documentation of the mood episode pattern over the last 12 months, including timing, duration, and symptoms [40]. Investigating potential precipitating or triggering factors is important. Factors such as hypothyroidism, antidepressant use, and use of psychoactive substances are associated with rapid cycling [31]. In this context, thyroid function should be investigated, and the discontinuation of antidepressants, stimulants, and other psychoactive substances that may contribute to cycling should be considered [31]. The treatment involves specific considerations, and the combination of mood stabilizers is commonly necessary when rapid cycling is present [42].

Manifestations of mixed features and rapid cycling may not be evident in a single evaluation. Therefore, a longitudinal follow-up is necessary as well as a systematic monitoring of symptoms and episodic dynamics. Early and accurate diagnosis is crucial for devising an appropriate therapeutic plan aiming to optimize clinical outcomes [43, 44].

21.5 Differential Diagnosis

21.5.1 *Mixed Features*

To identify differential diagnoses for mixed presentations, it is necessary to perform a meticulous physical examination to distinguish primary and secondary contributors. Furthermore, the differential diagnosis for mixed presentations includes targeted laboratory investigations, such as endocrinological disturbances (hypo or hyperthyroidism and hypo or hyperglycemia) [45].

Evaluating for personality disorders, particularly borderline personality disorder, alongside psychiatric conditions like anxiety and attention-deficit hyperactivity disorder, is crucial due to their potential overlapping phenotypes with mixed states [45]. Moreover, mixed states should be differentiated from rapid cycling, as they are similarly presented sometimes [7]. The physician also needs to exclude neurological insults (such as seizures, or cerebrovascular events), hematological abnormalities (such as anemia), and substance use [45].

21.5.2 *Rapid Cycling*

The psychopathology of rapid-cycling BD also intersects with symptoms of borderline personality disorder [46, 47]. Furthermore, both conditions can be simultaneously diagnosed within the same individual [46]. DSM-5 establishes a connection between BD and borderline personality disorder. However, it does not specifically mention rapid cycling as a part of this association [12]. The overlap between rapid-cycling BD and borderline personality disorder lies in rapid mood switches, such as mood elevation and depressive symptoms [46, 47]. Individuals diagnosed with borderline personality disorder tend to experience emotional lability as a reaction to environmental triggers, including failure, rejection, and fear while patients with a rapid-cycling diagnosis do not typically exhibit this characteristic [46, 47]. According to the DSM-5, borderline personality disorder patients make frantic efforts in their personal lives to avoid real or imagined abandonment, which makes clear a tendency to have unstable and intense interpersonal relationships. These individuals also experience affective instability rather than mood elevation, such as dysphoria, irritability, and anxiety; these previous features are not indicative of rapid-cycling BD [12].

Furthermore, the DSM-5 highlights similarities between rapid-cycling BD and cyclothymic disorder. Rapid-cycling BD may resemble cyclothymic disorder due to frequent mood shifts. Cyclothymic disorder is diagnosed when no criteria for depressive, manic, or hypomanic episodes have ever been fully met. In contrast, the diagnosis of rapid-cycling BD requires the presence of full-mood episodes.

Therefore, it is essential to carefully distinguish symptoms, and adhere to the diagnostic criteria in order to differentiate between these two disorders accurately [12].

21.6 Initial Management

21.6.1 *Mixed Features*

The appropriate management of an episode with mixed features, as with any other episode, begins with a proper evaluation of the presented symptoms. Initially, potential acute risks should be considered, aiming to maintain the patient's and others' safety. Severe psychomotor agitation with risks of self-harm, harm to others, or high suicide risk should be referred to emergency care or hospitalization [48]. This is particularly important in episodes with mixed features, as such episodes are associated with an increased risk of suicide attempts [49].

It is also recommended to conduct a clinical and laboratory evaluation, including complete blood count, fasting blood glucose, lipid profile, electrolytes, liver enzymes, serum bilirubin, prothrombin time, qualitative urine test, serum creatinine, thyroid function, prolactin, beta-HCG (for women in childbearing age), and electrocardiogram when indicated. This assessment is important to exclude major differential diagnoses and to monitor the main side effects induced by psychotropic medications. Additionally, discontinuation of substances that may be associated with the occurrence or worsening of the episode, such as antidepressants, caffeine, psychostimulants, and substances of abuse, should be encouraged [48].

Once potential risks have been assessed and possible differential diagnoses excluded, a therapeutic plan should be developed. Pharmacological management remains the main therapeutic intervention [48]. The doctor-patient relationship is important to ensure patient engagement in treatment. Psychotherapeutic interventions can be used as complementary strategies to pharmacotherapy, primarily aiming to prevent the recurrence of episodes and restore quality of life [31].

21.6.2 *Rapid Cycling*

Considering that prolonged exposure to a mood episode exacerbates the risk of an adverse course in BD, it is important to aim for treatment with lasting responses and to reduce factors that may predispose to new mood episodes. Substance abuse, hypothyroidism, and antidepressant use frequently correlate with rapid-cycling bipolar presentations. Therefore, it is important to investigate thyroid function, discontinue possible medications associated with the condition, such as antidepressants and stimulants, and investigate and treat substance abuse [31].

21.7 Treatment

21.7.1 *Mixed Features*

The treatment will be divided into topics, according to the symptomatic presentation (manic episodes with mixed features and depressive episodes with mixed features). The treatment is based primarily on the recommendations of the CANMAT for BD patients with mixed presentations, one of the main guidelines in the field [45].

21.7.1.1 Manic Episodes with Mixed Features

At present, there are no pharmacological agents with sufficient evidence to recommend first-line treatment for manic and depressive symptoms in an acute manic episode with mixed features. Therefore, second-line agents should preferably be chosen in the initial pharmacological management.

The second-line agents recommended for the treatment of mania with mixed features are asenapine, cariprazine, valproic acid, and aripiprazole.

Asenapine has evidence from post-hoc analyses when DSM-5 mixed features criteria were applied in three randomized, double-blind clinical trials [50]. The evidence showed positive results compared to placebo in improving both manic and depressive symptoms [51].

Cariprazine has also been shown to be effective in treating manic episodes with mixed features but its efficacy in improving depressive symptoms was observed only in individuals with higher symptom severity (MADRS scale score ≥ 10), indicating a possible lack of efficacy in patients with milder depressive symptoms [52].

Valproic acid has shown equal effectiveness in treating both pure mania and mixed features in a post-hoc analysis of a randomized clinical trial [53]. It has also been shown to be more effective than lithium in improving manic symptoms when mixed features are present. However, specific outcomes related to depressive symptoms were not evaluated. Due to the established efficacy of divalproex in treating depressive episodes, and also based on expert opinion recommending the use of this drug due to improvement in depressive symptoms in manic episodes with mixed features, this medication is also recommended.

Aripiprazole is effective in treating manic symptoms in episodes with mixed features associated with depressive symptoms of any intensity, although outcomes associated with depressive symptoms have not been demonstrated [54]. While there is negative evidence for the use of aripiprazole in pure depressive episodes [55, 56], this drug may be considered in episodes with mixed features due to potential benefits demonstrated in treating depressive symptoms in mixed episodes characterized by DSM-IV [54–57].

The third-line agents are ziprasidone, olanzapine in monotherapy, olanzapine + lithium/valproic acid, quetiapine, extended-release carbamazepine, and electroconvulsive therapy (ECT).

Ziprasidone has some evidence of efficacy compared to placebo in treating both manic and depressive symptoms in manic episodes with mixed features [58]. However, this medication is considered third-line due to safety and tolerability concerns.

Olanzapine in monotherapy has demonstrated superior efficacy to placebo in improving manic symptoms, although the improvement in depressive symptoms was not statistically significant [59]. However, this medication should be considered in mixed episodes, as it has evidence of improvement in depressive symptoms in episodes with mixed features, as well as in pure depressive episodes [31].

Olanzapine in combination with lithium or valproic acid has shown efficacy in manic and depressive symptoms in individuals with dysphoric mania in an open-label trial and also in a naturalistic study when compared to the combination of another antipsychotic (mainly haloperidol and levomepromazine) [60, 61].

Quetiapine has not been evaluated in manic episodes with mixed features in studies using the DSM-5 criteria. However, a randomized clinical trial with patients diagnosed with BDII who were experiencing hypomanic and depressive symptoms showed significant improvement in depressive symptoms but not in hypomanic symptoms [62]. This result could be explained by the use of doses lower than 300 mg/day in the study. Despite the results, the efficacy of this drug in treating pure mania and also in maintenance treatment to prevent manic symptoms is well known.

Extended-release carbamazepine has not been evaluated in studies for mania with mixed features but expert opinions support its use, which is consistent with results from studies of participants categorized as having a mixed episode by DSM-IV criteria. Evidence showed efficacy in treating both manic and depressive symptoms in that scenario [63].

ECT has also not been evaluated in studies with participants meeting DSM-V criteria for mania with mixed features but the experts' opinions suggest that this method can be effective in these cases. ECT should preferably be used in severe cases where patients have not responded to second or third-line pharmacological treatments.

Although lithium, paliperidone, and risperidone are recommended for pure manic episodes and lithium and lurasidone for pure depressive episodes [31], these drugs have not been adequately studied for mania with mixed features, and expert opinion does not recommend their use. First-generation antipsychotic agents are not recommended in the treatment of this type of episode due to their lack of efficacy in treating depressive symptoms. Haloperidol, in particular, appears to increase the risk of depression when used in the treatment of mania [64].

Treatment recommendations for the mixed features manic episode are summarized in Table 21.1.

Table 21.1 Treatment recommendations for manic episodes with mixed features

Manic episodes with mixed features (DSM-5-TR)	
First-line	None
Second-line	Asenapine, cariprazine, valproic acid, aripiprazole
Third-line	Ziprasidone, olanzapine, olanzapine + lithium/valproic acid, quetiapine, carbamazepine, ECT
Not recommended	Lithium, paliperidone, risperidone, first-generation antipsychotics

21.7.1.2 Depressive Episodes with Mixed Features

As in manic episodes with mixed features, there is not enough evidence for first-line pharmacological agents in depressive episodes with mixed features either. Therefore, second-line agents should be recommended as initial pharmacological management in these cases.

The second-line agents recommended for the treatment of depressive episodes with mixed features are cariprazine and lurasidone. Both agents were effective in managing depressive symptoms in post-hoc analyses, although they did not show superiority over placebo in the management of manic symptoms [65, 66]. It should be noted that in these analyses, the severity score of mania was low; therefore, the results are limited. Thus, expert opinion recommends the use of these drugs.

The third-line agents are olanzapine, olanzapine + fluoxetine, quetiapine, valproic acid, lamotrigine, ziprasidone, and ECT.

Olanzapine has proven efficacy in reducing depressive and manic symptoms but is listed as a third-line option due to tolerability and safety concerns associated with its use [67].

Patients treated with the combination of olanzapine with fluoxetine appear to have similar outcomes to olanzapine monotherapy in treating depressive symptoms in bipolar depressive episodes. However, in episodes with mixed features, this combination appears to have superiority compared to olanzapine monotherapy. The combination of these two drugs does not seem to result in a significant increase in manic or hypomanic switch compared to other treatments [68]. Similar to olanzapine monotherapy, issues related to tolerability and safety should be considered.

Although quetiapine is known to be effective in treating bipolar depression [69, 70] and mania [71], it has not been evaluated in studies for the treatment of bipolar depression with mixed features. Despite this, it should be considered in the treatment due to expert opinion, given its ability to treat both polarities [31].

Valproic acid and lamotrigine have established efficacy in treating pure depression [31]. Valproic acid is additionally effective in treating pure mania and mania with mixed features (as seen previously). Lamotrigine is not recommended for mania treatment and therefore lacks evidence for manic symptoms in a mixed depression scenario. These two drugs are considered third-line due to expert opinion.

Ziprasidone is effective in treating depressive symptoms in a sample of individuals with BDII and MDD, with a negative outcome for manic symptoms in the same

study [72]. Given the effectiveness of this medication in treating manic symptoms in other presentations, it is considered a third-line option according to expert opinion. For this drug, difficulties regarding tolerability and safety related to its use should also be taken into consideration.

ECT is also considered a third-line option by expert opinion, as there is no systematic data for patients in a depressive episode with mixed features. ECT is recommended for patients who have not responded to second and third-line pharmacological options.

Antidepressants, whether in monotherapy or as adjunctive therapy (except for the combination of olanzapine + fluoxetine), are not recommended for depressive episodes with mixed features, as data suggest that the use of antidepressants seems to increase the risk of manic switch even when the presence of manic symptoms is minimal [73].

Treatment recommendations for depressive episodes with mixed features are summarized in Table 21.2.

21.7.2 Rapid Cycling

When considering the pharmacological treatment of rapid-cycling BD, robust evidence remains scarce and, at times, divergent. For instance, the CANMAT recommends treatment to be guided by medications indicated for maintenance therapy, given the lack of evidence for managing acute episodes during a rapid-cycling phase [31, 74]. Conversely, the National Institute for Health and Care Excellence (NICE) suggests that treatment should proceed similarly to patients without the rapid-cycling specifier due to the lack of concrete evidence [74].

According to recent data from a systematic review and meta-analysis, the only class demonstrating effectiveness above placebo for manic episode treatment was second-generation antipsychotics [75]. Among them, particularly quetiapine, olanzapine, and aripiprazole stood out. Quetiapine emerged as the most studied drug, demonstrating efficacy in both depression and mania treatment [75]. Additionally, some studies suggest that divalproex could be employed in treating manic and mixed-feature episodes [74].

Table 21.2 Treatment recommendations for depressive episodes with mixed features

Depressive episodes with mixed features (DSM-5-TR)	
First-line	None
Second-line	Cariprazine, lurasidone
Third-line	Olanzapine, olanzapine + fluoxetine, quetiapine, valproic acid, lamotrigine, ziprasidone, ECT
Not recommended	Antidepressants

Although there is evidence against the use of antidepressants in treating rapid-cycling BD [76, 77], studies indicate that they may be considered for acute treatment of major depressive episodes in selected patients. SSRIs and bupropion appear to be moderately safe and effective [75, 78].

In prophylactic treatment, lamotrigine, aripiprazole, and adjunctive therapy with levothyroxine are options supported by some evidence [74].

Although some therapeutic options have been suggested, robust evidence is still lacking to establish a preferred treatment for patients with rapid-cycling BD [75].

Considering the limited response and the scarcity of robust evidence regarding pharmacological interventions in patients with rapid-cycling BD, it is important to consider non-pharmacological adjunctive strategies. Among the options, ECT can be utilized in mania, depression, and maintenance, with promising responses, particularly in depression with catatonic or psychotic symptoms [79]. Preliminary evidence suggests that chronotherapy in conjunction with pharmacological treatment may offer some benefits [79]. Other options that may be beneficial include psychoeducation, cognitive-behavioral therapy (CBT), supportive therapy, and family interventions [79]. Additionally, transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS) are also being studied as potential adjunctive treatments [74].

21.8 Management in Specific Populations

21.8.1 Children and Adolescents

It is quite common for the pediatric population with BD to present mixed symptomatology compared to adults [80]. Moreover, early onset of the disease seems to be associated with a higher likelihood of mixed presentation, rapid cycling, and worse prognosis [3, 81]. However, few clinical trials have evaluated pharmacological treatment in episodes with mixed features in the pediatric population so far. The results, as shown below, are based on studies that considered DSM-IV criteria for mixed episodes.

The first-line agents recommended for children in episodes with mixed features are asenapine and risperidone. Asenapine is effective in manic symptoms when compared to placebo [82–84], and expert opinion supports its use for depressive symptoms. Risperidone is considered effective in reducing manic symptoms in episodes with mixed features, but data regarding depressive symptoms were not reported in these studies [85, 86].

The second-line agents are olanzapine, ziprasidone, and lurasidone. Both olanzapine [87, 88] and ziprasidone [89] have demonstrated efficacy in controlling manic symptoms in adolescents in manic or mixed episodes but they are placed as second-line due to safety and tolerability concerns. Although there is a lack of evidence on efficacy for depressive symptoms, experts support their use. Lurasidone was shown to be effective in reducing depressive symptoms in depressive episodes with mixed features [90].

The third-line agents are quetiapine [91], divalproex [91, 92], lithium [85], and carbamazepine [93]. These drugs have limited evidence of efficacy but are recommended by experts. Carbamazepine, in particular, should be considered last due to safety concerns associated with its use, and the high risk of drug interactions.

Evidence for maintenance treatment is limited, but studies suggest the use of lithium or lamotrigine as adjuncts to other mood stabilizers [94, 95].

21.8.2 Older Adults

Just like in the pediatric population, few studies have assessed the response to pharmacological treatment in the elderly population in episodes with mixed features, and as a result, evidence is limited. Therefore, no specific recommendation is made for this population, and recommendations made for the adult population should be considered, taking into account safety and tolerability issues related to the elderly population.

21.8.3 Pregnancy and Postpartum

Presentation with mixed symptomatology is common during pregnancy and postpartum. About 74% of women with known BD who discontinue their treatment before or at the beginning of pregnancy experience a recurrence of depressive or mixed episodes during the first trimester [96]. Approximately 6.5% of women with BD type I (BDI) and 2.5% of women with BDII have mixed episodes in the postpartum period [97]. Recognizing these symptoms is important because the development of mixed symptoms in the postpartum period is associated with an increased risk of self-harm ideation [98].

Similar to the elderly population, there are no specific recommendations for treatment in this population. Evidence shows that quetiapine appears to be effective in treating postpartum bipolar depression [99], and low-dose quetiapine treatment can be used in women with postpartum depression with mixed features [100]. It is also important to consider the suspension of agents that present teratogenic risks. This topic is further discussed in another chapter.

21.9 Course of Illness and Prognosis

Understanding the course of illness and prognosis for patients with mixed features in BD is crucial, as these individuals face uniquely challenging and severe outcomes. Mixed states lead to a more complex, severe, and unfavorable prognosis compared to patients without such characteristics [7]. The addition of rapid cycling

further complicates the management of BD by signaling a more severe illness trajectory [32]. This phenomenon increases the frequency and severity of mood episodes, including those with mixed features, and complicates treatment response. Patients experiencing both mixed states and rapid cycling present a particularly challenging scenario, often showing resistance to standard mood stabilizers and necessitating a combination of therapies or the adoption of novel pharmacological approaches for effective symptom management. The prognosis for these individuals is notably poor, with a younger onset age, increased number of lifetime mood episodes, heightened severity of episodes, greater functional impairment, and elevated suicide risk. Additionally, the co-occurrence of rapid cycling and mixed states points to a deeper biological and genetic predisposition toward mood dysregulation, possibly tied to significant neurobiological changes and alterations in neurotransmitter systems [101].

In a longitudinal study conducted from 1994 to 2004, researchers examined the prognosis of 120 patients with BDI, focusing specifically on those who experienced at least one mixed episode [102]. Through bimonthly visits over a decade, the study recorded the number and severity of episodes, hospitalizations, and suicide attempts. Findings revealed that 37% of participants presented mixed episodes, which were associated with a younger average onset age of 25.3 years, in contrast to 30.8 years for those without mixed episodes. Even after adjusting for onset age, the mixed episodes group exhibited an increased risk of hospitalization and a higher frequency of episodes. While factors like alcohol abuse, psychotic symptoms, and suicidal tendencies were examined, significant differences were mostly not found after controlling for onset age. However, it was noted that patients with mixed episodes and a history of suicide attempts experienced a shorter interval until their first suicide attempt during the follow-up period. The study concluded that, despite some factors being influenced by the age of onset, the prognosis for patients with mixed episodes is generally more severe compared to those with non-mixed episodes.

Another notable finding was that the presence of mixed features was exclusively observed in bipolar patients with a family history of BD, indicating a potential genetic link [103]. Patients who exhibit mixed states, whether in manic or depressive form, report a greater number of lifetime episodes and suffer from prolonged durations of mood instability [104, 105]. Mixed episodes often last longer, leading to extended periods of mood instability, and tend to resolve more slowly than unipolar depressive or manic episodes, resulting in a tendency for earlier relapses following remission [7]. Furthermore, individuals with mixed episodes are more likely to have experienced early stressful events and develop stress-related disorders [106]. The prevalence of anxiety disorders is significantly higher among patients with mixed episodes, and the incidence of alcohol and substance abuse is elevated in mixed manic episodes, correlating with less favorable prognoses and reduced responsiveness to lithium treatment [107–109]. Though evidence on lifetime alcohol abuse is mixed, a clear association exists between a history of substance use disorder and greater mood instability in bipolar depression, increasing the risk of mixed features and suicidal behavior [7].

The unfavorable prognostic implications of mixed presentations can be attributed to several factors, including the greater complexity and severity of symptoms, more pronounced neurocognitive impairments, higher risks of suicidal behavior, and potential treatment resistance [5, 110, 111]. Mixed states present diagnostic and therapeutic challenges, requiring careful and balanced approaches of pharmacological and psychosocial interventions to address the concurrent manic and depressive symptoms effectively [7]. Clinicians must also be vigilant for possible underlying non-psychiatric or neurological medical conditions that could influence mixed episodes and necessitate specific treatments.

In summary, a substantial body of literature indicates that mixed features in BD, especially when compounded by rapid cycling, are closely associated with a more severe and adverse course of the disease. This condition is characterized by a higher recurrence of episodes, rapid cycling, early onset, suicidal behavior, frequent hospitalizations, significant functional impairment, and poorer treatment response compared to patients without mixed features [7]. The early recognition and appropriate management of mixed states and rapid cycling are crucial for improving outcomes and the long-term prognosis of these patients, underscoring the need for a multifaceted treatment approach to mitigate the severe impacts of these conditions.

21.10 Clinical Considerations

21.10.1 *Mixed Features*

- Defined by at least three symptoms from the opposite polarity during a depressive, manic, or hypomanic episode.
- Higher risk of comorbid anxiety disorders and early-life stressors, alcohol, and substance abuse.
- More severe outcomes compared to non-mixed episodes: early onset, longer periods of mood instability, more frequent episodes, greater functional impairment, higher suicide risk, neurocognitive impairments, and treatment resistance.
- Differential diagnosis: personality disorders, rapid cycling, neurological insults, hematological abnormalities, and substance use.
- Initial evaluation: proper symptom evaluation, considering acute risks (self-harm, harm to others, high suicide risk) and emergency care in case of severe psychomotor agitation.
- Clinical assessment: laboratory exams, monitoring side effects of psychotropic medications, discontinuation of substances worsening the episode (antidepressants, caffeine, psychostimulants, substances of abuse).
- Pharmacological treatment:

- Manic episodes with mixed features:
 - First-line: None.
 - Second-line: Asenapine, cariprazine, valproic acid, aripiprazole.
 - Third-line: Ziprasidone, olanzapine (monotherapy or with lithium/valproic acid), quetiapine, carbamazepine (extended-release), electroconvulsive therapy (ECT).
 - Not recommended: lithium, paliperidone, risperidone, first-generation antipsychotics.
- Depressive episodes with mixed features:
 - First-line: None.
 - Second-line: Cariprazine, lurasidone.
 - Third-line: Olanzapine, olanzapine + fluoxetine, quetiapine, valproic acid, lamotrigine, ziprasidone, ECT.
 - Not recommended: Antidepressants.
- Psychotherapeutic interventions: Complement pharmacotherapy to prevent recurrence and restore quality of life.
- Children and adolescents:
 - First-line agents: Asenapine, risperidone.
 - Second-line agents: Olanzapine, ziprasidone, lurasidone.
 - Third-line agents: Quetiapine, divalproex, lithium, carbamazepine.
 - Maintenance treatment: Lithium, lamotrigine (adjuncts to other mood stabilizers).
- Older adults: no specific recommendations; consider adult recommendations with safety and tolerability concerns.
- Pregnancy and postpartum: Quetiapine (particularly in postpartum depression with mixed features); discontinuation of agents with teratogenic risks.

21.10.2 Rapid Cycling

- Defined by at least four mood episodes within 12 months.
- Lifetime prevalence in bipolar patients: 30%.
- Symptoms developed earlier in life compared to non-rapid-cycling individuals.
- More common in women and significantly more frequent in BD type II.
- Higher comorbidity with lifetime anxiety disorders.
- Associated with a history of childhood abuse and hypothyroidism.
- Increased risk of suicide and suicidal ideation.
- Overlaps with borderline personality disorder and cyclothymic disorder.

- Pharmacological treatment:
 - Second-generation antipsychotics: Quetiapine, olanzapine, aripiprazole.
 - Divalproex: For manic and mixed-feature episodes.
 - SSRIs and bupropion: For acute treatment of major depressive episodes in selected patients.
 - Prophylactic treatment: Lamotrigine, aripiprazole, adjunctive therapy with levothyroxine when indicated.
- Non-pharmacological adjunctive strategies: Still requires more studies.
- Special populations: Lack of consistent data.

21.11 Future Perspectives

Given the current understanding of mixed states and rapid cycling in BD, several future research and clinical practice directions are anticipated to enhance patient outcomes.

21.11.1 Early Detection and Intervention

Early detection of these specifiers is critical for improving long-term outcomes. Advances in this field can help initiate timely and targeted interventions, potentially preventing the progression to more severe mood episodes.

21.11.2 Novel Therapeutic Approaches

Current pharmacological treatments for mixed features and rapid cycling often show limited efficacy and are associated with significant side effects. Future research should prioritize the development of novel therapeutic agents that specifically target the neurobiological mechanisms involved in mixed features and rapid cycling. Investigating the efficacy of combination therapies and adjunctive treatments may provide new avenues for effective management.

21.11.3 Adjunctive Interventions

While pharmacotherapy remains a cornerstone of treatment, integrating psychosocial interventions such as CBT, psychoeducation, and family therapy is crucial. Future studies should explore the synergistic effects of combining pharmacological

and psychosocial treatments, tailoring interventions to individual patient profiles. Additionally, promoting resilience and coping strategies through mindfulness and stress reduction techniques may enhance overall treatment outcomes.

21.11.4 Addressing Comorbidities

Since comorbid conditions are prevalent among patients with mixed states and rapid cycling, future clinical guidelines should emphasize comprehensive assessment and integrated management of these comorbidities. Research should also explore the bidirectional relationships between BD and comorbid conditions to develop treatment strategies that address the full spectrum of patient needs.

21.11.5 Improving the Clinical Course

Longitudinal studies are essential to understanding the natural course of mixed presentations and rapid cycling and to identifying predictive factors for treatment response and long-term outcomes. Additionally, real-world evidence from large-scale observational studies and patient registries can provide valuable insights into the effectiveness and safety of various treatment modalities in diverse patient populations.

21.11.6 Special Populations

Research on mixed features and rapid cycling in special populations, including children, adolescents, the elderly, and pregnant/postpartum women, is limited. Future studies should address the unique challenges and treatment needs of these groups, developing age- and condition-specific management strategies to improve their prognosis.

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Chapter 22

Treatment of Depressive Episodes



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22.1 Introduction

Bipolar disorder is a chronic condition that affects more than 1 % of the global population, and the complexity of its depressive episodes presents a unique challenge in the field of mental health [1]. In prospective studies of the natural history of the disease, patients diagnosed with bipolar disorder type I reported experiencing depression in 31.9% of weeks and hypomanic symptoms for 8.9%, while patients with bipolar disorder type II reported depressive symptoms for almost 27% of weeks and hypomanic/manic symptoms in 3% [2]. According to Kupka et al., the duration of depressive episodes is three times longer than that of mania or hypomania; this prevalence proves the critical need to understand and address the specific aspects of depression in the context of this pathology [3].

Not only is the burden of bipolar depression reflected in statistics, but also the comorbidities that often accompany it. Additional irregular medication adherence and the prevalence of substance use disorder are areas of concern; data suggests that between 30% and 50% of patients diagnosed with bipolar disorder do not comply with treatment, which is not only linked to the intensification of depressive

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symptoms but can also prolong their duration and increase the risk of suicide [4]. In this context, early detection is essential, especially in primary care and medical emergencies, in which the main reasons for consultation are suicidal ideation, anxiety disorders, self-injury, and autolytic attempts.

The impact of depressive episodes on the quality of life and the risk of suicide is concerning. It is estimated that between 25% and 60% of patients with this diagnosis will attempt suicide at least once during their lifetime, and between 4% and 19% will succeed [5]. In this context, the precise distinction between unipolar and bipolar depression becomes even more important, as the consequences of not doing so can be significant, with potential adverse repercussions. Studies have shown that patients with bipolar disorder, especially young individuals, carry the highest risk of suicide among all affective disorders [6]. Although both forms of depression tend to be chronic and recurrent throughout life, bipolar depressive episodes have a higher incidence of suicide than unipolar episodes [7]. Therefore, the right choice of therapeutic interventions is critical, as the wrong treatment can increase the risk of suicide, particularly in young patients, as well as trigger the switch to mania or hypomania.

To achieve a comprehensive and effective intervention in the treatment of depressive episodes, an integrated approach must be adopted, carefully selecting resources that best suit the specific characteristics of each patient, considering comorbidities, episode severity, concomitant symptoms, and possible interactions with other medications. It is crucial to explore the patient's medical history for previous depressive episodes, analyzing the past efficacy and tolerability of used therapies. Monotherapy, using mood stabilizers or antipsychotics, presents an initial option as the first line, but the combination of different drug classes emerges as an effective and more realistic strategy. The synergy between different pharmacological groups offers a comprehensive approach, addressing the depressive aspects of the disorder and protecting the patient from progressing to a hypomanic or manic episode.

For refractory cases, in which the response to conventional treatments is limited, ketamine, esketamine, and electroconvulsive therapy (ECT) emerge as valuable alternatives to deep brain stimulation for particular cases [8]. Transcranial magnetic stimulation has also shown promising results in the field.

The decision to hospitalize the patient or provide care through specialized devices should always be evaluated on a personalized basis considering the benefits and risks carefully. Factors such as the patient's age, level of functioning, episode severity, and especially social environment and access to the healthcare system should be taken into account. Some cases can be managed on an outpatient basis in primary healthcare, always with close and periodic follow-up.

Finally, we emphasize the importance of a multidimensional perspective. Pharmacological intervention, while essential, is complemented by psychotherapy. Working with the patient and their families is vital for proper psychoeducation, promoting stability maintenance, and preventing relapses. This comprehensive approach recognizes the interconnection between the biological and psychosocial aspects of bipolar disorder.

22.2 Pharmacological Treatment of Bipolar Depressive Episodes

Addressing bipolar depression requires a meticulous and comprehensive roadmap. Once the diagnosis is established, the treatment strategy is constructed by considering a network of crucial factors. This involves evaluating the medical history for previous episodes and assessing the efficacy of prior treatments, as well as weighing the presence of residual symptoms and aggravating factors, such as suicidal ideation or possible manic switch in rapid-cycling patients [9]. Additionally, on many occasions, we lack studies specifically focused on bipolar depression because the effective results of medications in unipolar depression have been adopted.

The perspective extends beyond the confines of symptoms, taking into account comorbidities, regular medication, and the patient's social context. This approach not only shapes the formulation of the therapeutic plan but also highlights the importance of treatment adherence in forging a path toward recovery between episodes.

In this complex web of considerations, finding the way to well-being becomes an art that combines diagnostic precision, clinical expertise, and a profound understanding of the individuality of each patient.

22.2.1 *Mood Stabilizers*

Lithium and valproate, among others, are pivotal in the treatment of bipolar disorder, recognized for their mood-regulation properties and their ability to mitigate affective disturbances. They also play a crucial role in both acute situations and the maintenance phase, significantly contributing to relapse prevention. Importantly, they serve as a protective barrier against the switch to manic episodes. In this section, we will dig into the pharmacology of these agents, assess their advantages and disadvantages, and compare their effectiveness in managing depressive episodes.

22.2.1.1 **Lithium**

Initially employed as an alkaline mineral for gout treatment in the mid-nineteenth century [10], lithium revealed its efficacy in the 1940s and 1950s, manifesting anti-manic properties and standing out in the management of bipolar disorder among other psychiatric conditions [11, 12].

Its mechanism of action at a neuronal level is intricate; it reduces dopamine and glutamate levels, both having excitatory roles, while enhancing the inhibitory function of gamma-aminobutyric acid (GABA). Intracellularly and molecularly, it affects, for instance, protein kinase C, modulating neuronal function through second messengers. Furthermore, it demonstrates the ability to decrease oxidative stress

associated with multiple manic and depressive episodes [13] and exhibits neurotrophic and neuroprotective effects linked to neuronal proliferation and differentiation [14].

Lithium consolidates itself as an effective option for the primary treatment of bipolar depression in monotherapy [15] and in combination with other agents, such as quetiapine and lamotrigine [16, 17]. Additionally, it proves efficacy in preventing recurrences and long-term maintenance. Studies have demonstrated that long-term lithium treatment reduces suicide attempts by approximately 10% and decreases suicide deaths by nearly 20% in patients diagnosed with bipolar disorder [18]. In a randomized controlled study led by Sachs et al., the effectiveness, safety, and tolerance of adding antidepressants to mood stabilizer treatment in patients with bipolar depression were evaluated over 26 weeks ($n = 366$). One group received a mood stabilizer plus an antidepressant (paroxetine or bupropion), while the other received a mood stabilizer plus a placebo. The results revealed that adding antidepressants did not provide greater efficacy compared to monotherapy with mood stabilizers and did not increase the risk of mood changes. It was also observed that less than 1% of patients attempted suicide, indicating an acceptable safety profile in this context and supporting lithium as a valid option in monotherapy [19].

Prudent management is essential, considering pharmacological interactions, constant monitoring, and the careful selection of responsible patients. Serum lithium levels ideally should be maintained between 0.6 and 1.2 mEq/l, with levels measured 12 hours after the last administration [20]. The daily dosage to achieve these serum levels is influenced by various factors such as renal function, concomitant administration of other medications, and water intake. Given the proximity between the therapeutic and toxic ranges [21], periodic serum checks are imperative. Patient education about the symptoms associated with toxicity and awareness of significant drug interactions, such as some NSAIDs and diuretics, as well as proper water intake control, are crucial. In cases of toxicity, most situations respond to drug discontinuation and hydration, although, in exceptional circumstances, hemodialysis may be necessary.

22.2.1.2 Lamotrigine

Lamotrigine was introduced in the early 1990s for the treatment of epilepsy, and it operates by stabilizing the presynaptic membrane through the modulation of voltage-dependent sodium channels. Additionally, it exerts regulatory control over the release of excitatory neurotransmitters like glutamate, substantiating its role as a mood stabilizer [22]. Monotherapy with lamotrigine was not superior to placebo in four double-blind placebo-controlled trials of acute bipolar depression on the primary outcome. However, in a meta-analysis led by Geddes et al., lamotrigine demonstrated greater efficacy than placebo in patients with bipolar depression ($n = 1072$), with high rates of remission in five randomized controlled trials [23]. Among potential adverse effects, manifestations of central nervous system toxicity,

including dizziness, ataxia, nausea, and vomiting, have been reported. Caution is advised in concurrent use with oral contraceptives, as it has the potential to alter their elimination, particularly impacting women of childbearing age under contraception [24]. Notably, lamotrigine is not the recommended choice in situations demanding a rapid response, such as cases involving suicide risk. This caution arises from the necessity for a slower titration due to the potential risk of rash development and the onset of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) syndrome [25]. Due to this cause and the short duration of clinical trials on acute treatment, the lamotrigine effectiveness may have been underestimated. Moreover, when considering a combination of lamotrigine with agents like valproic acid or aripiprazole, an increase in associated risks is observed, demanding a careful and closely monitored approach [26].

22.2.1.3 Valproic Acid

Valproic acid, in its active form, exhibits inhibitory properties at the neuronal level, intensifying and facilitating the action of the neurotransmitter GABA. This antiepileptic agent, also authorized for the treatment of bipolar disorder, has demonstrated greater efficacy in the management of manic episodes. A randomized controlled trial by Davis et al. compared valproate with placebo for 8 weeks ($n = 25$) and 46% of patients randomized to the drug showed over 50% improvement and a total score < 9 in Hamilton Depression Rating Scale [27]. However, it is considered a valid option in monotherapy for depressive episodes, although it is generally reserved as a second-line treatment [28, 29].

Prior to the initiation of treatment, a comprehensive evaluation is essential, including the review of possible hepatic and hematological pathologies through liver function tests and a complete blood count. Additionally, the possibility of pregnancy must be ruled out, as there is a significant risk of fetal malformations, such as those affecting the neural tube, cardiovascular, and musculoskeletal system, among others [30]. The potential association with neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), should also be considered.

The most frequent adverse effects related to the use of valproic acid are mainly associated with central nervous system toxicity, manifesting through symptoms such as drowsiness, dizziness, and tremors. Gastrointestinal events have also been reported. However, many of these symptoms can be prevented by adopting a cautious approach, starting with low doses and gradually increasing them. It is crucial to alert and educate the patient about the possibility of experiencing these secondary manifestations associated with the drug's consumption. Less commonly, complications such as hyperammonemia, thrombocytopenia, hepatotoxicity, and pancreatitis have been observed [31]. Attention to these potential side effects underscores the importance of close clinical monitoring during valproic acid treatment.

22.2.1.4 Others

Carbamazepine, an antiepileptic with applications in the treatment of neuropathic pain [32], has demonstrated some efficacy in both managing depressive episodes and preventing their recurrence, thanks to its antidepressant-like structure [33]. A review on carbamazepine for bipolar disorder has shown its superiority over placebo in treating depressive episodes as monotherapy at the 2-week mark [34]. Its hepatic metabolism suggests the need for caution in patients with compromised liver function or in the geriatric population. Periodic evaluation of liver function is advised, considering a slight increase in liver enzymes in approximately 5–10% of treated patients [35]. Although less frequently, carbamazepine can produce other adverse effects such as agranulocytosis, aplastic anemia, and skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [36, 37].

22.2.2 Antipsychotics

Antipsychotics, a diverse pharmacological class exhibiting considerable variability in chemical structure, converge on a commonality—the blockade of dopamine receptors, particularly D2, alongside other receptors like H1, alpha 1, and M1, known contributors to the manifestation of adverse effects. Originally bound to the management of manic episodes, their therapeutic reach has expanded to treat bipolar disorder. Regulatory approval for their application commenced around the beginning of the new millennium, with olanzapine, in tandem with fluoxetine, marking the pioneering approval in 2003 [38]. Their categorization into typical and atypical is grounded in their receptor affinity and, consequently, the emergence of adverse effects, with atypical antipsychotics, recognized for a lower propensity to induce extrapyramidal syndrome compared to their typical counterparts.

The impact of antipsychotics on depressive episodes is intricately tied to their capacity to antagonize 5-HT_{2a} neural receptors [39]. Moreover, evidence supports the notion that select members within this pharmacological cohort, such as olanzapine and quetiapine, exhibit the capacity to selectively elevate dopamine levels in the prefrontal cortex via 5-HT_{1a} agonist activity [40]. An additional layer to their mechanism involves the facilitation of norepinephrine release in the prefrontal cortex, notably pronounced with olanzapine, owing to its alpha 1 adrenergic antagonist activity. The effect is accentuated when concomitantly used with fluoxetine [41].

Despite their efficacy from psychotic symptoms to insomnia or psychomotor agitation, the expansive repertoire of these medications requires a precise approach, adapting choices to the specific needs of each patient, as the benefits must be weighed against potential adverse effects in the decision-making process.

22.2.2.1 Quetiapine

Quetiapine is an atypical antipsychotic that stands as a significant contender in the pharmacotherapeutic options for bipolar depression due to its well-established efficacy and favorable safety profile. Functioning through potent antagonism of 5-HT_{2a} and D₂ receptors, it also exhibits a moderate affinity for adrenergic and histaminergic receptors. This extends to its primary metabolite, norquetiapine, which adds to its therapeutic impact by inhibiting the norepinephrine reuptake transporter [42].

In the BOLDER studies, quetiapine in monotherapy, within the dosage range from 300 to 600 mg/day, mitigated depressive episodes associated with bipolar disorder when compared to placebo. By week 2, there was a notably higher percentage of patients meeting response criteria with both 300 mg/day (40.0%) and 600 mg/day (36.5%) doses of quetiapine compared to those on placebo (23.6%) [43]. The EMBOLDEN I study provided further credence to its efficacy by showcasing its superiority not only over a placebo but also over the traditionally used lithium [44]. These results were substantiated by meeting remission criteria as per the Montgomery-Asberg Depression Rating Scale (MADRS) [45].

In the EMBOLDEN II study ($n = 740$), quetiapine outperformed placebo and also showed comparable results to paroxetine 20 mg/day, whether administered at the 300 mg or 600 mg dosage threshold during an 8-week trial [46]. Beyond its therapeutic efficacy, quetiapine's tolerability shines, marked by mild adverse effects such as dry mouth, dizziness, sedation, somnolence, and constipation, associated with a low incidence of extrapyramidal effects [45]. In the complexity of the pharmacological treatment of bipolar depression, quetiapine emerges as a treatment option and offers a balanced interplay of efficacy, tolerability, and safety.

22.2.2.2 Olanzapine

This second-generation antipsychotic aligns with its counterparts in the group by exhibiting D₂ antagonistic activity in the mesolimbic pathway and 5HT_{2A} antagonism in the frontal cortex [47]. In the fields of bipolar depression treatment, olanzapine has proven its effectiveness when administered in monotherapy at doses ranging from 5–20 mg/day, not only during depressive episodes but also in mixed episodes [48, 49]. Its combination with fluoxetine has demonstrated enhanced efficacy, positively impacting concomitant symptoms like anxiety, appetite, and sleep dysregulations. In a randomized controlled trial, Tohen et al. compared its superiority over haloperidol in preventing depressive episodes following manic episodes [50].

Yet, notwithstanding the expected side effects inherent to its atypical antipsychotic nature, olanzapine has exhibited an unfavorable metabolic profile. Short-term studies have reported an average weight gain of 3.9 Kg, accompanied by metabolic changes, such as alterations in glycemic profiles and triglyceride levels [51]. FDA approval for the combination with samidorphan, a μ -opioid receptor (MOR) antagonist, seeks to mitigate this weight gain while maintaining a similar

efficacy in treating depressive episodes compared to olanzapine monotherapy [52]. This strategic move underscores a commitment to balancing therapeutic benefits with metabolic considerations, addressing a crucial facet in the interventions for bipolar depression.

22.2.2.3 Lurasidone

Lurasidone, with an additional antagonist activity targeting 5-HT₇ and 5-HT_{1a} receptors, unveils promising antidepressant characteristics. Clinical trials affirm its significant improvement of depressive symptoms in bipolar patients relative to the placebo, whether employed as monotherapy or in tandem with mood stabilizers such as lithium or valproate. In the 2014 trial led by Loebel et al., participants were randomly assigned to three groups, receiving lurasidone at doses of 20–60 mg/day, 80–120 mg/day, or a placebo for a duration of 6 weeks. The results indicated a statistically significant reduction in depressive symptoms based on the Montgomery-Asberg Depression Rating Scale. Specifically, 53% of patients in the 20–60 mg/day group met the response criteria, while the percentages for the 80–120 mg/day and placebo groups were 51% and 30%, respectively [53].

22.2.2.4 Cariprazine

Cariprazine is a new-generation antipsychotic that functions as a partial agonist of dopamine receptors. A randomized controlled trial published in 2020 has shown that, in monotherapy, at doses between 1.5 and 3 mg daily, it is effective in the treatment of depressive episodes in patients with bipolar I disorder compared to placebo. Cariprazine demonstrated a statistically significant reduction in MADRS total score of approximately 29% compared to placebo, regardless of the duration or severity of the depressive episode [54]. A meta-analysis from 13 different trials referred to its use may be associated with akathisia in 7.6% of patients, a factor that should be assessed individually as it can be a reason for discontinuation [55].

22.2.2.5 Lumateperone

Lumateperone is a novel atypical antipsychotic, recently introduced to the market, that modulates dopaminergic neurotransmission through D₂ receptors, as well as serotonergic through 5-HT_{2A} antagonism. It also enhances NMDA activity and modulates the function of glutaminergic neurons. Initially approved in the early decade for the treatment of schizophrenia, it is now also indicated for bipolar depression. It has demonstrated superiority compared to placebo in the treatment of depressive episodes in bipolar disorder, both as monotherapy and in combination, with positive changes observed on the MADRS scale from the first week of use

[56]. In a randomized controlled trial conducted in 2023, lurasidone, administered at doses of 28 mg/day and 42 mg/day in combination with lithium or valproate, was assessed over a 6-week period in patients experiencing a depressive episode associated with bipolar disorder. The group receiving 42 mg/day exhibited an average improvement of 24% in the MADRS total score compared with placebo [57].

22.2.2.6 Others

Aripiprazole, primarily designated for managing manic and mixed episodes, has also the indication for major depressive disorder as an adjunct treatment for antidepressants. However, its proclivity to induce adverse effects like akathisia contributes to a considerable rate of patient discontinuation [58].

Risperidone, classified as an atypical antipsychotic with approval for treating manic episodes, substantiates its efficacy in depressive episodes when coupled with mood stabilizers and antidepressants [59].

Last, but not least, clozapine, often considered the gold standard of antipsychotics in refractory schizophrenia, distinguishes itself not merely for its efficacy in addressing bipolar depression and mixed episodes but also for its remarkable anti-suicidal attributes [60]. The impact of clozapine, fostering synaptic remodeling and neuronal reorganization within the hippocampus, provides insight into its effectiveness, particularly considering the compromised neuroplasticity evident in bipolar disorder [61]. Prudent patient selection is important, given the remote yet severe risk of agranulocytosis mandating periodic blood monitoring.

22.2.3 Antidepressants

Existing literature raises questions about the use of antidepressants in the treatment of bipolar depression, weighing benefits and risks. Although historically widely used, it has been shown that in monotherapy, they can induce manic shifts or rapid cycling, unlike unipolar depression, a primary reason to differentiate between the two types [62].

Tranylcypromine, an irreversible monoamine oxidase inhibitor (MAOI), the second of its group to be discovered, functions as an irreversible enzyme inhibitor, as well as an inhibitor of catecholamine and serotonin reuptake. Although mainly used in the past for major depression, in 1982, a clinical trial (Himmelhoch et al.) demonstrated its efficacy and safety in the treatment of depressive episodes, showing 72% of participants experienced improvement of their symptoms, compared to only 24% of participants in the placebo group [63]. Due to its potential risk of acute toxicity and the arrival of new antidepressants, its use has decreased over time.

Among tricyclic antidepressants, imipramine can inhibit the reuptake of norepinephrine and serotonin. In a 6-week clinical trial, imipramine in monotherapy was

compared with placebo and fluoxetine. Almost 30% of patients receiving imipramine dropped out of the study due to side effects such as dry mouth and asthenia, although those who did complete it showed symptom improvement compared to placebo [64].

A third group, selective serotonin reuptake inhibitors (SSRIs), as the name suggests, act by increasing serotonin activity in the central nervous system by inhibiting presynaptic serotonin transporters. With a notable safety and tolerability profile, they show a low risk of toxicity and rarely fatal overdoses; they are also the least associated with manic shifts in bipolar patients [62]. They have not shown effectiveness in preventing long-term depressive episodes, so once clinical remission is achieved, their gradual withdrawal is recommended after at least 6 months have passed. This randomized controlled trial involving 833 patients with bipolar I depression exposed that olanzapine plus fluoxetine was more effective than olanzapine in monotherapy and placebo in reducing depressive symptoms according to the MADRS scale after 8 weeks of use. The combination showed a remission rate of 48.8% compared to 24.5% in the placebo group and 32.8% in the olanzapine monotherapy group [65].

22.2.4 Other Drugs

Ketamine, an anesthetic with analgesic properties, acts as an antagonist of the NMDA receptor in the central nervous system. Despite its hallucinogenic potential and recreational use with high risks of short and long-term toxicity, an observational study of 231 adults with treatment-resistant depression found that titrated serial ketamine infusions were effective in reducing suicidal ideation in 79% of patients, occurring after 1 infusion in 36% of them [66]. It is important to rule out differential diagnoses, especially its possible association with posttraumatic stress disorder, as ketamine could induce trauma re-experiencing [67]. Although its effectiveness in treating bipolar depression is still under investigation, it is also essential to assess the risks of dependence associated with its use.

Presenting a function similar to ketamine, intranasal esketamine was approved by the FDA in 2019 for treatment-resistant depression and, in 2020, to treat major depressive episodes with a high risk of suicide, is a recent proposal positioned as an alternative for the treatment of bipolar depression [68].

Modafinil, classified as a central nervous system stimulant, stands out for its action as a weak dopamine reuptake inhibitor, with a low propensity to induce euphoria and dependence compared to other stimulants like amphetamines. It has found application in the treatment of excessive daytime sleepiness associated with conditions such as narcolepsy and obstructive sleep apnea [69]. Study results support its potential use as an adjunct in the treatment of refractory bipolar depression [70].

22.3 Electroconvulsive Therapy and Transcranial Magnetic Stimulation

Electroconvulsive therapy (ECT) is a tool that has proven to be useful not only in the treatment of bipolar and unipolar depression but also in patients with a high risk of suicide, manic/mixed episodes, and catatonia, among other conditions [71]. It is a process that requires general anesthesia or sedation to induce a safe and pain-free generalized tonic-clonic seizure in the patient through locally administered electric current. The seizure should last no less than 30 seconds, as those lasting less than 15 seconds tend to be ineffective, while those exceeding 70 seconds may lead to cognitive side effects such as retrograde amnesia [72]. Bilateral application is more effective and faster, though it comes with a higher incidence of temporary cognitive side effects compared to unilateral modalities. Electroencephalographic monitoring is conducted during the session, although the recorded traces tend to be 25% longer than the actual seizure [73].

A Norwegian study in 2015 concluded that ECT may offer superior responses in the acute phase of bipolar depression compared to pharmacological therapy, with a response rate of 73.9% for ECT versus 35.0% for pharmacological treatment [74]. Common protocols involve 6–12 sessions, 2–3 times per week, with weekly follow-ups once clinical improvement is achieved [75]. Personalizing the treatment, including spaced or maintenance sessions based on each patient's needs, along with pharmacological and psychotherapeutic interventions, is considered an essential pillar in preventing relapses.

Several factors influence the response to ECT. Positive predictors include advanced age, the presence of psychotic symptoms, and greater episode severity [76, 77]. Certain comorbidities such as obsessive-compulsive disorder, personality disorder, alcohol use, or panic disorder may be associated with a less favorable response [78].

As of today, there are no absolute contraindications to its use, but certain characteristics and pathologies pose a higher risk and must be carefully assessed for each patient by the medical team and with the approval of an anesthesiologist. Epilepsy may hinder seizure induction and prolongation, especially with antiepileptic use; after a recent stroke, regardless of its etiology, ECT initiation is recommended to be delayed by at least 10 days to prevent complications; and certain cardiac conditions, such as arrhythmias, aneurysms, or insufficiency, should be evaluated by a cardiologist before the session, with vital signs monitored more closely during the procedure [79].

Patients with bipolar depression are predominantly under pharmacological treatment, so potential interactions between ECT and anesthetic drugs and antiepileptics must be evaluated. Nevertheless, despite the possibility of interactions between ECT and certain drugs, ECT is critical in the treatment of bipolar depression, in particular in patients with treatment-refractory episodes, due to its rapid response.

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, relies on electromagnetic principles and not electric current to induce continuous depolarization in cortical and subcortical regions through pulses, reaching depths of up to 4 centimeters from the cortex. Different effects occur during the application, depending on the stimulated cortex area; patients have reported motor effects and even phosphenes in the case of occipital stimulation [80]. Over the long term, it either increases or decreases neuronal excitability, modulating various neuronal circuits. In patients with bipolar and unipolar depression, it has demonstrated a higher rate of remission and symptom improvement compared to sham controls [81]; however, we still need further investigation to fully support its use.

22.4 Psychotherapy

Pharmacotherapy and ECT have certainly demonstrated an essential role in the treatment of bipolar depression. However, given the chronic and recurrent nature of depressive episodes, psychotherapy also plays a key role in successful management, not only during episodes but also during remission periods to prevent and address them early. The inclusion of psychotherapy in treatment has shown significant improvements regarding functioning and life satisfaction among patients, according to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study [82].

Cognitive-behavioral therapy (CBT) focuses on cognitive restructuring to modify information processing, addressing emotional disturbance in the patient and coping problems. Combined with pharmacological treatment, it has shown a significant reduction in depressive symptomatology and better symptom control compared to patients who do not receive it [83]. Studies have demonstrated that certain practices, such as sleep deprivation from the onset of the depressive episode supported by pharmacological treatment, are effective clinical practices that should be included in future guidelines [84, 85]. CBT has shown long-term benefits by reducing relapse frequency in the first year, reducing residual symptoms, and improving treatment adherence, especially when therapy is maintained over time, even in asymptomatic periods [86].

Interpersonal and social rhythm therapy, another psychotherapeutic model, focuses on social factors and interpersonal relationships as determinants in psychopathology. Initially designed for depression management, it is now used for various situations. Compared to patients who do not receive it, it has shown superiority in depressive episodes, and some studies suggest benefits over cognitive-behavioral therapy, especially in remission and improvement of depressive symptoms [87].

Another therapeutic approach, focalized family therapy, works through interpersonal relationships and emphasizes the role of the patient's inner circle in understanding the disease and its symptoms. Sessions are geared toward equipping the

family and the patient through communicating and problem-solving training, giving tools to each member on how to cope with stress and practicing active listening as well as expressing feelings [88]. In many instances, it is the family and friends who are the initial observers of early symptoms that may signal a potential relapse and empower the patient to seek assistance.

Mindfulness, through medication, is a technique that focuses attention on the present moment to achieve awareness and acceptance of reality [89]. Studies with daily sessions of approximately 2 hours have shown its effectiveness in relieving anxious-depressive symptoms and preventing recurrences [90]. Its importance lies not only in early application during episodes but also in integrating these concepts into daily life and remission periods.

Despite the evidence in favor of its implementation in episode treatment, it is still a technique that very few resort to, either due to patient refusal or limitations in access [91]. Given current telemedicine opportunities, it is expected that psychotherapy will play a more significant role in bipolar disorder management in the coming years, both during episodes and asymptomatic periods.

22.5 Treatment Plan

Although pharmacological treatment stands as a fundamental pillar for inducing remission, one should make the most of all available resources. The inclusion of the aforementioned psychotherapy and ECT can enhance results and improve the overall patient response. Before considering changing medication or transitioning to another line of treatment, it is essential to achieve adequate full doses of the appropriate drug for the patient's profile, ensure correct adherence, and allow the necessary time for the medication to reach its maximum efficacy. This methodical and patient-focused approach is essential for adequately assessing therapeutic responses and making fundamental decisions in disease management.

Moving into the first-line treatment as suggested by the Canadian Network for Mood and Anxiety Treatments (CANMAT), monotherapy options present atypical antipsychotics such as quetiapine and lurasidone, as well as lithium and lamotrigine [92–94]. The recommended reasonable waiting time to assess the drug's efficacy is 2 weeks. Although lamotrigine stands out for its efficacy and is placed in the first line of treatment, its more gradual titration may be a challenge in severe cases in which a quicker effect is sought [94].

In the second line of treatment, the possibility of rotating the drug or adding it in combination with first-line drugs is considered. The complement with fluoxetine or another SSRI to atypical antipsychotic is a therapy that, given its effectiveness, as mentioned in previous paragraphs, has become a highly valid option for some authors [94]. Combining olanzapine with fluoxetine has positioned itself as a possible first-line approach in some studies, but has been relegated to second-line

strategy because of the metabolic effects. This latter strategy not only broadens therapeutic options but also provides a positive benefit by preventing a switch to mania. Valproate, whether in monotherapy or in combination with other drugs such as lithium or lurasidone, is also considered an effective strategy [92]. Cariprazine has positioned itself as a second-line alternative, though its consideration should be tailored due to potential adverse effects. Electroconvulsive therapy, traditionally considered for refractory cases or the presence of psychotic symptoms, generates ongoing debates about whether it should be used in the early stages of treatment [95] (Table 22.1).

The third line of treatment, a more challenging terrain, raises the need to carefully evaluate resistance to it, adherence to the therapeutic plan, and even reconsider the diagnosis of bipolar depression. Monotherapy with carbamazepine is proposed as a valid option, or even adjunctive approaches to treatment such as intravenous ketamine, total sleep deprivation, and modafinil [94]. Tranylcypromine, studied as a current treatment, must be approached with caution, always in combination with mood stabilizers or atypical antipsychotics, and informing the patient about its dietary and drug interactions [92]. Repetitive transcranial magnetic stimulation (rTMS) should be considered as a potential complement to pharmacological treatment. The use of antidepressants or aripiprazole in monotherapy is not recommended, as well as the combination of lamotrigine and folic acid due to its antagonistic tendency [96].

In cases of comorbidity and elderly patients, drug interactions and side effects of medications used to treat the episode should not be overlooked, so an integrated approach with other specialties is always recommended, adapting the treatment to each patient and using minimal doses to avoid interactions.

Despite all the mentioned pharmacological, psychological, and physical strategies, patients with bipolar disorder, particularly having depressive episodes, still suffer from the burden of the disorder. Nowadays, different drugs on the neurosteroids, cannabidiol, and trace amine-associated receptor (TAARs) pathways are under study development to enhance the daily of patients with bipolar disorder.

Table 22.1 Pharmacological treatment of depressive episodes

Drug	Mechanism of action	USE			Relevant aspects	Adverse effects	Dosage
		Manic episodes	Depressive episodes	Maintenance			
Lithium	Decreases dopamine and glutamate levels	X	X	X	Monotherapy or adjunctive	Gastrointestinal.	0.6–1.2 mEq/l (serum levels)
	Enhances GABA function				Interacts with NDSAIDs and diuretics	Thyroiditis	
						Neurotoxicity (confusion, tremors)	
						Nephrotoxicity	
1° Lamotrigine	Inhibits voltage-gated sodium channels		X	X	Monotherapy or adjunctive	Neurotoxicity	100–400 mg/day
	Inhibits glutamate release				Slower titration, not recommended when demanding a rapid response	Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (NET)	
Quetiapine	Antagonist 5-HT _{2A} and D ₂ receptors	X	X		Monotherapy or adjunctive	Extrapyramidal symptoms	200–600 mg/day
						Somnolence and dizziness	
						Neuroleptic malignant syndrome	

(continued)

Table 22.1 (continued)

Drug	Mechanism of action	USE			Relevant aspects	Adverse effects	Dosage
		Manic episodes	Depressive episodes	Maintenance			
Lurasidone	Antagonist 5-HT _{2A} , 5-HT ₇ and D ₂ receptors	X	X		Monotherapy or adjunctive treatment	Akathisia	20–120 mg/day
					Minimum risk of cognitive impairment	Withdrawal symptoms in neonates (third trimester)	
Valproic acid	Inhibits voltage-gated sodium channels	X	X		Monotherapy or adjunctive	Somnolence, dizziness, asthenia.	
	Increases levels of GABA				Previous liver function study, blood count, and pregnancy test	Fetal malformations (neural tube and musculoskeletal system)	50–150 mcg/mL (serum levels)
2°						Hepatotoxicity	
						Hematological toxicity	
Olanzapine	Antagonist 5-HT _{2A} and D ₂ receptors	X	X	X	Monotherapy or adjunctive, especially with fluoxetine	Weight gain and metabolic effects	5–20 mg/day
					Combination with samidorphan to mitigate metabolic effects	Extrapyramidal symptoms	
						Somnolence and dizziness	
Cariprazine	Partial agonist of dopamine receptors	X	X		Monotherapy or adjunctive	Akathisia	1.5–6 mg
					Improvement of cognitive symptoms in the long term	Hepatotoxicity	

22.6 Conclusions

The comprehensive treatment of bipolar depression should not only focus on clinical remission but also on maintaining clinical stability during asymptomatic periods and promoting patient independence. The combination of pharmacology, psychotherapy, and physical therapies should consolidate an individual's treatment in the context of personalized psychiatry. It is crucial to emphasize the importance of empowering the patient and promoting self and proactive management, as fostering prevention. In addition to involving the family and creating a positive social environment, the ongoing fight against social stigma is an essential component in building a more understanding and inclusive society. One should never lose sight of the individual, social, and medical approach to achieve optimal results and comprehensive care.

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Chapter 23

Maintenance Treatment



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23.1 Introduction

In line with the current understanding of the multifactorial origins of bipolar disorder, maintenance treatment is fundamentally multidimensional [1, 2]. The various forms of therapy can be combined with each other in different ways, which applies in particular to pharmacotherapy with psychotherapy and psychoeducation. The weighting of the individual treatment methods varies over the course of the illness, with biological/pharmacological and supportive psychotherapeutic methods taking priority in the maintenance phase. The long-term treatment of bipolar disorders is essentially based on five pillars:

- Psychopharmacological and other biological therapies including brain stimulation techniques.
- Psychotherapeutic and psychoeducational therapies.
- Social therapeutic measures including rehabilitation.
- Lifestyle treatments.
- Self-help, for patients and caregivers.

Because of the high risk of relapse and the development of chronic affective disorder, defined as the persistent presence of affective symptoms for more than 2 years without remission, long-term treatment is essential and generally indicated

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for patients with bipolar disorder. The long-term use of medication is referred to as maintenance treatment (or relapse prevention) and involves several years or often lifelong treatment. Depending on the course, severity, and number of episodes, an attempt can be made to carry out relapse prevention with as little medication as possible. Ideally, this should be achieved as monotherapy with a mood stabilizer; however, the reality is that most patients receive two or even more medications during long-term treatment [3].

23.2 General Treatment Principles

The main goals of maintenance treatment are to prevent clinically significant episodes, to maintain complete remission without subsyndromal symptoms between episodes, and to prevent suicidal acts. Multidimensional therapy attempts to influence the course of the illness so that there are no or at least fewer, shorter, and milder episodes. Proper prevention of relapse, which will allow the patient to lead as normal a life as possible, is of vital importance. The question of when to start long-term prophylactic treatment is extremely important to patients and clinicians for obvious reasons. The decision depends on the assessment of the risk of relapse and the psychosocial impact of relapse as perceived by the patient and family. Acceptance of long-term treatment by many patients is relatively low in the early stages of the illness. Understandably, because bipolar disorder typically presents in adolescence and early adulthood (usually between the ages of 15 and 25), it is often very difficult to convince patients of the need for daily—or even lifelong—medication at a time in their lives when a primary developmental goal is independence from their parents. Unfortunately, taking medication in the long term often symbolizes dependence on outside forces and interferes with emerging feelings of autonomy.

The decision for prophylactic treatment should be made as early as possible. The main reason for this is the high probability of relapse, which is >90% in bipolar type I. An indication for relapse prevention treatment should be given after the first episode if it is severe, suicidal, or if there is a family history of bipolar illness. In other cases, prophylactic treatment should be started after the second episode (manic or depressive) if both episodes occur within 5 years. After many decades in which lithium salts were the only treatment option, new therapeutic approaches have been developed in recent years that include psychoeducational and psychotherapeutic methods in addition to pharmacological treatment, which is adapted to the individual course of the patient and is often complex.

Upon initiation of long-term prophylactic treatment, the patient should be fully informed about the nature of the illness course and the individual treatment plan. Combination treatments are often necessary (e.g., to treat depression in the context of bipolar disorder), require a particularly trusting doctor-patient relationship (to promote compliance) and necessitate more intensive monitoring. Keeping a mood

diary (“life chart”) is a helpful tool for assessing the course of the illness and is therefore important for deciding on therapeutic measures. Medication-related side effects and monitoring strategies highlight the importance of safety and tolerability considerations, which, along with efficacy information, should be given equal merit [1].

23.3 Overview of Pharmacological Maintenance Treatment

The central component of maintenance pharmacotherapy is mood stabilizers [4]. The term mood stabilizer is widely used in the context of the treatment of bipolar disorder, but the US Food and Drug Administration (FDA) does not officially recognize the term, and there is no consensus among researchers or clinicians as to its definition. Pragmatically, the definition of an optimal medication that would qualify as a mood stabilizer would be an agent that demonstrates efficacy in treating acute manic and depressive symptoms while preventing future manic and depressive episodes. There is now a consensus that the group of mood stabilizers consists of lithium salts, the anticonvulsants carbamazepine/oxcarbazepine, valproate and lamotrigine, and some of the atypical antipsychotics.

23.3.1 *Lithium*

23.3.1.1 History

The psychopharmacological use of lithium is believed to have originated from John Cade’s 1949 paper, in which he detailed its antimanic effects [5]. In the 1960s, Hartigan in the UK [6] and Baastrup in Denmark [7] made occasional observations. Baastrup and Schou conducted systematic but open investigations in 1967 [8], suggesting that lithium had prophylactic properties against recurrent mood disorders, both bipolar and unipolar. The naturalistic study by Baastrup and Schou showed that recurrences were less frequent and severe during long-term lithium treatment than before the administration of lithium. It should be noted that some but not all patients achieved full remission in their seminal report. Following these initial positive results, Danish physicians collaborated with other European researchers to increase the number of patients treated with lithium. They later published a large prospective follow-up study of 250 patients, which once again demonstrated effective prevention of recurrence [9]. The first lithium study that introduced a placebo to demonstrate lithium’s efficacy was a discontinuation trial: all subjects in the study had been taking lithium in the long term before entering the trial; a significant number relapsed shortly after receiving the placebo instead of lithium [10].

23.3.1.2 Recognition in Guidelines

Over the past three decades, there has been increasing recognition of lithium's efficacy in conferring long-lasting mood stability, a perception of its capabilities that is reflected in clinical practice guidelines worldwide. For instance, international guidelines, including those from Australia and New Zealand, North America, and European societies and organizations, all recommend lithium as the first-line treatment for bipolar disorder (reviewed in Malhi and Bauer [11]). In practice, most clinicians agree that lithium is suitable for the prophylaxis and maintenance treatment of many patients with bipolar disorder. However, despite its first-line status for the long-term management of bipolar disorder, its clinical application seems to be decreasing and continues to lag behind the use of alternatives in recent years [12].

23.3.1.3 Evidence from Placebo-Controlled Trials and Meta-Analyses

Beginning in the early 1970s, several randomized, placebo-controlled trials demonstrated the efficacy of lithium in preventing mood episodes in bipolar disorder. Later, new evidence emerged from large trials designed primarily to test the efficacy of newer agents against placebo, but which also included a lithium arm as an active comparator. Subsequently, over the past decade, several meta-analyses, each with slightly different analytical approaches and inclusion criteria, have consistently confirmed the efficacy of lithium in preventing relapse in bipolar disorder [13–15]. The systematic review and meta-analysis by Geddes et al. [13] evaluated the efficacy and acceptability of lithium for relapse prevention in bipolar disorder. Their meta-analysis of five placebo-controlled lithium maintenance trials (including 770 participants) showed that lithium reduced the risk of manic relapse by 38% and depressive relapse by 28%; the relative risk (RR) was 0.65 and the number needed to treat (NNT) was 5. Lithium showed a statistically significant benefit over placebo in preventing manic episodes, but no statistically significant benefit over placebo in preventing depressive episodes [13]. Since then, the evidence base has grown substantially, particularly with the use of lithium as an active comparator in pivotal trials of new medications. Two recent independently published meta-analyses included all available placebo randomized controlled trials (RCTs) and reached similar conclusions: lithium was statistically significantly superior to placebo for the prevention of affective episodes of any polarity, manic episodes, and, depending on the methodology used, depressive episodes [14, 15].

23.3.1.4 Effectiveness in Naturalistic Studies

Although RCTs are fundamental for demonstrating the efficacy and safety of medications, their results do not reflect the entire population of patients with bipolar disorder seen in clinical practice. Given the limitations and uncertainties of RCTs,

it is important to compare evidence from RCTs with evidence from observational studies of patients treated in the so-called real-world clinical settings, e.g. using a naturalistic design and typically including a wide range of patients. A systematic review of non-randomized controlled observational studies by a task force of the International Society for Bipolar Disorders (ISBD) found that in eight of nine studies identified, with a total of more than 14,000 patients, maintenance lithium therapy was associated with improved outcomes compared with another mood stabilizer in monotherapy, lithium maintenance monotherapy was associated with improved outcomes compared with another mood stabilizer in monotherapy, including valproate, lamotrigine, olanzapine, quetiapine, unspecified anticonvulsants, carbamazepine/lamotrigine, unspecified atypical antipsychotics, and unspecified antipsychotics [16]. These observational findings demonstrate the superiority of lithium monotherapy over monotherapy with other maintenance mood stabilizers in real-world settings, and add substantially to the evidence from randomized controlled trials, whose designs often limit the validity of comparisons between medications [16].

23.3.1.5 Predictors of Response

A significant proportion of patients with bipolar disorder (estimates range from 25% to 40%) can be very effectively stabilized with lithium maintenance treatment if their lithium-responsive clinical profile is correctly identified and they are adequately treated and monitored. These patients usually respond well to lithium in the acute phase, but benefit most from long-term treatment. Specific studies of these so-called excellent responders to lithium in prophylaxis have deepened our understanding by clarifying the factors that characterize those patients who, despite a history of severe illness, remain completely well for years on adequate lithium treatment. The distinctive features of these patients are captured in their clinical course, family history, comorbidity profile, psychopathology, and early development. These characteristics are essential for identifying those patients for whom long-term lithium stabilization should be the treatment of first choice. A recent systematic review and meta-analysis of 71 studies examining clinical predictors of lithium response in bipolar disorder, including over 12,000 patients, identified six predictors of good response: mania-depression interval sequence, absence of rapid cycling, absence of psychotic symptoms, family history of bipolar disorder, shorter pre-lithium illness duration, and later age of onset [17]. In addition, higher body mass index (BMI) was associated with poor response in two studies. There was weak evidence for the number of episodes before lithium treatment, number of hospitalizations before lithium, and family history of lithium response [17]. Because of the limitations of the data, particularly the limited number of RCTs, it is difficult to separate predictors of lithium response from predictors of a benign course of illness.

23.3.1.6 Risks of Stopping Long-Term Lithium Treatment

At some point during long-term treatment, patients express a desire to discontinue lithium despite its beneficial effects, e.g., because of adverse effects, a desire to become pregnant, or a desire to live without long-term medication after a long period of freedom from illness. There is some convincing evidence that when a patient decides to stop lithium treatment, it should be tapered gradually to avoid the early relapses that can occur after rapid discontinuation [18]. If this tapering strategy is followed and rebound episodes do not occur in the following months without prophylactic pharmacotherapy, there is still a persistent risk of future episodes.

Other concerns have been raised about non-response after discontinuation and resumption of previously effective lithium prophylaxis. These concerns have increased among both patients and professionals since Post et al. [19] reported four patients who discontinued effective long-term lithium treatment, relapsed, and were unresponsive after the resumption. They termed this “lithium discontinuation-induced treatment refractoriness”. A recent analysis of the literature found that there may be a subgroup of people who are refractory to treatment when lithium is discontinued. However, the authors concluded that the vast majority of people respond when lithium is restarted. In addition, it may be necessary to continue lithium beyond the first relapse to restore long-term prophylactic efficacy [20].

23.3.1.7 Optimal Lithium Serum Levels

Lithium levels should be drawn approximately 12 h after the last dose. Lithium levels should be drawn five days after a constant daily dose (longer in older patients) when a steady state has been reached. The range of lithium serum levels generally recommended for maintenance treatment lies between 0.6–0.8 mEq/l. Levels up to 1.2 mEq/l are often needed in case of acute breakthrough mania. Serum lithium concentrations below 0.5 mEq/l are rarely effective [21]. In elderly people, a serum level of 0.40–0.60 mmol/L is usually aimed for, with the option to go up to a maximum of 0.70 or 0.80 mmol/L at 65–79 years of age, and to a maximum of 0.70 mmol/L over 80 years of age [21].

23.3.1.8 Treatment Initiation and Monitoring

Lithium is a medication that is sometimes more difficult to use than most psychotropic medications, largely because of its narrow therapeutic index. However, when used properly, lithium is generally well tolerated and not too complicated to administer. The need for regular monitoring is widely recognized, although several studies have reported that monitoring is often performed less frequently in clinical practice than is usually recommended by practice guidelines. Lithium may be prescribed once daily, typically in the evening, using either slow-release or lithium carbonate capsules. In principle, taking lithium twice a day does not lead to a better result than

taking it once a day. Lithium doses are regulated and monitored by serum lithium levels. Before starting lithium, a number of tests should be carried out and the patient should be well educated about side effects, monitoring, and other relevant medical information, e.g., signs of intoxication and their prevention, potentially dangerous comedication. Table 23.1 summarizes the recommended tests before starting and during long-term treatment.

Table 23.1 Monitoring: recommended tests and other investigations before and during lithium treatment (monitoring)^a (modified from Bauer and Gitlin, [22])

Organ/System	Screening before starting	Monitoring during lithium treatment	
	Parameter	Parameter	Time interval
Physical status	Physical/neurological status	Physical/neurological Status	Every 6–12 months
	Height		
	Weight/BMI	Weight/BMI	Every 6–12 months
	Neck size	Neck size ^a	Annually
Cardiovascular	Electrocardiogram (ECG)	Electrocardiogram ^a	Annually
	Blood pressure	Blood pressure	Every 3–6 months
	Heart rate	Heart rate	Every 3–6 months
Renal	Serum creatinine	Serum creatinine	Every 3–9 months
	Creatinine clearance	Creatinine clearance	Every 3–9 months
	Glomerular filtration rate	Glomerular filtration rate	Every 3 - 9 months
Thyroid gland	Ultrasound of the thyroid gland	Ultrasound of the thyroid gland	Annually
	Triiodothyronine (T3)	Triiodothyronine (T3) ^a	Every 12 months
	Thyroxine (T4)	Thyroxine (T4) ^a	Every 12 months
	Thyroid-stimulating hormone (TSH)	Thyroid-stimulating hormone (TSH)	Every 6 months
Parathyroid gland	Parathyroid hormone	Parathyroid hormone	Annually
Blood count	White blood cell count ^a	White blood cell count	Every 6–12 months
	Red blood cell count ^a	Red blood cell count	Every 6–12 months
	Hemoglobin (Hb) ^a	Hemoglobin (Hb)	Every 6–12 months
	Hematocrit (Hk/Hct) ^a	Hematocrit (Hk/Hct)	Every 6–12 months

(continued)

Table 23.1 (continued)

Organ/System	Screening before starting	Monitoring during lithium treatment	
	Parameter	Parameter	Time interval
Electrolytes	Sodium	Sodium	Every 6–12 months
	Potassium	Potassium	Every 6–12 months
	Calcium	Calcium	Every 6–12 months
Metabolism	HbA1c; fasting glucose level ^a	HbA1c; Fasting glucose level ^a	Every 6–12 months
Other	Side effects from other medication	Side effects from other medication	Every visit

^aOptional tests; most tests recommended for monitoring metabolic conditions

23.3.1.9 Side Effects

Lithium is associated with a number of side effects (Table 23.2). In short-term treatment, the most common of these are nausea, thirst (with associated polydipsia), polyuria, tremor, and fatigue. Other common side effects are gastrointestinal distress/diarrhea and weight gain [23, 24].

The most commonly affected organ systems by lithium treatment are the kidney [25], thyroid gland [23, 26], and parathyroid gland [27] (Table 23.3.)

The adverse effect of lithium on renal function has been the main concern over the past decade. Renal dysfunction develops slowly, is asymptomatic for years, and has been the subject of ongoing debate [25, 28]. Although research findings over the past decade have not been entirely consistent, there is a general consensus that prolonged lithium therapy can have adverse effects on kidney function. The risk of polyuria, reflecting renal tubular dysfunction, is seen in a significant proportion of patients treated with long-term lithium therapy. The duration of lithium treatment may be the most important risk factor for lithium-induced polyuria. Most, but not all, studies find that lithium is associated with higher rates of chronic kidney disease compared with either age-matched controls or patients treated with other mood stabilizers. Age, duration of lithium therapy and medical disorders such as hypertension and diabetes mellitus are risk factors for chronic kidney disease. Although not all studies agree, it is likely that lithium may increase the risk of end-stage renal disease, but only in a very small proportion of treated patients.

Patients with relatively preserved renal function will show either no progression or improvement in renal function after stopping lithium. Hoekstra et al. [29] concluded from their study results that, analogous to the statements of some previous studies, there could be a threshold (approx. at eGFR <40 ml/min) below which the discontinuation of lithium has no positive effect on renal function. In people with a higher estimated glomerular filtration rate (eGFR), however, discontinuation of lithium usually leads to an improvement in eGFR or at least to a slowing of the deterioration in renal function.

Table 23.2 Common side effects associated with lithium treatment

Short term	Long term
Nausea	Goiter
Thirst	Weight gain
Polyuria	Polyuria
Tremor	Tremor
Fatigue	Skin conditions

Table 23.3 Lithium’s effects on organ systems

Organ system	Possible effects
Kidney	– Tubular>glomerular
	– Long-term effect
	– Common thirst, polyuria
	– Infrequent renal insufficiency
	– Rare end-stage renal disease
Thyroid	– W > F: hypothyroidism
	– W > F: goiter
	– Associated with anti-thyroid antibodies
	– Easily treated (with levothyroxine), not a reason for not starting lithium or discontinuation
Parathyroid	– Increase of parathyroid hormone (PTH) and calcium serum levels
	– Hyperparathyroidism

Optimal management of lithium treatment requires baseline measurement of renal function (typically estimated glomerular filtration rate [eGFR]) and regular monitoring of eGFR during treatment. If eGFR falls rapidly or below 60 ml/minute, patients should be referred for consultation with a nephrologist. The decision to discontinue lithium because of progressive renal insufficiency should be based on a risk–benefit analysis (by psychiatrist, nephrologist, and patient), taking into account other potential causes of renal dysfunction (e.g., cardiovascular and metabolic diseases, nicotine dependence), current renal function, and the effectiveness of lithium in the individual patient.

23.3.1.10 Lithium Intoxication

Lithium intoxication is usually preventable if the patient has been properly screened for lithium treatment, educated, monitored, and given an individually tailored dose. Nevertheless, lithium intoxication is unfortunately not uncommon. Several subtypes of lithium intoxication have been described: acute, acute-on-chronic, and chronic forms, which differ in their symptomatology due to the pharmacokinetic properties of lithium [30]. Table 23.4 displays the most commonly seen signs of lithium intoxication.

Table 23.4 Signs of lithium intoxication

Mild	Moderate	Severe
Mild, apathy, and lethargy	Increased lethargy	Somnolence
Weakness	Confusion and drowsiness	Gross confusion
Unsteady balance	Gross ataxia	Profound loss of balance
Nausea	Vomiting	Urinary incontinence
Decreased concentration	Slurred speech	Random muscle twitching
Worsening hand tremor	Muscle twitching	Coma
Diarrhea		

There are no consistent recommendations regarding the initiation of hemodialysis in lithium intoxicated patients. Based on the current evidence, hemodialysis should be performed in any patient with serum lithium levels >4 mEq/l, regardless of clinical status and etiology of intoxication. If lithium levels >2.5 mEq/l are detected, hemodialysis should be started in any patient with severe signs of lithium intoxication, if renal impairment is evident, if the patient has other conditions with limited lithium excretion, or if other conditions (e.g., heart failure) could potentially be exacerbated by extensive intravenous hydration [30].

23.3.2 Valproate

Despite its clear efficacy in treating acute mania, valproate's efficacy as a maintenance treatment in bipolar disorder is far from clear. In the only large ($n = 372$) RCT, divalproex did not separate from placebo in preventing mood episodes [31]. However, in that study, since lithium, as an active comparator also did not separate from placebo, this should be considered a failed rather than a negative study. These results may be the consequence of methodological features including a non-enriched design (in contrast to the design of virtually all other RCTs in the area), and the exclusion of severely ill patients, which resulted in fewer relapses in the placebo arm of the study. Secondary analyses suggested valproate's efficacy in preventing depression.

The BALANCE study ($n = 330$) compared valproate to lithium to the combination of the two medications in a non-blinded, non-placebo randomized design [32]. After two years, combination treatment was superior to valproate in preventing mood episodes while lithium monotherapy was superior to valproate on some but not all measures. On the primary outcome variable-time to intervention for an emerging mood episode, lithium was more effective than valproate ($HR = 0.71$; $p < 0.05$). In contrast to the Bowden et al. study (2000), lithium was significantly more effective than valproate in preventing depressive episodes ($HR = 0.63$, $p < 0.04$).

Despite this weak data base, a recent network meta-analysis found valproate to effectively prevent mood episodes driven primarily by its prevention of mania efficacy [33]. The CANMAT/ISBD guidelines ranked divalproex as having level 1 preventive efficacy with level 2 evidence for mania prevention and level 3 evidence for

depression prevention [4]. Their conclusions were based on both secondary analyses of the Bowden et al. study [31] as well as other studies examining subgroups of bipolar patients (e.g., rapid cyclers).

Optimal serum valproate levels for maintenance treatment in bipolar disorder are poorly characterized. One study found optimal levels to range between 75–100 mcg/ml [34] while two other studies suggested a lower threshold of 50 mcg/ml [35, 36]. Common side effects associated with valproate include sedation, gastrointestinal side effects (nausea, vomiting, and/or diarrhea), tremor, weight gain and alopecia (which can be particularly distressing for women) [37]. In a head-to-head study, valproate was associated with more weight gain than lithium (21% vs. 13%) [31]. Valproate can cause mild elevations in hepatic transaminases and thrombocytopenia. It rarely causes severe hepatotoxicity. It is associated with the development of polycystic ovarian disease more than other mood stabilizers [38]. Valproate is an enzyme inhibitor and can increase the plasma level of other medications, including lamotrigine.

The most worrisome clinical concern about valproate's use as a maintenance treatment in bipolar disorder is its negative effects on fetal development. Valproate is the most teratogenic agent among all psychiatric medications. The most common fetal abnormality seen with valproate's use in pregnant women is neural tube defects such as spina bifida, seen in 5–9% of fetuses exposed in the early part of the first trimester [39]. Other fetal abnormalities have also been reported in neonates exposed to valproate during the first trimester. Some expert clinicians feel that valproate should not be prescribed to bipolar women of childbearing age. At the least, however, valproate should only be prescribed to women of childbearing age if they are using a documented and effective form of birth control.

23.3.3 *Lamotrigine*

Alone among the anticonvulsants, lamotrigine has an American FDA indication as a maintenance treatment for bipolar disorder. The data supporting this are derived from two RCTs in enriched samples of bipolar I patients, either recently manic/hypomanic [40] or recently depressed [41] treated with lamotrigine, lithium, or placebo for 18 months. A combined analysis of these two studies (total $n = 638$) demonstrated equivalent efficacy between lithium and lamotrigine in preventing any mood episodes, and both active treatments were significantly more effective than placebo [42]. Lamotrigine was effective in preventing depression robustly compared to placebo and numerically, but not statistically, compared to lithium. Lamotrigine was somewhat effective in preventing mania but statistically inferior to lithium in this regard.

Because of concerns about the enriched designs of these registrational trials, Licht et al. [43] examined the efficacy of lamotrigine vs. lithium in 155 bipolar subjects followed for up to 5.8 years using a random assignment, open, non-placebo-controlled non-enriched design. Lamotrigine and lithium were equivalently

effective in preventing any mood episodes. Lithium was numerically but not statistically more effective in preventing mania, while lamotrigine was numerically but not statistically more effective in preventing depression. Thus, using a substantially different design, the results of this study generally mirrored the results of the industry-sponsored registrational trials.

On the strength of these two trials, lamotrigine was considered as a first-line maintenance treatment in the CANMAT/ISBD guidelines with level 1 evidence for prevention of any episode and depression prevention and level 2 evidence for mania prevention [4]. Because of its greater efficacy in preventing depression vs. mania/hypomania, lamotrigine is often prescribed as a first-line medication in bipolar II disorder in which prevention of depression is more primary, given the inherently milder hypomanic episodes.

Serum lamotrigine levels are not routinely monitored in bipolar disorder. In epilepsy, optimal levels are thought to range between 3–14 mcg/ml [44]. However, there is inconsistent evidence for a therapeutic range of lamotrigine in bipolar disorder, although 3 mcg/ml may define a minimum threshold to target [45]. Among lamotrigine's advantages is its benign side effect profile. Neither weight gain nor sedation are seen more frequently with lamotrigine vs. placebo. A benign rash occurs in 5–9% of patients with occasional insomnia and/or nausea. The major side effect concern with lamotrigine is its capacity to cause an immunological rash: Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The risk is generally considered to be 1/1000 or less [46]. This risk is higher than valproate or carbamazepine but less than other anticonvulsants such as phenytoin or phenobarbital. The classic slow dose titration for lamotrigine, taking six weeks to increase from 25 to 200 mg has been shown to be associated with a lower risk of benign rash, but not necessarily of the severe immunological rash [47].

23.3.4 Carbamazepine/Oxcarbazepine

Carbamazepine was the first anticonvulsant evaluated as an effective preventive treatment in bipolar disorder [48]. (For more detailed reviews, see [49, 50]). A definitive data base, however, is lacking since many of the studies compared carbamazepine to lithium without a placebo arm that would allow more meaningful efficacy data. (As examples, see [51–53]). In these studies, overall, lithium seemed somewhat more effective as a maintenance treatment but carbamazepine demonstrated some efficacy. In the largest controlled study, which was randomized but not blinded, non-classic bipolar features—e.g., mood incongruent delusions or mixed features—predicted a relatively better response to carbamazepine vs. lithium in bipolar I, but not bipolar II patients [51, 54]. Classic bipolar features predicted better responses to lithium. Because of consistent suggestions of efficacy but without sufficient definitive data, the CANMAT/ISBD guidelines placed carbamazepine as a second-line maintenance treatment with level 2 evidence for overall preventive efficacy and equal efficacy for mania and depression [4].

However, carbamazepine is associated with a substantial side effect burden, many pharmacokinetic interactions with other medications and two rare but potentially fatal immunological reactions, thereby decreasing its attractiveness as an alternative mood stabilizer. Common side effects include dizziness, rash, somnolence, ataxia, fatigue, diplopia, cognitive slowing, rash, and psychomotor incoordination. Carbamazepine also occasionally causes hyponatremia. Of note, carbamazepine is not associated with substantial weight gain. Carbamazepine has potentially significant pharmacokinetic interactions through the induction of hepatic microsomal enzymes resulting in a decrease of the plasma levels of many co-administered medications, including valproate, benzodiazepines, some antipsychotics and antidepressants and lamotrigine [55, 56]. Of note, carbamazepine increases the metabolism of estradiol and progesterone and, without dose alteration, may render oral contraceptives less effective. Finally, carbamazepine has substantial teratogenic effects [57]. Therefore, its use in women of childbearing age should be approached with caution with a plan for effective birth control in place.

Although among the anticonvulsants, lamotrigine is the medication most associated with immunological rashes (SJS and TEN), the risk with carbamazepine is only slightly lower with carbamazepine [46]. Additionally, rare cases of aplastic anemia and agranulocytosis, primarily at the beginning of treatment can occur with carbamazepine [58]. The optimal frequency of complete blood counts, especially during the first year of treatment is unclear with psychiatrists tending to monitor these parameters more frequently than do neurologists.

Oxcarbazepine, an analog of carbamazepine, has even fewer controlled studies evaluating its efficacy as a mood stabilizer [50, 59]. The best and largest study compared the efficacy of oxcarbazepine to placebo when added to lithium for one year [60]. No difference in time to a new episode was found. However, a re-analysis of the study suggested a trend toward the prevention of manic and depressive episodes [61]. Oxcarbazepine's attractiveness as a mood stabilizer reflects its more benign side effect profile especially compared to carbamazepine. Although the same general profile is seen (including the relative paucity of weight gain), the frequency and intensity of these side effects are lower. Hyponatremia is somewhat more common with oxcarbazepine compared to carbamazepine [62]. Agranulocytosis/aplastic anemia is not associated with oxcarbazepine's use. Pharmacokinetic interactions are also less frequent and milder although oral contraceptives may have reduced efficacy when prescribed with oxcarbazepine [63].

23.3.5 *Second-Generation Antipsychotics*

Among the more surprising evolutions in the maintenance pharmacotherapy of bipolar disorder has been the emergence of efficacy and common use of many, if not most of the second-generation antipsychotics (SGAs). Two recent studies, from the United States and Finland, found that SGAs were more commonly prescribed than mood stabilizers (lithium and anticonvulsants) as bipolar maintenance treatments

[64, 65]. Within the United States, prescription of antipsychotics increased from 12% to 51% between 1997–2000 and 2013–2016 [64]. In Finland, 31% of first-episode bipolar patients were prescribed antipsychotics within three months of their first episode, higher than that for mood stabilizers (29%) [65]. Furthermore, there are more RCTs on SGAs as maintenance treatments for bipolar disorder than for lithium and all anticonvulsants combined ([66, 67]; Table 23.5). Assuredly, this reflects patent issues: as recently developed compounds, the SGAs were proprietary and the vast majority of these studies were funded and designed by pharmaceutical firms who owned the patents on individual SGAs. In contrast, older medications anticonvulsants lost their patented status earlier, thereby precluding more pharmaceutical firm-funded studies. (Lithium cannot be patented since it is an essential element mined from the earth).

Fifteen RCTs with a total of 6142 subjects have evaluated the efficacy of SGAs, either as monotherapy vs. placebo or as adjunctive treatments to either lithium or valproate [66]. Studies included both oral medications as well as long-acting injectable (LAI) preparations. In clinical practice, however, LAIs are relatively infrequently prescribed with a prescription prevalence of <1% of pharmacotherapies in Finland [65]. Most of these studies used a design enriched for the antipsychotic evaluated and almost all included only bipolar I patients. Additionally, most studies specifically targeted only recently manic patients. Because of these limitations, relatively short follow-up periods (often only six months) and low follow-up rates/high dropouts, many authors are less than convinced that SGAs are as effective as they are touted to be [68, 69]. Nonetheless, most studies in the area find efficacy for SGAs in preventing any episodes, but primarily manias. Depression prevention efficacy is less clear. Whether this reflects a true lesser efficacy or the design consequence of (mostly) studying recently manic patients is unclear. Both oral and LAI SGAs seem to be effective. Adjunctive SGAs added to lithium or valproate consistently enhance preventive efficacy [61]. Eight adjunctive studies, evaluating five different SGAs found consistently lower recurrence rates with combination treatments with relative risk (RR) = 0.51 for any mood episodes, 0.42 for manic/hypomanic/mixed episodes and 0.39 for depressive episodes [61].

Table 23.5 Antipsychotics as maintenance treatment in bipolar disorder

Medication name	FDA approved		CANMAT/ISBD guidelines		
	Monotherapy	Adjunctive therapy	First line	Second line	Adjunctivetherapy
Quetiapine		+	+		+
Olanzapine	+			+	
Aripiprazole	+	+	+		+
Ziprasidone		+			+
Risperidone ^a	+	+		+	+
Paliperidone				+	
Lurasidone				+	

^aAs RLAI

Given the different neurotransmitter profiles across the different SGAs, it is still unclear whether the maintenance efficacy observed for the SGAs represents a class effect or whether some specific medications are more effective than others, or whether some agents are simply ineffective in preventing bipolar mood episodes. Because of this, clinical guidelines such as those of the CANMAT/ISBD evaluate each antipsychotic separately. Table X lists both the ISBD/CANMAT ratings for the SGAs along with the United States FDA approvals.

Side effect/safety considerations are another important concern with long-term maintenance use of SGAs. Because of their D2 blocking effects, all SGAs confer some risk of acute neurological side effects, such as akinesia and/or akathisia with differential risk across agents. All SGAs (with the likely exception of clozapine) also confer a risk for tardive dyskinesia with long-term use. SGAs have a lower risk for tardive dyskinesia than first-generation agents but the risk is certainly not negligible [70, 71].

Other than sedation—which also differs across individual SGAs—, the major side effect concerns reflect the weight-gaining properties of these medications and their propensity to cause metabolic syndrome and/or the emergence of type 2 diabetes mellitus [72]. Weight gain generally correlates with the risk for the emergence of type 2 diabetes mellitus although new-onset diabetes has been observed in the absence of weight gain. In a recent network meta-analysis evaluating 100 RCTs of short-term studies of schizophrenia, not bipolar disorder, the risk for weight gain differed dramatically across individual agents [73]. As measured by either the percentage of patients who gain weight or the mean weight gain across all patients, ziprasidone is the least weight gaining of the SGAs. Aripiprazole, lurasidone, cariprazine, and brexpiprazole are associated with relatively little weight gain while clozapine, olanzapine, and quetiapine are the most weight gaining [73]. Weight gain tends to occur relatively quickly with SGA treatment [74]. Higher baseline weight was predicted by higher baseline weight and being male. Interestingly, improvements in psychopathology correlated with greater disturbance in metabolic parameters [73]. In a bipolar cohort, the use of antipsychotics was associated with an increase in overall and cardiovascular mortality in a dose-related manner [75].

23.3.6 Antidepressants

Antidepressants, especially second-generation antidepressants, are widely prescribed for unipolar depression because of their favorable tolerability, minimal monitoring requirements, and benign toxicity profile. However, the advisability of using antidepressants in the acute and maintenance treatment of bipolar disorder remains a controversial issue, with strong advocacy for and against their use.

23.3.6.1 Methodological Considerations

Conclusively determining the efficacy of antidepressants in the maintenance treatment of bipolar disorder is inherently complex for several reasons: (a) studies must simultaneously assess multiple, interrelated outcomes. These typically include recurrence, duration, frequency, or intensity of depressive episodes, contrasted with treatment-induced manic episodes, mixed states, or rapid cycling; (b) the episodic nature of bipolar disorder often leads to discontinuation of antidepressants in trials due to real or perceived worsening of manic or depressive symptoms, resulting in substantial dropout rates; (c) trial designs often inadvertently favor patients who respond positively or tolerate the acute phase of treatment, thereby consciously or accidentally creating an enriched cohort. (d) observational or registry-based studies may underrepresent effects due to confounding by indication. (e) Pharmacologically, antidepressants represent a diverse group with highly variable pharmacodynamic properties. Consequently, it is often difficult to extrapolate findings from one antidepressant to another. Comparative studies between different antidepressant classes are rare [76].

23.3.6.2 Efficacy

Non-randomized, naturalistic studies have generally failed to demonstrate the efficacy of antidepressants in preventing depressive episodes, and some have even observed higher episode rates in treated versus untreated individuals [77]. Clinical trials offer more varied but inconsistent results regarding efficacy. A 2013 meta-analysis concluded that there is no evidence to support the long-term use of antidepressants in bipolar I and bipolar II disorder [78]. However, in bipolar II disorder, several pivotal maintenance trials demonstrated superiority of fluoxetine over placebo [79] and non-inferiority of venlafaxine over lithium [80]. As a result, venlafaxine was recommended as second-line and fluoxetine and escitalopram as third-line maintenance treatment in bipolar II disorder [4]. However, a more recent study in both bipolar I and bipolar II disorder found no acute or long-term benefit of adding citalopram to a mood stabilizer in either diagnostic group [81].

Conversely, a landmark, non-randomized, naturalistic discontinuation trial indicated an increased depressive relapse rate in individuals who discontinued antidepressants within six months of remission compared with those who continued beyond six months [82]. A more recent placebo-controlled discontinuation trial in bipolar I disorder after remission from a depressive episode compared ongoing flexible-dose escitalopram or bupropion with placebo. Over a 52-week period, there was no significant reduction in depressive relapse rates in the continuation group compared with the discontinuation group [83].

23.3.6.3 Safety

The primary safety concern with antidepressants in maintenance therapy for bipolar disorder is the potential for inducing (hypo-)manic episodes, mixed states, and rapid cycling. Registry-based studies, such as one by Viktorin [84], have found an increased incidence of manic episodes in bipolar disorder patients receiving antidepressant AD monotherapy. However, this study also showed that the combination of antidepressants with mood stabilizers does not result in a higher rate of manic episodes compared to mood stabilizer monotherapy. The risk of mood switching is significantly higher in patients diagnosed with bipolar I disorder than in those diagnosed with bipolar II disorder. Agomelatine has been proposed as a safer alternative due to its unique mechanism of action. A specific acute + maintenance RCT of agomelatine in bipolar I disorder not only showed any increased risk of mood swings over 52 weeks but also failed to demonstrate clinical benefit [85]. Comparative safety data among second-generation antidepressants are limited, but a study comparing sertraline, bupropion, and venlafaxine over 10 weeks found a higher rate of manic switches with venlafaxine [76]. A 2008 meta-analysis highlighted significantly increased rates of manic switches in bipolar I disorder in clinical trials [86], while a 2017 meta-analysis suggested the safety of antidepressants, particularly in bipolar II disorder and when used with a mood stabilizer [87]. However, two recent RCTs challenge this view. The citalopram add-on study reported increased mania scores [81], and a discontinuation RCT observed a numerical (although not statistically significant) increase in manic and mixed events in the treatment group [83].

In conclusion, current evidence does not strongly support the use of second-generation antidepressants to prevent depressive relapse in the maintenance treatment of bipolar I disorder, even in those who initially respond. There is replicated evidence of a potential increase in manic events. In bipolar II disorder, cautious continuation of second-generation antidepressants in combination with a mood stabilizer may be considered in those with an acute response, after a comprehensive individual risk assessment. Contrary to existing guidelines, it may be generally advisable to avoid prescribing venlafaxine or other serotonin-norepinephrine reuptake inhibitors (SNRIs).

23.3.7 Thyroid Hormones

Reports of an increased frequency of thyroid axis dysfunction in affective disorders have led clinical researchers to use thyroid hormones in people with these disorders [88]. Three groups of studies on the technique of thyroid supplementation of antidepressant or mood-stabilizing drugs can be distinguished: acceleration and augmentation (short-term) studies, and maintenance (prophylactic) studies, in which thyroid hormone (typically levothyroxine, L-T₄) has been investigated as monotherapy or adjunctive (add-on) treatment to prevent future episodes of recurrent mood

disorders. Open-label studies investigating the prophylactic effects of supraphysiologic L-T₄ doses in addition to conventional mood stabilizers have suggested that L-T₄ may improve the course of patients with rapid-cycling [89] and non-rapid-cycling bipolar disorder [90]. In one study that used L-T₄ alone as a prophylactic medication, authors [91] reported that rapid cycling ceased in five out of eight women with bipolar disorder, but not in two men, following treatment with supraphysiologic doses of L-T₄. In prospective open studies, investigations demonstrated that adjunctive supraphysiologic doses of L-T₄ may be beneficial in patients with mood disorders resistant to established medications for these disorders. For instance, in an 8-year maintenance study, adjunctive treatment of seriously ill and previously prophylaxis-resistant unipolar and bipolar patients with supraphysiologic doses of L-T₄ proved successful in preventing affective episodes in approximately 60% of the patients: treatment during LT₄ treatment compared with the same time period before L-T₄ administration resulted in a significant reduction of the number of depressive and manic relapses and of the Morbidity Indices [92]. A double-blind, placebo-controlled trial comparing L-T₄ and triiodothyronine (T₃) as adjunctive treatment in patients with treatment-resistant, rapid-cycling bipolar disorder who had failed a trial of lithium also reported beneficial effects of L-T₄ [93]. The study provided evidence for the benefit of adjunctive L-T₄ in alleviating resistant depression, reducing time in mixed states and increasing time euthymic.

23.4 Clinical Tips

- Maintenance treatment in bipolar disorder is essential in preventing future illness episodes.
- Maintenance treatment is multidimensional and includes for example psychotherapy and psychoeducation, but pharmacotherapy remains the mainstay of treatment.
- Lithium is the first-line medication (“gold standard”) in the maintenance treatment of bipolar disorder. Maintenance lithium serum levels should be between 0.6–0.8 mmol/L.
- Clinicians should be aware of the narrow therapeutic index (risk of intoxication) and risks of developing thyroid renal dysfunction during long-term lithium treatment.
- Despite its clear efficacy in treating acute mania, valproate’s efficacy as a maintenance treatment in bipolar disorder is far from clear.
- Alone among the anticonvulsants, lamotrigine has an American FDA indication as a maintenance treatment for bipolar disorder but it does not prevent manic relapses significantly.
- Current role of carbamazepine has diminished because its use is associated with a substantial side effect burden, many pharmacokinetic interactions with other medications, and two rare but potentially fatal immunological reactions.

- Lately, SGAs are more commonly prescribed than mood stabilizers (lithium and anticonvulsants) as bipolar maintenance treatments. Most studies in the area find efficacy for SGAs in preventing any episodes, but primarily manias; depression prevention efficacy is less clear.
- Long-term use of most SGAs should be used with caution because of the unknown metabolic risks.
- Evidence does not strongly support the use of second-generation antidepressants to prevent depressive relapse in the maintenance treatment of bipolar I disorder.
- Additional therapy with thyroid hormone (L-T₄) to mood stabilizer treatment may help stabilize patients.

23.5 Future Perspectives

Many patients with bipolar disorder benefit significantly from currently available therapeutic options during maintenance treatment, which is typically long term. However, for patients with bipolar disorder, which is usually a lifelong, severe mental illness, novel agents that result in higher response rates during maintenance treatment and lower side effect burden would be more than welcome. Areas for future research include the identification of biomarkers (e.g., imaging, genetic or blood markers) that can predict response to compounds used in maintenance treatment, as well as predicting an impending episode. Other areas of research include the identification of lithium-treated patients at high risk of developing severe chronic kidney disease and strategies to prevent these complications of long-term treatment. Although many patients with bipolar disorder are treated with a combination of psychopharmacological agents, with double and triple combinations of mood stabilizers being the standard, there is a lack of research on the effectiveness of such combinations, and on the combined use of medication and psychotherapeutic interventions.

23.6 Conclusion

Treatment of the maintenance phase of bipolar disorder is multidimensional and includes various treatment modalities, but pharmacological treatment is of paramount importance to prevent future episodes of bipolar disorder. Other goals of maintenance treatment are to maintain complete remission without subsyndromal symptoms between episodes and to prevent suicidal acts. Lithium has been the most valuable medication for patients with bipolar disorder for more than 70 years. Lithium's efficacy is based on its ability to provide long-term mood stability, a perception of its capabilities that is reflected in clinical practice guidelines worldwide. Patients who have an excellent response to lithium can lead a nearly normal life. For

those who do not respond adequately, alternative medications are available, including the anticonvulsants valproate, lamotrigine, and carbamazepine/oxcarbazepine, and SGAs.

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Chapter 24

Evidence-Based Clinical Guide to Suicide Risk and Prevention in People with Bipolar Disorders



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24.1 Introduction

There is widespread acceptance that evaluating suicide risk and implementing strategies for suicide prevention are key elements in the management of patients with bipolar disorder (BD). However, many clinicians are uncertain as to how precisely this should be done. Some of this uncertainty arises from the inherent complexity in such a challenging set of tasks, but also from the prevailing lack of clarity regarding which approaches are both specific to BD and supported by the general suicide prevention evidence base. Most studies on suicide prevention strategies are not conducted in samples of BD patients, so considering the applicability of more general findings and how to translate them to the specific are difficult hurdles. Similarly, though much is known about specific risk factors and warning signs for suicidal behavior, clinicians may be uncertain as to whether these can simply be applied “as is” to BD groups or whether modifications are needed.

In recent years, there has been increased clinical, research, and health systems interest in this area, driven by disheartening data showing persistently high rates of suicide in general and among people with BD. Suicide is understood to be a preventable outcome, but the available approaches from a broader perspective are also quite varied. Initiatives such as the Zero Suicide model initially garnered significant attention, leading to a renewed focus on establishing systems of care that comprehensively assess suicide risk and implement appropriate management strategies. At a broader international level, the World Health Organization LIVE LIFE program/implementation guide [1] provides an important framework for intervention, but the

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142-page implementation guide does not include even one mention of BD, raising questions about specificity.

One of the key findings on suicide prevention from recent clinical and public health research has been that focusing only on treating the underlying illness is insufficient. For BD and other conditions, there is a compelling rationale to support the broad-based use of suicide prevention strategies in addition to symptom management. This chapter explores these issues and identifies key knowledge on suicide risk and prevention approaches, both specific and highly relevant to BD.

Various models of suicide may help to explain why people with BD may be at particularly high risk. For example, the Integrated-Motivational-Volitional (IMV) model of suicide [2]; It posits that suicide arises in the context of the experience of a sense of being defeated and/or humiliated that leads to feeling trapped with no hope of improvement, and that this cognitive process may be particularly likely in those prone to rumination. This sequence of events and experiences is common among people with BD, especially in the context of a depressive episode, the most common illness state at any particular time for someone with BD. The IMV model suggests that people who believe they are trapped will experience suicidal ideation if certain other factors are present, such as the sense that they do not belong or are a burden on others (note: these notions derive from the earlier Interpersonal Theory of Suicide [3]). Again, such thoughts are common among people experiencing bipolar depression. Importantly, the IMV model has an emphasis on the moderating factors that facilitate the transition from suicidal thoughts to suicidal behavior. Prominent among these is access to the means of suicide. Given that psychopharmacology is a mainstay of treatment in BD and there exists toxicity concerns for a number of the medications used for this condition, people with BD are also a group that necessarily has increased access to the potential means of suicide. This confluence of circumstances may underscore why people with BD are at such high risk of suicide compared to the general population and also why their risk is especially heightened during the depressive phase of illness.

24.2 Epidemiology

The task force of the International Society for Bipolar Disorders (ISBD) on Suicide in Bipolar Disorder conducted a systematic review and pooled analysis of the absolute risk of suicide in people identified as having BD. Using a mix of clinical and population-based samples, the analysis estimated the suicide rate to be 164 deaths per 100,000 person-years, or approximately 10–20 times the general population rate [4]. Since national suicide rates include those with BD, the relative risk is likely to be even higher compared with non-BD or non-clinical samples. The results from other reports vary based on the nature of the study samples and analyses. Tondo et al. reported an earlier pooled analysis in which the overall standardized mortality ratio (SMR) was 22.1 (95% CI = 20.0–24.1) compared to that in the general population [5]. A more recent systematic review and meta-analysis of 57 studies of

mortality in BD revealed a relative risk of 11.7 (95% CI = 9.2–14.8) for suicide deaths compared to that in the general population [6]. According to data from suicide death cohorts, people with BDs account for 5–8% of all suicide deaths.

Individual studies have reported on various aspects of the epidemiology of suicide in BD, with results likely mediated by sample characteristics (e.g., population-based versus clinical), aspects of the follow-up period (e.g., duration, relation to illness state or health care contact), and source of ascertainment of data on suicide death. National cohort studies provide some of the highest quality data, including pivotal population-based Swedish samples [7], which found that suicide was second only to cardiovascular disease in terms of the number of deaths among people with BD during decades of follow-up. The age of the cohort clearly influences the death rate from other top causes of death such as cancer and respiratory diseases; nonetheless, these data provide an important estimate of the premature mortality associated with suicide in cohorts of people with BD. Other large administrative-clinical cohort studies, such as the data from Nordentoft et al. [8], identified a 35 + -year cumulative incidence of suicide deaths of 7.8% for men with BD and 4.8% for women with BD. Taken together, these data provide reasonable estimates of the long-term risk of suicide among patients with BD and can provide a baseline level of risk upon which other modifying factors can be added to adjust the risk estimate for a specific patient.

24.2.1 Clinical Factors that Influence the Risk of Suicidal Behavior in People with Bipolar Disorder

Clinical vignette

Eva is a 28-year-old female sent by her psychotherapist to the emergency department (ED) due to concerns about increasing suicide risk. On assessment, Eva endorsed experiencing suicidal thoughts with a plan to ingest a large number of her prescribed medications. She has been using increasing amounts of cannabis to try and reduce her distress, but she reports this is not working.

Upon further exploration of her history, you identify that Eva was diagnosed 4 years ago with BD type II. She had a history of several past major depressive episodes and a current episode that began 2–3 weeks ago as stress from her new job increased. Her mental health care is provided by her family physician and a community-based social worker/therapist, and she is on the waitlist for assessment by an outpatient psychiatrist. Her current medications include lamotrigine (200 mg qhs) and quetiapine XR (100 mg qhs), and she uses methylphenidate on a prn basis for query attention deficit disorder (ADD). She is interested in seeking further assistance and is eager to engage in discussion on how to ensure that she is safe.

There are several clinical issues specific to suicide prevention that arise when considering the care of a patient such as Eva.

1. What is her short-term and long-term risk of suicide?
2. What aspects of her care should be emphasized to reduce her suicide risk?
3. Who should be responsible for or involved in the management of her suicide risk?

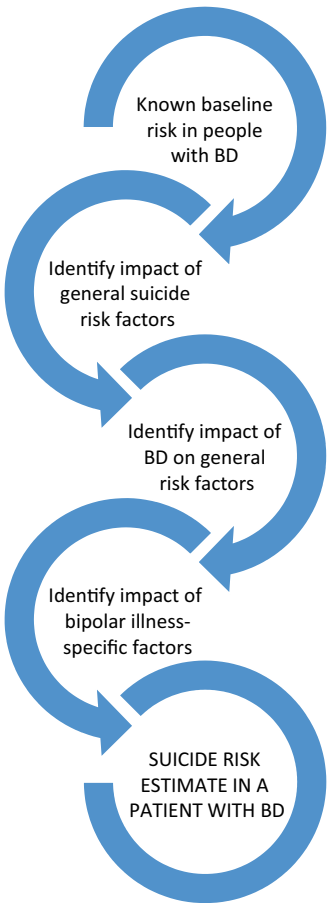
24.2.2 Understanding Short-Term and Long-Risk of Suicide in People with BD

As introduced earlier, there are a number of established models that explore factors associated with the development and advancement of the suicidal process [3, 2–10]. Within BD, Malhi et al. have provided a notable contribution with a proposed model emphasizing various neurobiological mechanisms interacting with clinical and environmental factors [11]. The ISBD Task Force on Suicide [12] constructed a clinical model that grouped factors into distinct categories (baseline risk, general factors, impact of BD on general factors, and illness-specific factors), which would result in a BD-specific suicide risk assessment (see Fig. 24.1). This framework operationalizes the principle that the diagnosis of BD is relevant not only as a focus for estimating suicide risk, but also because numerous aspects of the illness itself directly and indirectly impact risk. The culmination of this approach would be that estimating and integrating the contribution of each of these factors into the risk assessment will result in a more specific and likely accurate estimate of risk.

There is ample evidence that many sociodemographic and clinical factors impact suicide risk. Age, sex, race, adverse childhood experiences, economic and other psychosocial stressors, pain or other medical difficulties, presence of suicidal ideation, hopelessness, isolation, prior suicide attempts or self-harm, family history of suicide, and numerous other factors are important contributors to suicide risk assessment [12–14]. These factors are likely highly relevant across most, if not all, psychiatric diagnoses, and these should always be incorporated into a comprehensive suicide risk evaluation. Returning to the case of “Eva,” there are already several known risk factors for suicidal behavior, including the presence of suicidal ideation with a specific plan, substance use, current major depressive episode, and psychosocial stressors.

Moving on from the general risk factors, the next step is to consider the interaction between BD and these general factors. One notable example is the sex-based difference in suicide deaths. While the population-based literature on suicide normally identifies a three-fold or higher ratio of suicide deaths in men than in women, this is not the case for BD. The previously mentioned ISBD Task Force on Suicide identified an odds ratio for suicide deaths of 1.83 (95% CI = 1.41–2.39) for males compared to females with BD. This finding revealed that the impact of a BD illness on suicide risk is relatively greater among women than among men.

Fig. 24.1 Clinical model for developing a BD-specific suicide risk assessment



“Eva” also identified that she is using increased amounts of cannabis. While societal attitudes and legislation regarding cannabis use have shifted in many countries, recent evidence suggests that the presence of a cannabis use disorder remains a risk factor for suicidal behavior in people with mood disorders [15]. The degree to which lower quantities of use of cannabis may be associated with suicidal behavior remains understudied.

There are also a number of BD-specific clinical factors that also impact suicide risk, including earlier age of illness onset, depressive polarity of first episode, duration of overall illness, number of mood episodes, predominant depressive polarity, polarity of most recent/current episode being depressed, presence of mixed features, and anxious distress. The inclusion of BD-specific clinical variables in the model shown in Fig. 24.1 completes the fulsome list of factors.

Table 24.1 summarizes all factors from different elements of the clinical presentation that may impact the estimated suicide risk. However, simply listing and estimating the impact of specific factors does not lead to a precise predictive model. An

Table 24.1 Factors associated^a with suicide attempts and suicide deaths in bipolar disorder (Adapted from ISBD Task Force Paper [Ref. 12])

VARIABLES	INCREASED LIKELIHOOD OF SUICIDE ATTEMPTS IN BD	INCREASED RISK OF SUICIDE IN BD
<i>Sociodemographics</i>		
Sex	Female	Male Females have higher SMR
Age	Younger Older age – higher lethality attempts	No overall effect Older age – lower ratio of attempts / completions
Race	Minorities – specific to youth	Non-Hispanic while – indirect evidence
Living status	Single parents	
Religious affiliation	Lack of religious affiliation	
<i>Characteristics of Bipolar Disorder</i>		
Age of illness onset	Younger age of first mania or depression	
Polarity of 1 st episode	First episode depression Mixed state Mania – more violent attempts	
Duration of illness	Longer duration	
Polarity of current / recent episode	Predominant depressive polarity Depressive episodes Mixed states	Uncommon during mania Depressive episodes Mixed states
Episode characteristics	Mixed features Greater number and severity of episodes Anxiety Atypical features Suicidal ideation	Hopelessness Psychomotor agitation

(continued)

Table 24.1 (continued)

Psychosis	Absence	Absence
Bipolar disorder subtype	BD II > BD I (mixed results)	
High risk time periods		Weeks to 1+ years post-admission Spring and early summer
Comorbidity		
Axis I Comorbidity	Substance use disorder Anxiety disorder Eating disorder	Substance use disorder - no significant increased risk Anxiety – increased risk
Personality disorders and characteristics	Personality disorders – including Borderline PD in particular Aggression or irritability Impulsivity (mixed results)	
Sexual dysfunction	Presence	
Other History		
Family history	Mood disorders Bipolar disorder Suicide	Mood disorders Bipolar disorder Suicide
Prior suicide attempts	Any	Any
Trauma	Childhood abuse	
Psychosocial precipitants	Interpersonal problems Occupational problems	
Treatment exposure		
Duration of untreated illness	Longer duration	
First treatment contact	Admission to hospital	

^aBased on findings in at least one study

intricate calculation that incorporates interactions and other effects, and is shown prospectively to have accurate predictive metrics is ideal, but such a validated model currently does not exist in clinical practice. In the past few years, efforts have been made to develop a more structured approach to risk estimation via the development of a risk calculator specific to BD. Based on data from the Course and Outcome of Bipolar Youth (COBY) study, a risk calculator for the prediction of suicide attempts (not deaths) was published [16] with encouraging findings based on a model of ten predictors. A subsequent validation study [17] in an adult sample was similarly noteworthy for finding acceptable accuracy ($AUC = 0.78$) for suicidal behaviors over a one-year time period. Newer methods using AI platforms to potentially increase the accuracy of suicide prediction are emerging, but have yet to reach the level of accuracy required for translation into clinical practice. Moreover, most models focus on suicidal behaviors rather than suicide deaths.

While these are excellent methodological advances that utilize novel approaches, the broad literature on suicide prediction continues to send more dire signals. A large systematic review published in 2019 has reinforced the view that predicting not only the presence but also the timing of suicide deaths is extremely challenging [18]. Given that death by suicide is a low base-rate event that can occur essentially anytime from adolescence to old age, most suicide prediction models ultimately possess very low positive predictive values, sometimes approaching zero. The absence of an accurate risk calculator for suicide deaths in the broader clinical population evades us, so it is not surprising that such an instrument is not yet available in the context of BD. There is also UK data on suicide deaths in people with BD [19], which found that the majority of these decedents were classified as having “low risk” of suicide during the last mental health contact prior to death, highlighting the lack of predictive capacity from standard clinical assessments.

This leaves clinicians in a very difficult situation. There are potentially unrealistic individual and system-wide expectations that mental health professionals can predict suicidal behavior, at least at a level that makes a clinical decision seem evidence-based. These expectations exist despite the literature sending a strong signal that, at least to date, we cannot predict suicide regardless of what type of predictive model is used. This does not mean that efforts to develop such risk models or calculators should not continue; rather, until these calculations are consistently shown to have a strong predictive capacity for clinical subgroups, they cannot be relied upon. So what is a clinician to do?

Thankfully, large parallel research, clinical, and policy efforts have been underway for decades that focus less on predicting suicide deaths and more on trying many methods to prevent suicide deaths across all risk strata. Being unable to rely on prediction also leads to the important shift in approach that concludes that ALL patients with BD should be provided with suicide prevention strategies and interventions, irrespective of presumed suicide risk. Relieving the unrealistic burden on clinicians of predicting suicide can paradoxically unleash greater efforts at across-the-board prevention which, in the long run, is likely to be the most effective approach.

24.3 Management

The clinical approach to suicide prevention among patients with BD should conceptually and practically incorporate two aspects. At a foundational level, effective acute and maintenance treatment for the underlying symptoms and episodes of BD and any associated comorbid conditions will clearly have a positive effect on reducing the risk of suicide [20, 21]. However, that is not enough. Efforts should also be made to implement evidence-based approaches and interventions that have been specifically shown to reduce suicide risk, which may or may not relate directly to symptom burden (see Fig. 24.2).

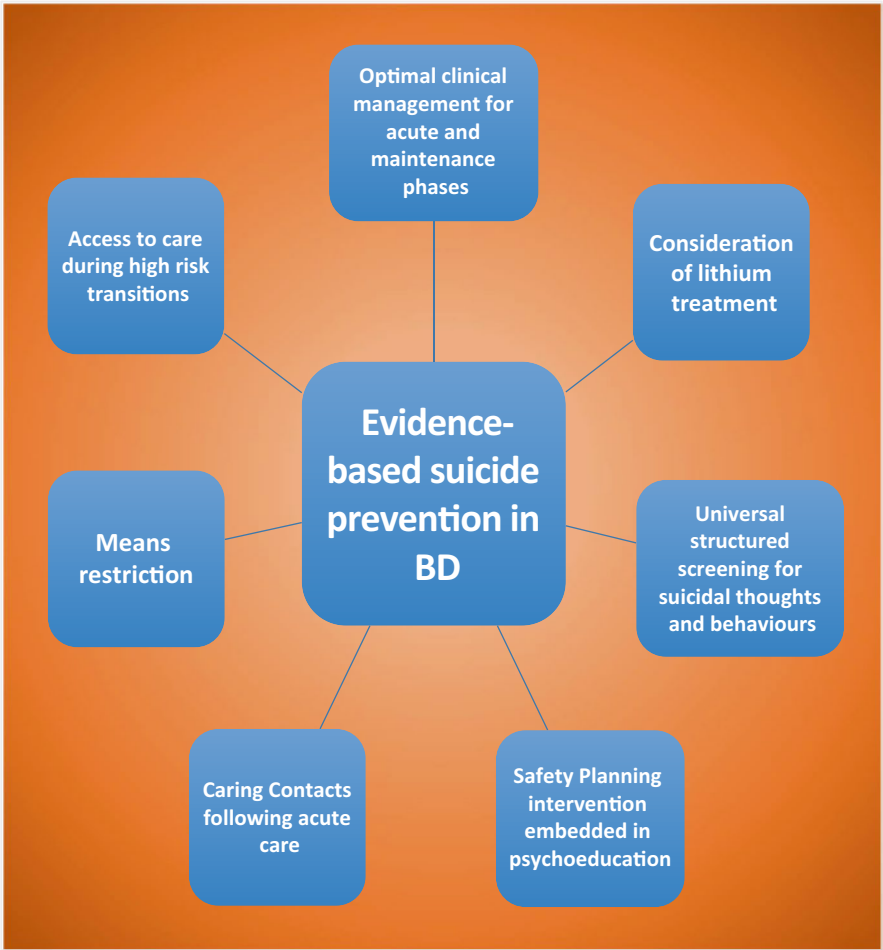


Fig. 24.2 Evidence-based suicide prevention interventions highly relevant for bipolar disorder

For many years, the focus on suicide prevention in BD has mostly dwelled on the role of lithium as a putative anti-suicide treatment. While lithium is well established as a first-line mood stabilizer based on prevention of recurrence and effectiveness in specific subgroups of lithium-responsive patients, the direct evidence for an anti-suicide effect above and beyond illness management is more nuanced. Meta-analytic results have shown that lithium treatment is clearly associated with a reduced risk of suicide, but most of this data comes from large observational or epidemiological studies which are informative but ultimately have substantial limitations [22]. The prospective randomized controlled trial (RCT) data is much more limited when exploring suicide death as the outcome due to the inherent methodological challenges of sufficiently powering such studies. Results from the combination of RCT data across wider mood disorder diagnostic groups are certainly supportive of an anti-suicide effect, but the findings are still the topic of debate and diversity of interpretation. Rather than replicate the extensive writings already available on this topic, we are comfortable with the middle-of-the-road conclusion that lithium is a gold-standard mood stabilizer, that patients who take lithium are much less likely to die by suicide, and that lithium may have specific anti-suicide effects compared to other treatments in BD, but that the confidence in this statement needs to be moderated by the current state of the evidence.

In this chapter, we have instead chosen to focus on other suicide-specific interventions that have received less attention. Just prescribing lithium for a patient with BD is not enough of an intervention on its own in terms of a suicide prevention strategy. Before we explore non-pharmacological modalities, there is some modest evidence on the use of other pharmacological agents for suicide risk reduction. However, most of the data are not specific to BD or are of limited quality.

Several studies have confirmed that anticonvulsants are not associated with increased suicide risk, finding no convincing evidence to support this concern that was briefly a focus of attention [23, 24]. Furthermore, initiation and continued use of anticonvulsant medications have been shown to be associated with reduced rates of suicide attempts and/or suicides [25, 26]. The evidence with respect to differences between lithium and anticonvulsants is relatively inconclusive. While there are reports of higher rates of suicide-related behavior during periods of anticonvulsant use versus lithium use [27, 28], these findings mostly come from observational, non-randomized studies. The exception is RCT data showing higher suicide deaths in those receiving carbamazepine versus lithium. This may have to do with higher toxicity associated with carbamazepine self-poisoning, but this possibility is difficult to firmly establish. The overall observational results may be impacted through confounding by indication, since there is a perception among clinicians and in some reports that anticonvulsants may be more effective for complex patients with psychiatric comorbidities or a rapid cycling pattern. Additionally, the perception of greater lethality in patients with lithium self-poisoning compared to divalproex sodium self-poisoning may paradoxically lead clinicians to avoid lithium use during periods of perceived higher risk of suicide.

Beyond lithium and anticonvulsants, there is a precipitous decline in the availability of data on suicide-related outcomes associated with the use of antipsychotic

or antidepressant medications in people with BD. For antipsychotics, the putative anti-suicide effect of clozapine appears to be specific to schizophrenia. With regards to antidepressant use in patients with BD, there is of course the increased risk of emergent mixed or manic symptoms, including insomnia and agitation, which could exacerbate acute suicide risk, but there is little data to support this assumption.

There is sparse data for other interventions as well. Limited evidence suggests that initiating chronotherapies (light therapy and sleep deprivation) with lithium can produce a rapid reduction in suicidal ideation during bipolar depression, but further data is needed. Despite the growing interest in the use of interventional approaches (e.g. repetitive transcranial magnetic stimulation) in treating patients with BD, the data is still much more preliminary and observational in nature in comparison to major depressive disorder [29]. Ketamine/esketamine has also garnered significant interest in this area but most studies use mixed mood disorder samples, although BD-specific data is emerging and generally quite positive [30].

24.3.1 Beyond Pharmacological Treatments

Within the broader suicide prevention literature, there is extensive discussion on varied approaches that span both clinical and public health-related spheres. Clinical and health care system evidence-based interventions of relevance to BD populations include systematic screening for suicidal thoughts and behaviors, coordinated after-care following contact with acute care services, general practitioner training, access to psychotherapeutic treatments, peer support, and common-sense means restriction that reduces access to lethal means. At a community and societal level, evidence-based interventions include the implementation of media guidelines on safer reporting of suicides, public awareness campaigns, gatekeeper training, and physical infrastructure that limits access to hot-spot sites for suicide. When widely implemented, these interventions are estimated to have the potential to reduce suicide by 20–25% [31].

Delivery of specific psychotherapy modalities has been associated with a reduction in suicide-related behaviors, and should be considered for their role in the management of patients with BD. There is evidence supporting the use of dialectical behavioral therapy (DBT) [32], CBT for suicide prevention [33], and Collaborative Assessment and Management of Suicidality (CAMS). Replicated data on novel interventions such as “caring contacts” after delivery of acute mental health services have also been shown to reduce the risk of suicide-related behavior and even suicide deaths [34]. There has also been great interest in strategies to enhance coping, with different versions developed based on the framework of the Stanley and Brown Safety Planning Intervention [35].

Figure 24.2 highlights a number of key evidence-based suicide prevention interventions that are highly relevant for BD. In the case of “Eva” introduced earlier, a number of these would be very applicable. From a pharmacological perspective, consideration should be given to including lithium as part of her treatment. The lack of

apparently sufficient prophylactic effect from lamotrigine could justify a switch of this for lithium. While the evidence on lithium in relation to suicide-related outcomes for patients specifically with BD type II is less well established, the combination of needing greater mood stabilization and focus on putative anti-suicide effects is compelling toward initiating a lithium trial. While Eva is receiving care within an acute setting such as the emergency department or inpatient unit, a safety planning intervention is critically important, and should be introduced as a central aspect of her care. The completion of a safety plan (paper or electronic) should be shared with her support system and be available in a place that she can easily access. Her health care team should also engage in a discussion that explores her access to potentially lethal means of self-harm, and if present then steps should be taken to distance her from those means and ensure all those involved in her care are engaged in this process. Once she leaves the acute care setting, she should also be provided with access to timely follow-up care that is ideally integrated into her overall health care services, including primary care and her community social worker. This set of steps would ensure the delivery of some of the key suicide prevention interventions, and would support her management of the illness plus reduce her risk of suicidal behaviors.

While the case vignette of Eva is limited in scope, it does raise the question of who should be responsible for delivering all these interventions. She has a primary care physician who prescribes her medications and monitors her illness, she has a community-based social worker/psychotherapist who conducted the safety assessment that led to the ED visit, she now has an ED physician and likely emergency-based psychiatrist to provide acute care, and an outpatient psychiatrist that she is waiting to see. In the expanded scenario by which Eva gets admitted to the hospital, then a full inpatient team is also included in the mix. Given the risk of the *Bystander Effect* playing out across silos in her care, this is an important aspect for consideration. The acute care providers may be focused on the management of her current symptoms, and the outpatient providers may assume that an acute care setting is prioritizing her safety. In this context, the inverse of the *Bystander Effect* could be the adage that *It Takes a Village*. Every member of her health care team has an important role to play and the interventions should be incorporated into the comprehensive care that she receives across all the settings she is engaged with.

24.4 Future Perspectives

- Ongoing efforts at the development of suicide prediction models focused on people with BD would benefit from a blending of large epidemiological or observational datasets with more proximal, person-specific data emphasizing warning signs, clinical details, and protective factors.
- Efforts are underway at passively collecting vast amounts of data on people with BD, and incorporating these new datasets into our prediction models will likely require collaboration with data scientists familiar with the latest advances in AI

modeling. There will also be opportunities for broader collaboration across research groups from more diverse geographic areas.

- With increasing appreciation that clinically applicable prediction calculators of suicide in BD may still be a long way off, attention can shift toward a model of care that is based on the idea that ALL people with BD should receive care focused on suicide prevention over and above symptom or episode management. This may spark new studies and quality improvement efforts aimed at matching this goal with the delivery systems and care pathways that are currently the foundation for the care of BD patients.
- All care providers for people with BD should be involved in planning and implementing the delivery of these suicide prevention strategies. This raises the opportunity for more interdisciplinary research and policy teams to break out of silos and develop more practical approaches.
- The voice of those with lived experience has been nearly absent in the current literature. Future studies should use up-to-date approaches to incorporating patients and families into the design, study, and implementation of suicide prevention.

24.5 Conclusion

There are many elements to the care provided to people with BD, as shown in the case vignette of Eva. Suicide prevention is not singular in this regard, but it can certainly be argued that there are no aspects of care that are more important. While advances are being made on prediction models of suicidal behavior broadly and within BD, at their present state these remain imperfect and of limited clinical value. At their worst, they can provide false reassurance or re-allocation of resources to high-risk settings only that could be of value for more across-the-board interventions. Suicides occur across all risk profiles and the literature is clear that all people with BD should receive access to suicide prevention interventions. These include clinically-based approaches for implementation across care settings and by all health care providers. Suicide prevention is also a system and public health imperative, and the advances in our approaches apply very much to those with BD. Overall, while suicide rates remain terribly high, there is optimism that the basket of evidence-based interventions reviewed in this chapter can be feasibly implemented with positive results.

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Chapter 25

What Not to Use in the Pharmacological Treatment of Bipolar Disorder



Natalie Palma and Fabiano Alves Gomes

25.1 Introduction

Bipolar disorder (BD) is a complex, chronic, and often severe mood disorder that presents significant management challenges [1]. There are many pharmacological and non-pharmacological approaches approved or under investigation to treat acute mania, acute bipolar depression, as well as maintenance treatment to prevent mood episodes [2]. Clinical practice guidelines (CPGs) are the main source of reliable information regarding treatment options [3]. CPGs synthesize literature, rely on expert opinion, and are an important tool for the implementation of evidence-based clinical care among practitioners [3, 4]. Despite the wide availability of CPGs to guide practice, the adherence to CPGs in real-world clinical settings is poor [3]. In fact, most physicians worldwide frequently practice guideline-discordant care for patients with BD [5]. Although the focus of most CPGs is to provide recommendations about what treatments to use in each clinical situation, there has been an increased interest in communicating what treatments should not be used, either because of a lack of studies or due to negative results in clinical trials. In this chapter, we aim to clarify the non-recommended treatments in BD based on the CPGs. In addition, we will discuss potential reasons for clinical non-adherence as well as other recommendations for improving future adherence.

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25.2 Non-Recommended Treatments for Bipolar Disorder in Clinical Practice Guidelines: Evidence from a Systematic Review

A recent study systematically reviewed the CPG recommendations on pharmacological interventions for bipolar disorder with evidence against their use due to lack of efficacy data and/or due to serious safety concerns [3]. A systematic literature search identified 29 national and international guidelines on the pharmacological treatment of adults with BD type 1 or BD type 2 [3]. Twenty-three of the guidelines mentioned at least one non-recommended treatment [3]. Terms such as “should be avoided,” “not recommended,” “weak/strong recommendation against,” and “negative evidence” were used throughout the selected guidelines to identify non-recommended treatments [3]. The researchers then synthesized the most non-recommended treatments for each phase of bipolar disorder. A summary of the most frequent non-recommended treatments can be found in Table 25.1. A more detailed discussion of each phase is provided next.

25.2.1 Non-Recommended Treatments—Mania

Clinical practice guidelines most frequently recommend against the use of some anticonvulsants for the treatment of acute mania [3]. Lamotrigine monotherapy [2, 6–19] or in combination with a mood stabilizer or quetiapine [6], topiramate especially as monotherapy [2, 6, 8–10, 12, 14–19], or in combination with a mood

Table 25.1 Summary of the most frequent non-recommended treatments for bipolar disorder

Clinical condition
Mania
Lamotrigine
Topiramate
Gabapentin
Carbamazepine + olanzapine/risperidone
Depression
Monotherapy with antidepressants
Aripiprazole
Ziprasidone
Risperidone
Maintenance
Inconsistent data
Special Populations
Valproate for women in childbearing age/pregnancy

Adapted from [3]

stabilizer [17], gabapentin (especially as monotherapy) [2, 6, 8–10, 12, 14–18], and carbamazepine in monotherapy [12, 15], or in combination with olanzapine/risperidone [3] or allopurinol [17] were not recommended in several CPGs.

25.2.2 Non-Recommended Treatments—Depression

In bipolar depression, most CPGs recommend against the use of antidepressants, in monotherapy [2, 6, 10, 12, 15, 18–27]. Interestingly, the French guidelines do not recommend their use even in combination with a mood stabilizer, especially if there is a history of mixed symptoms, rapid cycling, and manic switch [21]. It is noteworthy that tricyclic antidepressants (TCAs) are the most cited, but there are some CPGs recommending specifically against paroxetine [10, 17, 25].

There is some debate over whether antidepressant monotherapy should be regarded as non-recommended for the treatment of bipolar depression [28]. It may be more accurate to regard antidepressant monotherapy as a non-recommended treatment for bipolar I disorder but not for bipolar II disorder [28]. According to the 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT)/International Society of Bipolar Disorders (ISBD) guidelines, venlafaxine monotherapy and sertraline monotherapy are recommended as second-line treatments, and fluoxetine monotherapy is recommended as a third-line treatment for patients with bipolar II depression [28]. Moreover, a meta-analysis of 11 trials with 692 patients with bipolar I and II depression revealed that antidepressant monotherapy or combination treatment (with a mood stabilizer) outperformed the placebo at reducing depressive episodes without increasing the risk of new manic/hypomanic episodes [28]. Subgroup analyses revealed that greater benefit and lower risk may be achieved in patients with bipolar II depression than in those with bipolar I depression [28]. It was found that antidepressant monotherapy had a relatively higher efficacy than antidepressant/mood stabilizer combination therapy [28]. Additionally, it was found that second-generation antidepressant monotherapy resulted in substantially improved prevention of new depressive episodes and did not significantly increase the risk of manic/hypomanic episodes compared to first-generation antidepressant monotherapy [28]. A comparison of the antidepressant effects between selective serotonin reuptake inhibitors (SSRIs), serotonin and nor-adrenaline reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) showed that SSRIs are the least likely to induce manic or hypomanic switches during depressive episodes [28]. SNRIs are the next least likely to induce this effect [28]. Overall, antidepressant monotherapy may be useful for treating patients with bipolar II depression, but further studies are required to clarify these conclusions [28].

The use of aripiprazole [2, 6–10, 12, 14, 15, 17, 20, 25], ziprasidone [2, 6, 8, 10, 12, 14, 15, 17, 20, 25], and risperidone was also frequently discouraged, especially in monotherapy [7, 14, 17], but some guidelines recommended against its use even in combination with a mood stabilizer [2, 7, 8, 10, 15, 18].

25.2.3 *Non-Recommended Treatments—Maintenance*

Non-recommended treatments for bipolar disorder maintenance treatment varied considerably among CPGs [3]. Lamotrigine was commonly cited as an ineffective intervention to prevent mania [8, 12, 14]. Aripiprazole [8, 14, 29], haloperidol [14, 30], risperidone [14, 29, 30], paliperidone [14, 29], and ziprasidone [14, 29] were cited in different guidelines as non-recommended maintenance treatments. It is not clear on which grounds those recommendations were made, but it might reflect outdated information since the use of most atypical antipsychotics as maintenance treatments is supported by current evidence and are listed in more recent guidelines [3]. Other commonly proscribed medications were first-generation antipsychotics and the anticonvulsants topiramate and gabapentin [3].

25.2.4 *Non-Recommended Treatments—Mixed Features*

Most CPGs included in the review did not make any statement about proscribed treatments in mood episodes with mixed features [3]. Three CPGs make suggestions for mixed features: not to use carbamazepine in monotherapy [8] and to avoid the use of antidepressants [31], but one of them [27] specify against this use in patients with BD II with mixed manic symptoms [3].

25.2.5 *Non-Recommended Treatments—Special Populations*

There are numerous statements advocating against the use of valproate in women of childbearing age and pregnancy due to the risk of fetal malformation [11, 12, 15, 17, 23, 30]. There is only one guideline that allows the use of valproate during pregnancy, recommending keeping the dose below 1000 mg/day, especially in combination and/or in the first trimester [27]. Topiramate, gabapentin, and carbamazepine were also cited as drugs to avoid in women of childbearing age [11, 21]. In patients with rapid-cycling BD, it is recommended that antidepressants should be avoided [18, 25]. In this subgroup, there are also isolated recommendations against the use of lamotrigine [13, 25].

25.2.6 *Clinical Practice Guidelines (CPGs)—Limitations*

Although most of the evaluated CPGs (79%) included non-recommended BD treatments, throughout the evaluation, the researchers found that most guidelines were inconsistent in recommendations [3]. For example, while some guidelines

such as CANMAT [2], WFSBP [31], and CINP [17] clearly state that lamotrigine monotherapy should not be used in acute mania, several others [20, 23, 30, 32] do not mention this. Additionally, while the CPGs tended to be consistent regarding non-recommended treatments when it came to safety considerations (i.e. in the case of valproate for pregnant women with BD), there is a lack of uniformity across guidelines with regard to interventions that lack data on efficacy [3]. For example, there is a lack of data on gabapentin efficacy in the treatment of acute bipolar depression [3]. While the CANMAT [2] and the German guidelines [15] were more conservative and considered this in the category of “no specific recommendations,” CINP [17], the Czech guidelines [9], and the Chilean guidelines [20] classified it as a “non-recommended treatment” [3]. Most guidelines also failed to provide clear statements in terms of the consequences of the implementation of treatments with a lack of efficacy, such as the risk of mortality or poor adherence among others [3].

While the CPGs are important tools for making treatment decisions, there is still room for improvement [3]. In particular, the informational gaps and inconsistencies across the CPGs should be addressed to prevent the transmission of potentially ambiguous messages to prescribers [3]. These deficiencies are also unhelpful considering the already problematic implementation of evidence-based medicine in the clinical care of individuals with BD [3]—a broader issue that will be discussed in more detail next.

25.3 Continued Prescription of Non-Recommended Treatments for Bipolar Disorder

As mentioned, the uptake of CPGs among practicing practitioners is poor [3]. Surveys of practicing psychiatrists reveal high rates of unawareness about and non-adherence to published CPGs [33, 34]. This means that some clinicians continue to implement BD treatments that are ineffective and not recommended by CPGs [3]. In fact, the assessment of prescriptive practices over time reveals that interventions with evidence against their use in BD are becoming more common [3]. For example, a recent study demonstrated an increase in the use of antidepressant monotherapy (without a mood stabilizer or second-generation antipsychotic associated) from 17.9% of the outpatients' visits in 1997–2000 to 40.9% in 2013–2016, suggesting the growing use of a potentially deleterious intervention in BD [35]. Furthermore, there is some albeit inconsistent evidence that patients with BD treated by clinicians who do not adhere to CPG are at a higher risk of poor outcomes, such as persistent depressive symptoms and persistent general psychopathology [36, 37]. Overall, the lack of adherence to evidence-based guidelines means that potentially harmful and ineffective treatments are being prescribed to patients with BD. Next, we will take a closer look at potential reasons why such critical guidance tools are not being adopted.

25.3.1 Reasons for Ineffective Interventions—Prescribers Receiving Insufficient Information

Although most widely used guidelines for the treatment of BD such as the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society of Bipolar Disorders (ISBD) Guidelines review evidence and provide recommendations against the use of treatments with negative evidence for efficacy, most other guidelines do not make explicit recommendations about which treatments should not be used [38]. Also, terms such as “evidence against the use,” “non-recommended treatments,” “contraindicated,” and “use wisely” are often found in the literature which can be confusing for practicing clinicians [38]. For a busy clinician, this makes it difficult to retrieve pertinent information regarding treatment options and prevents them from adopting it into their practice [38]. On top of this, positive trials are much easier to publish and tend to appear in higher-profile journals than negative trials, which also contributes to limited awareness of data on ineffective interventions [39]. For example, one study using Medicaid data described an increase of 4700% in the prescription of gabapentin for BD in 2002, compared to the baseline in 1994 [3]. Notwithstanding the publication of two RCTs with negative results in BD, the rates remained the same and only decreased after a policy of previous authorization was adopted [40].

25.3.2 Reasons for Ineffective Interventions—Marketing

Prescribers’ relationship with industry and their representatives influence prescribing habits and may contribute to irrational prescribing patterns of their drugs [38]. Unfortunately, the investment made to promote a new medication does not always correlate well with the robustness of the research findings supporting its use [38]. For instance, in the past, some medications were promoted based on methodologically limited studies, with preliminary evidence of efficacy that was not replicated [38]. In addition, the evidence against the use of an intervention already incorporated in the clinical practice tends to be much less discussed in advisory boards, sponsored symposia, and continued medical education activities unless there is a strong rationale to switch to a newly marketed agent [38].

25.3.3 Reasons for Ineffective Interventions—Prescriber’s Experience and Expectations of Medications

Physicians largely integrate their own experiences and the views of peers into prescriptive practices [38]. However, some physicians rely on a “my way” approach, where they systematically choose medications that do not align with the

evidence-based approach [38]. A perception of safety or a false perception of the efficacy of a medication can potentially maintain the use of ineffective treatment [38]. There is also the potential for the “wish bias” which is a tendency of people to fit evidence into their preformed personal worldview of how they believe things should be [38]. This can distort the way that we interpret the literature and how we translate the information we receive in our clinical practice [41]. A clinician may be convinced that their medications are working, when in reality, they are not. Finally, CPG recommendations are informed by results from randomized controlled trials (RCTs) and other interventional studies that report aggregate results [3]. Clinicians may be reluctant to implement CPG recommendations because of debatable methodological decisions as well as concerns about the generalizability of study findings into real-world settings [3].

25.3.4 Reasons for Ineffective Interventions—Inherent Complexity of Bipolar Disorder Treatment

Treating patients with BD can at times be a challenging and frustrating experience [38]. Many patients do not fully respond to existing treatments while others exhibit complex clinical presentations with multiple comorbidities requiring polypharmacy [38]. Especially in these complex scenarios, medications with little or no efficacy may be added to a treatment regimen [38]. When treating BD, it can also be tempting for prescribers to believe in a class effect [38]. For example, since anticonvulsants like valproate and lamotrigine work for mania and bipolar depression, it could be seen that all other anticonvulsants would work too [38]. Similarly, some atypical antipsychotics treat bipolar depression, so all atypical antipsychotics could be seen to work for bipolar depression [38]. Finally, given the limited number of evidence-based options, it is not uncommon to run out of choices, and then even a sensible clinician may trial a non-evidence-based option rather than leave a patient with persistent or unremitting illness [38].

25.4 Improving Adherence to Clinical Practice Guidelines

As you can see, there are many factors that may contribute to the lack of adherence to recommendations for BD treatment according to CPGs. To enhance understanding and adherence to the CPGs, future versions of the CPGs should prioritize the inclusion of clear statements about non-recommended treatments [38]. As well, future updates of these CPGs should consider abstracted and simplified versions for busy clinicians, streamlining the language used to designate non-recommended treatments in BD, consider including a section about the risks of use of these interventions, and providing clear statements why some interventions should not be used

[3]. All of these suggestions should help prevent confusion and make it easier for clinicians to adopt evidence into their everyday practice. Meta-guidelines research might help highlight deficient areas not only related to guideline development but may also increase the consistency and the language standards used in treatment guidelines [3]. To further increase awareness of ineffective interventions, there should be a more balanced discussion of proscribed treatments in the literature and in systematic reviews and meta-analyses [38]. It is also important that clinical trials and observational studies use populations that represent the broad spectrum of BD patients seen in clinical practice [38]. This may encourage clinicians to implement the CPG recommendations more readily. To address the issue related to marketing, a clear separation between scientific and commercial promotional actions in the treatment of BD should be made [38]. Above all, there is a need to increase awareness of our own prescribing habits, keeping in mind the personal and financial costs of unnecessary interventions [38]. Peer review and structured forums are useful tools for addressing this need [38].

25.5 Conclusion

In the treatment of BD, there are some non-recommended treatments for each phase that prescribers should be aware of. In this chapter, we summarized the non-recommended treatments for bipolar disorder, mania, depression, maintenance, mixed features, and BD in special populations. The most frequent non-recommended treatments for BD are summarized in Table 25.1. These results come from a systematic review of CPGs, which are widely available and reliable tools for guiding evidence-based prescription practices. As discussed in this chapter, there is inconsistent adherence to the CPGs among practitioners for various reasons, including gaps in the CPGs themselves. The goal of this chapter was to clarify the non-recommended treatments for BD. Ideally, practitioners will not employ these therapies when treating BD in order to promote the best outcomes for their patients and prevent unsafe or ineffective treatment. In this chapter, we also explored possible reasons for discordant prescribing habits and potential interventions to promote better practice in the future.

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Chapter 26

Lithium



Claire O'Donovan and Martin Alda

26.1 Introduction

Lithium is one of the oldest treatments in psychiatry. It is the third smallest element in the periodic table, a simple ion with an atomic weight of 7. Available in the form of several salts, it has been used in the treatment of certain psychiatric disorders since the middle of the nineteenth century. The most notable description of the effects of lithium in periodic depression was given by Carl Lange in the 1870s. In the twentieth century, lithium was “rediscovered” by John Cade who described the beneficial effect of lithium specifically in patients with mania [1]. Clinical studies in Australia and Denmark in the 1950s and 1960s established lithium not only as an effective antimanic agent but also as a unique medication for the prevention of manic and depressive recurrences. Yet, at the same time, the efficacy of lithium continued to be questioned in spite of the accumulating data from randomized and observational trials. In the last three decades, the position of lithium has been strengthened owing to double-blind registration trials of newer medications. These studies, often enriched for acute efficacy of the newly tested mood stabilizers, used lithium as a comparator and established its evidence in bipolar disorder as a first line. A comprehensive overview of the history of lithium in psychiatry can be found in Schioldan [2].

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26.2 Pharmacology of Lithium

Decades of research have generated a number of hypotheses about lithium's *mechanism of action*. Investigations of blood chemistry, blood cells and fibroblasts, animal studies, and brain imaging among others suggest that the lithium ion affects multiple biochemical and physiological processes. What is still missing is the link that reliably maps such mechanisms to the clinical effects [3]. The early investigations focused on electrolyte changes observed both in the course of bipolar illness and during the treatment with lithium. With an expanding spectrum of research methods, the focus of research shifted to neurotransmitter changes, showing that lithium enhances serotonergic transmission, and then to ion membrane transport with important observations of the role of Na^+/K^+ ATPase possibly as an etiological factor in bipolar disorder and a target of lithium. Later, a number of studies demonstrated the effects of lithium on signal transduction, namely G proteins, cyclic adenosine monophosphate (cAMP) and adenylate cyclase, and interaction with the phosphoinositol system by blocking the enzymes inositol monophosphatase and inositol polyphosphate-1-phosphatase. The inhibition leads to a decreased availability of inositol and several downstream targets including the protein kinase C activity, and reduced calcium release from intracellular storage sites [4, 5]. Another molecular target of lithium is the inhibition of glycogen synthase kinase 3 (GSK3) as well as regulation of cAMP response element binding protein (CREB), increased expression of neurotrophic factors, including bcl-2, changes in mitochondrial function, and oxidative phosphorylation—see review [3] for more details. The multitude of effects on different biochemical and molecular levels inevitably leads to a question of whether there is a common denominator to most or all. One such possibility could be the competition of lithium with magnesium, which is an important cofactor of a number of enzymes and its ion has a radius close to that of lithium. Ultimately, the biochemical effects translate into multiple physiological effects ranging from circadian regulation, neuroprotection, to neural plasticity.

The *pharmacokinetics* of lithium preparations is usually described by either one- or two-compartment model. The absorption rate and plasma peak levels vary depending on the type of salt and whether the preparation is a slow or regular release. Lithium is eliminated almost exclusively via the kidneys. The terminal half-life of lithium is dependent on the glomerular filtration rate and in healthy people ranges from 18 to 36 h. Less considered but potentially relevant clinically is the distribution of lithium between the extra- and intracellular compartments. The ratio of the intra- and extracellular concentration depends on several active membrane transport processes and on passive diffusion. The transporters, in particular Na^+/K^+ ATPase and Na^+/H^+ exchanger are under genetic control and have been studied as putative risk factors for bipolar disorder as well.

26.3 Lithium in Psychiatry

On a clinical level, lithium is useful in several psychiatric as well as non-psychiatric indications. In psychiatry, they include acute effects in mania and depression, augmentation of antidepressants, long-term mood stabilizing effects, and a reduction of suicidal behavior [6]. It has been also tested in mild cognitive impairment for the prevention of progression into dementia. Outside psychiatry, lithium has been shown to stimulate the production of white blood cells and to have antiviral effects.

26.4 Treatment of Mania

The first modern use of lithium dates to the 1940s. John Cade treated 19 inpatients with diagnoses of mania, schizophrenia, and melancholic depression [1]. He observed a distinct response in patients with mania while the other groups showed no improvement. Since then, numerous studies and several meta-analyses confirmed the initial observations [7, 8]. Practically all guidelines for the treatment of bipolar disorder consider lithium among the first-line antimanic treatments. However, it is used less than other classes of medications (anticonvulsants and particularly antipsychotics) for several reasons. The antimanic response to lithium takes longer and lithium is often perceived as more difficult to use. The distinct advantage of lithium in mania is its superior long-term efficacy. The long-term data for the other antimanic medications are comparatively limited [9], making the transition from acute to maintenance treatment less straightforward.

26.5 Lithium for Bipolar Depression

Compared to the clear evidence of antimanic efficacy, the effect of lithium on bipolar depression continues to be debated. Several studies, both controlled and observational, showed a benefit both in monotherapy and in combinations. However, pooled data from multiple trials suggest a small-to-moderate effect at best [10]. Given these considerations, lithium may be recommended mainly in patients with previously documented good response and/or in those at risk of suicide (see below). The low efficacy of lithium in bipolar depression also needs to be put in the context of limited benefits of most treatments for bipolar depression to date, and bipolar depression remains a major unmet need.

26.6 Long-Term Treatment of Bipolar Disorder

Prevention of recurrences of bipolar disorder is the most important and clinically relevant role of lithium. Both randomized clinical trials and meta-analyses support the long-term benefit of lithium, e.g. [11, 12] with a stronger effect on the prevention of manic versus depressive recurrences [13]. The naturalistic and cohort data complement these meta-analyses, add valuable information about the efficacy of lithium beyond the usual 6–24-month-long trials, and generally argue for the superiority of lithium over other commonly used medications [14].

The response to lithium, however, is not universal, and in most recent data, it is only about 30% of the patients who show full therapeutic response with an additional third achieving only partial response. Given the highly variable clinical course of bipolar disorder with many patients experiencing spontaneous remission, we need long observation to establish whether a given patient is responding to treatment or not. Furthermore, the time to response also varies, with some patients stabilizing within weeks and yet others experiencing mood fluctuations and breakthrough symptoms for many months before achieving full remission. Therefore, it is clinically important to identify those unlikely to respond as early as possible. A number of studies attempted to find predictors of lithium response and their results have been summarized by Hui et al. in a meta-analysis [15]. The most significant predictors (or rather correlates) were the absence of rapid cycling, absence of psychosis, mania-depression polarity sequence in those with multiphasic episodes, family history of bipolar disorder, and later illness onset as well as shorter pre-treatment illness duration. Similar results have been reported by Nunes et al. in a large study using machine learning methods and out-of-sample prediction [16]. A good response to lithium was predicted by fully episodic course prior to treatment, low rates of rapid cycling, psychiatric comorbidities, and low rates of psychotic symptoms, especially mood-incongruent ones. Subsequent analysis of the same sample showed that “prototypical” responders and non-responders could be differentiated on the basis of whole-genome markers with a classification accuracy of 88% [17]. An earlier single study also suggested that response to lithium is familial and that having a close relative who has benefited from lithium increases the likelihood of a good response more than three times [18]. Taken together, these data suggest that responders to lithium may constitute a distinct subtype of bipolar disorder corresponding to the “classical” Kraepelinian” clinical profile [19–21]. It is important to remember that partial response/non-response in particular, can be also due to factors only indirectly related to bipolar disorder, such as non-adherence, substance abuse, or insulin resistance [22].

26.7 Treatment of Major Depression

In a systematic review, Undurraga and colleagues concluded that lithium has not been adequately tested in acute treatment of unipolar depression [23]. On the other hand, there is good evidence that it is useful as an augmentation of antidepressant

treatments in acute episodes [24, 25] as well as being comparable to antidepressants in its ability to prevent recurrences of major depression [23]. It has been speculated that the antidepressant-augmenting effect is most relevant in the so-called pseudo-unipolars: patients who suffer from an illness that is essentially bipolar disorder but have not experienced a manic or hypomanic episode yet, or possibly ever. In fact, such patients are not rare—most forms of bipolar disorder start with episodes of depression, and the interval from the first depression to the first mania is highly variable; it can last many years. Also, family studies consistently report an increased risk of not only bipolar disorder but also unipolar depression in relation to bipolar probands (see the chapter on genetics in this volume).

26.8 Lithium Reduces the Risk of Suicide

Bipolar disorder has increased mortality with a standardized mortality ratio at least twice that of the general population [26]. Systematic observations of patient cohorts treated with lithium and followed longitudinally noted a diminished mortality in general, and decreased risk of deaths due to suicide and cardiovascular causes in particular [27]. The effect of lithium on suicide risk in bipolar disorder has been studied in both observational studies and documented in randomized clinical trials with data summarized in several meta-analyses [28, 29]. This effect has been attributed mostly to the mood-stabilizing effect of lithium. However, it is possible that the anti-suicide effect of lithium is due to a distinct mechanism as suggested by Ahrens and Muller-Oerlinghausen who found a substantial reduction of suicide risk even in patients who continued experiencing mood episodes under lithium treatment [30]. Replicated intriguing reports described reduced risk of suicide in geographical areas with higher concentration of lithium in drinking water. A systematic review of 15 studies from diverse countries concluded that there was, indeed, an inverse relationship between lithium concentration and suicide mortality [31].

26.9 Neuroprotective Effect of Lithium

Apart from being used in people with mood disorders, lithium has several other potential applications. Of major interest is its neuroprotective mechanism first shown in animal and brain imaging studies. Overall findings of these studies point to increased (or preserved) gray matter volumes and better white matter integrity in lithium-treated individuals [32, 33]. The preliminary data from the International Group for Study of Lithium (IGSLi) suggest that the neuroprotective effect may be independent of recurrence prevention [34]. The fairly strong evidence of an increased cortical and subcortical gray matter on lithium raised a question of whether lithium could be useful in various neurodegenerative disorders. So far, the most compelling data are from a study of mild cognitive impairment by Forlenza et al. [35].

26.10 The Clinical Use of Lithium

Despite the gold-standard status of lithium and its extensive clinical history, the use of lithium is in decline. A recent review of 20-year trends reveals a decrease from 30.4% to 17.6% in the time frames of 1997–2000 versus 2013–2016 [36]. It has been referred to as a “Cinderella” drug deserving to be well-valued but instead often ignored. Several key factors are thought to be relevant to this. Firstly, there is the issue of stigma as lithium became inextricably associated with the severe illness of manic depression, as one of the earliest psychotropics, in the 1960s and 1970s. Thus, it is seen as a “serious drug,” while SSRIs, atypical antipsychotics, and anti-convulsant medications have had broader usage not only in major psychiatric illnesses, and better public relations from pharmaceutical companies. This continues to be a relevant stigma for patients in considering the option of lithium. Psychiatrists and family physicians, particularly the younger cohort, are not comfortable with the use of lithium, its narrow therapeutic index, the need for regular blood monitoring, the risk of toxicity and overdose, drug interactions, concern about cognitive flattening, and the long-term potential for renal failure. This is negatively compared to more recently developed drugs, which have more common long-term metabolic risks such as severe weight gain, diabetes, hyperlipidemia, cardiovascular risk, hyperprolactinemia, somnolence or activation, sexual side effects, extrapyramidal and/or tardive symptoms, rare neuroleptic malignant syndrome for antipsychotics, as well as common congenital/neurodevelopmental malformations, hyperammonemia and weight gain with divalproex, and potentially lethal Stevens–Johnson syndrome with lamotrigine. So, for example, while quetiapine tends to be viewed as more benign than lithium, the CANMAT Guidelines rank it as similar to lithium for safety concerns, and less tolerable than lithium in the short term [9]. Paradoxically, lithium has been gaining in popularity in the non-psychiatric sphere of longevity, in tiny over-the-counter doses, touted as a naturally occurring element, nutritionally available from water and plant foods, and providing immune benefits and neuroprotection to the brain [37].

26.11 Choosing Lithium and Lithium Adherence

The two issues here are encouraging patients to choose lithium if it is the most appropriate medication, and achieving lithium adherence. The average length of lithium adherence by patients in a sample of 1500 patients was 76 days [38]. The risk of relapse in bipolar disorder is related both to non-adherence and early symptoms leading to non-adherence, with consequent full relapse. Non-adherence can be mitigated by a number of factors that can be addressed: attitude including stigma, beliefs in relation to the illness and medication, illness denial, pursuing the “highs,” as well as physician factors such as comfort level using lithium, the therapeutic alliance and providing psychoeducation. Attention to these factors can more than

double adherence rates [9]. This is especially important when there is a history of non-adherence leading to relapse, giving another opportunity for reviewing barriers to adherence. The same strategies can be used in forecasting non-adherence with early symptoms of relapse in relapse prevention work. Socratic questioning in a collaborative fashion with the patient is most likely to yield the best outcome. It is important that patients receive adequate rationale and information on using lithium both verbally and in written/electronic form and this information should be repeated regularly and accessible to the patient [e.g., https://www.nami.org/NAMI/media/NAMI-Media/Research/Lithium_Jan-2023.pdf; accessed 2023-12-07)].

26.12 Lithium Initiation, Dosing, and Blood Levels

Before lithium initiation, a baseline urea, creatinine, electrolytes, eGFR, TSH, calcium, parathyroid hormone, and urinalysis should be assessed. If the patient is over 40 years old, an ECG may be recommended. Baseline weight and height should also be measured. Initiation of lithium is often at 300 mg twice daily in order to minimize side effects. A lithium level should be taken 5–7 days later when a steady state is achieved and at this stage, all doses may be shifted to nighttime. The typical dose range is 900–1800 mg, except in the elderly when it may be lower. A lithium level and TSH should be repeated every 6 months and the other tests repeated yearly, or as clinically indicated [9].

It may also be helpful to measure a 24-h urine volume and urinary creatinine clearance before commencing lithium and then once a year. This will provide even more accurate kidney function provided that the urine collection is complete. Height and weight need to be stated in the laboratory request and serum creatinine tested within 24 h for calculation. The 24-h urine volume, often as high as 8–12 L, urine osmolality less than 300 mOsm/kg along with questions about polyuria, nocturia, and polydipsia will assess for nephrogenic diabetes insipidus [NDI].

Unlike most other psychiatric medications, lithium has reliable therapeutic plasma levels which are measured 12 h after the last dose for accuracy. While the typical recommended range in guidelines now is 0.6–0.8 mmol/L, this should be personalized based on clinical response and tolerability, between 0.4 and 1.0 mmol/L [39].

In severe mania, time is of the essence, and faster-acting agents such as atypical antipsychotics are started initially in combination with lithium, or there is a later addition of lithium for prophylaxis in the following 3 months. Care should be taken to consider the taper of the atypical antipsychotic after 3 months as one-third of patients may do well on lithium monotherapy. Overall, the long-term lithium level should be kept to a minimum for clinical efficacy and measured 6-monthly or as clinically needed. Changes in potential interacting medications, e.g., short-term use of non-steroid anti-inflammatory drugs or factors affecting renal function, require a lithium level 1 week later and 1 week after any necessary adjusting of dose. Almost all of lithium side effects are dose/plasma level related.

Plasma levels correlate only partially with brain concentrations and typically the steady-state concentration in the brain takes longer to reach. In patients with an unusual dose–response relationship (side effects with very low plasma levels or non-response and no side effects with high levels), erythrocyte lithium concentration can provide useful guidance.

While there are occasional patients, particularly in the family of lithium responders, who respond almost immediately to lithium, its full benefit and prophylaxis take between 6 months and a year, with benefits accruing over time [40].

26.13 Lithium Use in Special Populations

Issues with lithium in the older population relate to side effect profiles, changes in both pharmacokinetic and pharmacodynamics, and in particular age-related decrease in glomerular filtration rate. A lithium level of 0.4 mmol/L in an older population is roughly equivalent to a level of 0.8 mmol/L in the general adult population because of increased permeability of the blood-brain barrier, with implications for both the beneficial effect and neurological side effects of lithium in old age. Lithium should be started at 150–300 mg. Lithium levels should be measured after 10–12 days given the slower time to steady state. Lithium and renal monitoring may be considered as often as every 3 rather than 6 months, and a close eye should be kept on concomitant medications and medical conditions [9].

Women of childbearing age should have contraceptive counseling and a pregnancy test prior to starting lithium, and counseling should be provided if there is a planned pregnancy. If lithium is necessary, special caution should be taken in the first trimester of pregnancy because of the risk of Ebstein's anomaly in 1:20,000 live births. There are also issues with hypotonicity that need to be monitored in the neonate, and lithium is usually considered contraindicated in breastfeeding. Special attention should be given to thyroid levels during pregnancy and postpartum. It is sometimes possible to defer lithium to the second trimester based on prior frequency of illness or substitute at least temporarily, a medication with a better profile in pregnancy based on up-to-date data. The minimum level of effectiveness should be used.

Lithium levels tend to change dramatically in pregnancy in relation to cardiac output, and the dose may need to be increased by as much as a third to maintain lithium level and the level should be monitored as frequently as weekly or biweekly. If delivery is planned, lithium can be skipped for 24 h, because of the rapid elevation in level with fluid change, and then immediately re-initiated on day 1 after delivery, targeting the original dose, as postpartum is an extremely high-risk time for relapse. It is important to maintain hydration during delivery and blood levels should be twice weekly for the first 2 weeks postpartum [41].

26.14 Lithium Side Effects and Toxicity

Significant side effects with lithium can be avoided if lithium can be introduced slower than typically described (see above), something more possible when lithium is introduced as the prophylactic agent, while another drug is used for managing acute symptoms. A slower titration is also helpful when re-starting lithium in patients who tolerated lithium poorly in the past. Other strategies include twice-daily dosing in the first week or two, use of an extended-release lithium, a different commercial preparation, and in the case of gastrointestinal side effects, a trial of lithium citrate in liquid form. The most common side effects and suggestions for their clinical management are listed in Table 26.1.

Table 26.1 Most common side effects of lithium

Acute side effect	Prevalence	Management
Nausea	10–20% early on. Vomiting is rare and typically associated with high lithium levels [40, 42, 43].	Wait for dissipation, slower titration, divided dose, take after meals, change formulation, extended-release lithium, lithium citrate.
Diarrhea	Up to 10%. It can be seen both early and late as well as in lithium toxicity [41–43].	Dose-related, especially above 0.8 mmol/l decrease dose. Try switching away from sustained release. Monitor lithium levels with dehydration. It may settle with time or decrease frequency [41–43].
Acute polyuria/polydipsia	Patient may be very thirsty and wake at night with nocturia. Acute rates are up to 70% and very early on. Defined as >3 L per 24 h. It is related to serum level and combination with atypical antipsychotics. Later nephrogenic diabetes insipidus (NDI), which may or may not be preceded by earlier symptoms occurs in 25–40% and is reviewed below [40–43].	Reversible with lower levels and discontinuation. Advise rehydration with water and not calorific drinks. Nighttime dosing may exacerbate nocturia. For urine volumes substantially higher, consider amiloride diuretic at 5 mg BID or hydrochlorothiazide 50 mg. The latter may require dose reduction and monitoring plasma potassium [40–44].
Neurological movement disorder	Fine action tremor in approximately 27%, more frequent in combination with other psychotropics and with caffeine or anxiety. Cerebellar symptoms are occasionally seen including ataxia at normal levels but more common with toxicity [40, 42–44].	Tremor is occasionally an issue sufficient to lower dose or add propranolol 10–20 mg BID, or propranolol or low dose lorazepam prior to social/performance occasions. High dose pyridoxine (1 g) can be sometimes useful [40–44] Muscle twitches respond to lower dose.

(continued)

Table 26.1 (continued)

Acute side effect	Prevalence	Management
Weight gain	Past data reported weight gain in 11–65% in the order of 0–6 kg and aggravated by other psychotropics [40]. Typically occurs in first year. A recent case–control study showed a non-significant trend for weight gain (10% of baseline) versus lamotrigine as the only weight-neutral agent, with greater weight gain with olanzapine, valproate, and quetiapine [42, 43, 45, 46].	Educate and monitor in first year with dietary advice. This is a common cause of non-adherence. Monitor use of other psychotropics, particularly olanzapine, valproate, and quetiapine.
Cardiovascular	Sinus bradycardia is commonest. There may also be sinus node dysfunction, QTC and T wave abnormalities, less common in the young and in monotherapy [43].	ECG should be monitored when there are concomitant medications prolonging QTC or aggravating sinus node dysfunction and in older age.
Endocrine	Presence of goiter is four-fold the general population. Rates of hypothyroidism, both clinical and subclinical, occur at a six-fold rate in the general population and are more common in women. Thyroid antibodies are common [40, 41, 43, 45]. There are conflicting results about risk of hyperthyroidism [45]. Hyperparathyroidism: Acutely, elevations in parathormone (PTH) are seen but with normal calcium and no symptoms and are reversible. There is a 1.5-fold increased risk of hypercalcemia in patients on long-term lithium [45, 47].	Assess for goiter. Measure TSH, T3 and T4, q6-monthly, and, if clinically indicated, supplement with T4 to normalize. In rapid cycling, consider a mix of T3 and T4. Hypothyroidism is common in the general population, increases with age, and may be familial. Hyperparathyroidism: monitor PTH and calcium yearly and more frequently if PTH is raised. If hypercalcemic or has symptoms (“bones, groans or abdominal moans”) refer to workup for all causes. Consider, reducing or discontinuing lithium, trial of cinacalcet, or may need surgery in rare cases. The cut-off plasma calcium for specific treatment is usually 2.85 mmol/L [47].
Cognition	An experience of flattening early on may settle. Fatigue, sedation, decreased processing speed and memory as well as psychomotor function are more common, with better results in monotherapy. Lithium compares favorably with quetiapine monotherapy for cognitive effects in randomized clinical trials. Data in good lithium responders report improved current and future cognition [40, 42, 43].	Decrease dose. Consider modafinil or methylphenidate [42].

(continued)

Table 26.1 (continued)

Acute side effect	Prevalence	Management
Skin	Range 3–45% depending on criteria. New onset or exacerbation of skin disorders, particularly maculopapular rashes, folliculitis, psoriasis, and acne [40, 42, 45].	May respond to lithium discontinuation or ameliorate with dose reduction. Lower dose or discontinue. Treatment of specific condition by primary care practitioner or dermatologist is commonest.
Sexual	Literature is sparse in this area. Estimated prevalence of 30% (reduced libido or erectile dysfunction). This is a cause of non-adherence [42, 43].	Lower the dose. Trial of phosphodiesterase inhibitor (sildenafil, tadalafil) [43].

26.15 Controversy: Lithium and the Kidney

There continues to be debate regarding renal dysfunction, and more importantly renal failure in patients on long-term lithium especially in the absence of an episode of lithium toxicity. Of renal effects, by far the most common is diminished concentration ability marked by polydipsia/polyuria/nocturia which can occur in as many as 40% of patients early on in treatment. This often leads to sleep impairment, embarrassment, and often calorie-laden drinks, a hidden cause of weight gain with lithium. It does merit attention to fluid intake and hydration, and a yearly 24-hour urine volume as well as urine osmolality. A level above 3 L requires review. A more insidious onset, often after more than 15 years, heralds nephrogenic diabetes insipidus (NDI), which is more likely to be irreversible and may merit lowered lithium level or sometimes discontinuation. Treatment is commonly with amiloride 5–10 mg, or occasionally hydrochlorothiazide 25–50 mg. The latter will likely require dose reduction of lithium due to reduced renal clearance [42]. In terms of prevention, the effect is dose-related and less likely on single-day dosing particularly with the higher levels [48, 49].

Chronic renal impairment related to the separate process of tubulointerstitial nephropathy tends to occur after 10–20 years and the risk accumulates with the dose, duration, and especially any instances of lithium toxicity. There continues to be debate about any increased risk of renal impairment when age and comorbid conditions, with associated metabolic effects, are taken into account.

A meta-analysis in 2021 suggests that the risk of chronic kidney disease with lithium is double that of non-lithium-treated patients in the very long term, at 25% [50]. This is similar to the finding in a sample of 1012 lithium-treated patients (1.3-fold) [51], while a population-based case–control study in 2022 suggested up to five-fold, more consistent with the older literature. In a quarter of cases, other risk factors are present, especially hypertension and diabetes.

The decline in eGFR typically starts after more than 10 years of treatment and a recent cross-sectional cohort study reported a decline of 0.54 mL/min per lithium-treated year [51]. End-stage renal disease has been seen in 0–0.5% of all patients [52]. There may be a minority where the eGFR starts to drop earlier in treatment and a genetic component has been questioned. An eGFR of 40 mL/min generally indicates irreversibility [52]. A recent study in a cohort of patients who stopped lithium suggested reversibility or at least stability at a level of 60 mL/min or stage 3 kidney disease (where 90 mL/min is considered normal) [53]. Referral to nephrology is suggested if eGFR is <30–40 mL/min or the decline in eGFR is more than 4 mL/min/year [43]. Nephrotic syndrome and renal stones secondary to hypercalcemia (see below on hyperparathyroidism) are rare side effects [54].

In practice, trends in eGFR and creatinine levels should be followed, and attention paid to control of comorbid risk factors such as diabetes and hypertension. Minimum required levels for prophylaxis should be used, single dosing and, perhaps an extended release to avoid any toxic peak concentrations. As the patient ages, GFR naturally decreases and consequently, lithium levels rise, necessitating more attentive monitoring and dose adjustments.

If the eGFR declines below normal, it is necessary to review all medications and investigate for all possible causes of renal impairment, especially screening for hypertension and diabetes. If lithium appears to be the cause or a contributing factor, then collaborative decision-making on the cost–benefit of lithium starts. There is no established level of eGFR where lithium is discontinued and the timing of referral to nephrology will vary by health care system. In most cases, the patient is in their senior years, having been on lithium for 20–40 years, and there are other relevant factors. Any decision will depend on the likelihood that the patient would respond to a different agent as well as on the severity and impact of the past illness episodes. In the subgroup of excellent lithium responders, it is less certain that other medications will substitute effectively.

Given the rarity of lithium nephropathy in all-cause renal failure, the question more commonly is how to deal with lithium in the context of general renal impairment. Lithium can be continued if essential, gradually tapering the dose to provide the same level, using as little as 150 mgs. Given steady-state levels, lithium does not need to be taken daily, and this can be continued through dialysis with careful monitoring for those where no other drug is effective. Lithium is a good choice of mood stabilizer for patients in dialysis.

In cases where lithium is discontinued, it is important, if possible, to do this over a minimum of 2 weeks and preferably over months. Rapid lithium discontinuation may lead to rapid relapse and the possibility of increased suicidality [55].

26.16 Lithium Drug Interactions, Toxicity, and Overdose

Lithium is well-known for its potential for drug interactions, and these become more common as medications are added and age increases. The key drugs of concern are those that alter hydration levels or impact kidney function. Nonsteroidal

anti-inflammatory drugs are the biggest risk as they are commonly used and available without prescription. Their impact is variable, and usually, they increase lithium levels by 10–25%.

Diuretics which are also commonly used, mostly increase lithium plasma level, with the exception of osmotic diuretics such as mannitol which actually decrease the plasma level. Of greatest concern are thiazide diuretics (e.g., hydrochlorothiazide), with a level increase of approximately 25%, and loop diuretics (e.g., furosemide); potassium-sparing diuretics such as amiloride are considered the safest.

Angiotensin-converting-enzyme inhibitors, most commonly used for hypertension and heart failure (e.g., perindopril), cause a significant increase in plasma levels, often with delayed toxicity. Angiotensin receptor blockers increase plasma levels to a lesser degree. It is generally advised that the dose be decreased by 20% in advance for thiazide diuretics and ibuprofen; in other cases, the dose should be adjusted based on the plasma level. Other drug interactions can occur with lithium through less-known mechanisms. Calcium channel blockers such as verapamil, do not appear to increase lithium level, but do sometimes lead to signs of toxicity despite normal plasma lithium. Sodium bicarbonate lowers lithium level which presents itself as an issue if the patient is ingesting copious amounts of antacids or indeed a bicarbonate infusion was used. Caffeine, a methyl-xanthine diuretic, also lowers lithium which occasionally has presented itself as an issue when a patient abruptly discontinues caffeine. Lithium may prolong or potentiate neuromuscular blockers such as succinylcholine, and lithium combined with ECT may cause delirium post-treatment. This is usually managed by temporarily stopping or decreasing it at the time. For a more complete review of drug interactions, see Finley [56].

The patient with lithium toxicity may be initially asymptomatic but typically symptoms escalate at a level of 1.2 mmol/L and higher, and include aggravation of any previous side effects, muscle weakness, coarse tremor, ataxia, dysarthria, confusion, choreoathetoid movements, seizures, nausea, vomiting and diarrhea, brisk reflexes, muscle twitches, bradycardia, and confusion. Lithium toxicity can lead to irreversible brain and kidney damage and may be fatal. ECG changes include bradycardia, sinus node dysfunction, prolonged QTC and T wave changes, with a risk of arrhythmia. At lower levels, lithium is stopped, and the patient is managed supportively with saline infusion. With levels above 2.0 mmol/L, dialysis or less commonly extracorporeal exchange is indicated with rapid reduction in level to minimize the exposure to lithium toxicity. Patients benefit from repeated specific instructions on risk factors for toxicity including drug interactions with common over-the-counter medications and should be advised to double check with the pharmacist before taking newly prescribed medication. They also need to be aware of risk factors for dehydration including vomiting, diarrhea, heavy sweating, and elevated temperature, with instructions to halve or stop lithium for 24 h [42].

As reported earlier in this chapter, lithium reduces the risk of suicide. However, this does not imply an absence of the acute suicide risk and potential for overdose. A past history of overdose on lithium requires a careful individualized assessment in considering prophylaxis with lithium [57].

26.17 Conclusion

Lithium plays a key role in the management of bipolar disorder and treatment-refractory depression and has stood the test of time. Skills in the use of lithium are readily teachable, and skills in addressing stigma and fears in initiation and adherence come with clinical experience.

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Chapter 27

The Role of Antidepressants in Bipolar Disorders



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27.1 Introduction

Bipolar disorder (BD) is a chronic and recurrent illness characterized by the presence of depressive, manic, hypomanic, or mixed episodes alternated with periods of clinical remission or euthymia, in which a maintenance treatment is recommended [1, 2]. Individuals with BD can suffer long-term consequences, such as reduced functionality, impaired quality of life, or medical comorbidities [2].

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Bipolar depression is the predominant psychopathology in BD and is associated with increased morbidity and mortality from co-occurring medical disorders and suicide risk [1]. Risks for medical disorders, such as diabetes or metabolic syndrome, and cardiovascular diseases, and their associated mortality rates are higher than in the general population or other psychiatric conditions [3].

Bipolar depression is a key contributor to long-term dysfunction in individuals with BD due to psychosocial impairment, reduced work productivity, and comorbid substance abuse [4]. The diagnosis of bipolar depression is often delayed due to psychiatric comorbidity, the overlapping symptoms with unipolar depression, and also due to the difficulties in diagnosing lifetime hypomanic episodes or mixed features within depressive episodes. Its clinical approach becomes a challenge in different ways due to a number of factors including the relative paucity of studies in the area; the discrepancy in conclusions between meta-analyses; the debates on the specific role of antidepressants (ADs) for the treatment of bipolar depression, added to the fact that the approved therapeutic options are associated with limited response rates [3–6].

Actually, there are few treatments approved for the treatment of bipolar depression, bipolar depression being far less well investigated than unipolar depression, particularly with regard to long-term prophylaxis. Monotherapy with ADs is not recommended as a first-line treatment, and their use remains controversial [4], since they may entail an increased risk of manic or hypomanic episodes, especially in mixed states and rapid-cycling patients [3]. In this chapter, we will delve deeper into the role of ADs in bipolar depression. We will explore the profile of bipolar patients in which their use may be allowed and other specific populations in which AD use should be avoided.

27.2 Differences Between Unipolar and Bipolar Depression

According to the most commonly used classification systems, the same cross-sectional diagnostic criteria are used for bipolar and unipolar depression [7, 8]. Hence, the diagnosis of bipolar depression is based on the presence of previous manic or hypomanic symptoms. Given that some patients diagnosed with a major depressive episode may actually suffer from an undiagnosed BD and that therapeutic strategies differ between bipolar and unipolar depression, some studies have focused on the differentiation between both types of depression [9–11], since an initial misdiagnosis of BD results in the delay of appropriate treatment and the potential for mistreatment with AD monotherapy as a first option, which may subsequently increase the risk of recurrence and chronicity in this disorder.

Since diagnostic criteria for a major depressive episode do not differ between unipolar and bipolar depression, clinicians should be aware that specific symptoms have a higher probability of being associated with each diagnosis. Some of the symptoms that are more common in bipolar depression compared to unipolar depression include hypersomnia, hyperphagia or weight gain, anxiety, psychotic

features, mixed features, basal cyclothymic temperament, psychomotor retardation or agitation, as well as mood lability and cognitive impairment [11–14]. Conversely, patients with unipolar depression are more likely to display typical depressive symptoms, such as insomnia, depressive mood, and somatic and anxiety symptoms [11].

Neuroimaging evidence from magnetic resonance studies found that, compared to individuals with unipolar depression, participants with BD were more influenced by emotional and sensory processing when responding to their environment, with increased central executive network function during rest and cognitive tasks, reduced gray matter volume in the middle frontal cortex, and differences in the default mode network and salience network activities [9].

In addition, patients with bipolar depression are much more likely to have a family history of BD, have an earlier age of onset, a greater number of prior affective episodes, a globally increased instability of BD disease, and a history of treatment-resistant depression, or presenting irritability or mood elevation symptoms during AD treatment [11]. They may also display marked seasonality, with greater depressive episodes during winter and more prior suicide attempts compared to individuals with unipolar depression [11].

27.3 Antidepressant Use in Bipolar Depression

The use of ADs in patients with BD is still a matter of a long-lasting debate amongst experts in this field. Antidepressant treatment of bipolar depression has been associated with specific risks, such as manic switch and cycle acceleration. However, many clinicians use ADs in BD, especially in the management of severe depression that is resistant to mood stabilizers or available antipsychotics currently approved for bipolar depression [15]. The International Society for Bipolar Disorders (ISBD) task force reported that, according to the available literature, the evidence on the benefits and risks of AD treatment in BD is remarkably limited since BD has usually been an exclusion criterion in placebo-controlled studies [16]. Most clinical guidelines also mention that ADs should not represent a first-line treatment in bipolar depression [17, 18], that they should not be used in monotherapy, and that pharmacological treatment different from ADs should be considered before their use in bipolar depression.

A systematic review and meta-analysis, based on six placebo-controlled clinical trials, assessed the safety and efficacy of adjunctive second-generation AD therapy with a mood stabilizer or an atypical antipsychotic in acute bipolar depression. This found that second-generation ADs were associated with a small but significant improvement in depressive symptom scores; however, clinical response and remission rates did not differ significantly from placebo [19]. The study also suggested that ADs should be avoided as a maintenance treatment since their prolonged use was associated with an increased risk of treatment-emergent mania or hypomania [19]. The risk of the manic switch was found to be significantly reduced when ADs

were given in combination with a mood stabilizer and when new-generation ADs were used compared to old tricyclic ADs [15]. Thus, with regard to the use of ADs in clinical practice, it is important to be cautious and individualize their use, assessing potential benefits and risks case-by-case.

Despite expert recommendations, different studies report a frequent use of ADs in the clinical setting. A multinational, multicenter, observational cohort study that described the use of ADs in BD in real-life settings found that, even though antipsychotics were the most commonly prescribed drugs in mania and euthymia, ADs were the most commonly prescribed in depression, and their use was also frequent during euthymia and even during a mixed episode [20, 21]. A National Swedish Registry study including 3240 patients with BD showed that 34% of patients were treated with ADs as monotherapy, and 51% in combination with mood stabilizers, the most commonly used ADs were citalopram, sertraline, mirtazapine, and escitalopram [22].

The main issues associated with AD use in bipolar depression are their efficacy, the risk of a treatment-emergent affective switch, the risk of cycle acceleration, and the worsening of the depressive episode associated with the presence of mixed features. In this line, according to expert recommendations, ADs should be avoided as monotherapy in BD type I, and in BD types I and II with two or more concomitant core manic symptoms [16, 18]. As an acute treatment, adjunctive ADs should be avoided in BD types I and II when there are two or more core manic symptoms, in the presence of psychomotor agitation, rapid cycling, or mixed states, and should be used only if there is a history of positive response [16, 18]. As maintenance treatment, ADs might be considered in cases in which depressive relapses occur after stopping AD therapy and in those with a depressive predominant polarity.

A diagnosis of BD entails a high risk of mood recurrences in the postpartum period, with a special risk in women with previous postpartum episodes. With regard to bipolar postpartum depression, although ADs have been studied in combination with mood stabilizers, these drugs should be avoided due to the likelihood of elevated risk of induction of manic symptoms in the postpartum period [23].

27.4 Antidepressant Use in Bipolar Depression with Mixed Features

Patients with BD can present depressive episodes with mixed characteristics, and their early identification is crucial for proper management. In DSM-IV-TR, a mixed episode was defined as superposed manic and depressive episodes only in the context of BD type I, with a duration of at least 1 week [24]. However, in DSM-5, mixed characteristics were considered a specifier of the mood episode. This specifier is characterized by the presence of at least three nonoverlapping symptoms of the opposite pole during a major depressive episode or a manic or hypomanic episode for at least 1 week and can be applied to BD types I and II, as well as to

depressive episodes in major depressive disorder [8]. As a consequence, hypomanic symptoms do not determine the presence of BD in some cases.

Bipolar depression episodes with mixed features have been linked to a higher lifetime number of depressive episodes, a lower likelihood to respond to ADs, a higher prevalence of anxiety, substance use disorders, and other comorbidities, including cardiovascular diseases, and an increased risk of suicide [25–28].

The presence of mixed episodes during the course of illness was found in nearly 40% of BD type I patients treated with ADs followed for up to 20 years. In a logistic regression analysis, the use of serotonin and norepinephrine reuptake inhibitors was significantly associated with the occurrence of at least one mixed episode during follow-up ($p = 0.041$) [29].

Koukopoulos and his collaborators conducted a review study that revealed that, in 56% of the cases of agitated depression, the onset of agitation was related to pharmacological treatments, mainly ADs, and occurred shortly after the introduction of these treatments [25]. Some of the symptoms assessed to consider the presence of an agitated episode were psychic or motor agitation, insomnia, impulsivity, and suicidality, which are often observed in depressive episodes with mixed features. These results suggest that such states could be managed effectively by discontinuing ADs or avoiding their use and using mood stabilizers or other antimanic agents since ADs have the potential for inducing, maintaining, or worsening mixed features during depressive episodes. In a similar way, the presence of a “mixture” factor, defined as excited-anxious arousal as a core feature, including symptoms like anxiety, inner tension, suicide ideation, or psychomotor agitation, was associated with a more frequent use of ADs [30]. Among the most common intradepressive hypomanic symptoms, a systematic review reported irritability, motor agitation or restlessness, distractibility, racing thoughts, and flight of ideas, with less than 10% of the patients reporting euphoric mood, inflated self-esteem, or grandiosity [31].

The BRIDGE-MIX-II study assessed the presence of mixed symptoms in nearly 3000 depressed patients according to the DSM-5 criteria and found that several aspects of the clinical presentation of the major depressive episode with mixed features commonly seen in the clinical setting were not included in the DSM-5 diagnostic criteria for mixed characteristics [32]. In this study, the frequency of mixed features was determined by applying both DSM-5 criteria and a priori described research-based diagnostic criteria (RBDC) for mixed states. The results showed that 7.5% of patients fulfilled DSM-5 criteria for major depressive episodes with mixed features, and 29.1% for a predefined RBDC depressive mixed state. Here, the most frequent manic or hypomanic symptoms were irritability (32.6%), emotional/mood lability (29.8%), distractibility (24.4%), and psychomotor agitation (16.1%). Compared to DSM-5, patients with mixed features according to RBDC presented more robust associations with several illness characteristics of BD, including family history of mania, lifetime suicide attempts, atypical features, early onset, history of antidepressant-induced mania/hypomania, and lifetime comorbidity with anxiety, alcohol and substance use disorders, attention-deficit/hyperactivity disorder, and borderline personality disorder [32], which demonstrates an excellent specificity but low sensitivity for DSM-5 criteria. This led researchers to report the unsatisfied

needs of the DSM-5 regarding mixed features in depression, who proposed a deep revision of this specifier for future versions [33]. Regarding the presence of mixed characteristics and the use of ADs, this group demonstrated the association between mixed characteristics and a higher frequency of manic episodes associated with AD use, as well as higher treatment resistance and more often worsening of depression with the onset of irritability, regardless of the diagnosis of BD [34].

The antipsychotic and AD combination, and specifically the combination of olanzapine plus fluoxetine, was shown to predict a similar response in cases of depression with concurrent manic or hypomanic symptoms compared to olanzapine monotherapy, but did not increase significantly the risk for manic switch [35].

Mixed states set a complex challenge for clinicians, with consequently a delay in their detection, diagnosis, and management. The CANMAT guidelines recommend avoiding ADs in bipolar patients with mixed features, with the exception of an olanzapine-fluoxetine combination, and other options, such as asenapine and lurasidone, are recommended. For manic patients with mixed features, the use of antipsychotics, such as asenapine, aripiprazole, olanzapine, or ziprasidone, together with a mood stabilizer, is recommended [18]. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines focus on BD type I and recommend caution in the interpretation of most studies [36]. They recommend avoiding AD prescription to patients with BD with a mixed state, except for fluoxetine-olanzapine combination in mixed depression, as they may worsen the clinical state and increase the risk of suicidal behavior. They stated that olanzapine, paliperidone, and aripiprazole have the best evidence for the management of mixed manic states and that there was only enough evidence for recommending ziprasidone, carbamazepine, lurasidone, olanzapine, and electroconvulsive therapy for bipolar depressed mixed states. As maintenance treatment after a mixed episode, quetiapine, lithium, and olanzapine, either as a monotherapy or in combination, were the most recommended treatments for preventing new mixed episodes [36].

Thus, both guidelines identify the potential risk of the use of ADs in mixed states and show consensus in not recommending their use in these cases, even though risks vary depending on the type of ADs prescribed and clinical profiles. Experts recommend, in a mixed state, tapering or ceasing any prescribed AD, and adding an atypical antipsychotic drug to achieve clinical remission [18, 36, 37].

27.5 Antidepressant-Induced Mania and Hypomania

The main concern in the treatment of bipolar depression with ADs is their risk of inducing a manic or hypomanic switch. Antidepressant-induced hypomania/mania (AIHM) has been associated with increased mood cycling and worsened course of illness [22], and still remains a controversial concept for some reasons. For instance, it implies an attribution of causality instead of assuming a natural pattern of BD, as observed in cases of patients who experience manic or hypomanic symptoms without the use of an AD. Even though ADs are not recommended as first-line options

in BD, the available literature reports a prevalence of AD use of 46.9% in BD type II and 30.5% in BD type I [38].

Even though previous evidence highlights the potential risk of AIHM, an underestimation of the rates in randomized clinical trials compared to observational studies was demonstrated by an umbrella review [39]. A review conducted by Baldessarini and collaborators including 95,786 depressed patients and aiming to assess the diagnostic change from major depressive disorder to BD reported that AIHM occurred at an average frequency of 8.18% of cases; however, they could not establish to what extent antidepressant-associated mood switches disentangle non-diagnosed BD [40]. Other evidence in patients treated with a major depressive episode showed a prevalence rate of manic/hypomanic switch of 13.1% [41]. Evidence from a recent systematic review revealed AIHM in BD ranged from 17.3% to 48.8% and was more frequent with AD monotherapy compared to combination treatment with mood stabilizers, especially lithium, or second-generation antipsychotics (SGA) [42].

The controversy regarding the risk of AD use in bipolar depression led experts to define AIHM as a manic/hypomanic episode within 8 weeks after the initiation of the AD or an increase in its dose [43]. A National Swedish Registry Study aimed at assessing the risk of hospitalization due to a manic episode in BD patients treated with ADs found that the risk was 2.8 times higher with ADs in monotherapy compared to those not receiving AD treatments [22]. As an add-on therapy, the risk at three months was similar to monotherapy but lower at 9 months of follow-up. Generally, the risk of a mood change with ADs has been considered low, with a number needed to harm vs. placebo around 200; however, this switch can cause profound negative psychosocial consequences [44].

Some studies have assessed sociodemographic and clinical factors associated with AIHM and propose to individualize this risk according to patients' clinical profiles; for instance, psychomotor agitation was found to exhibit a higher risk compared to psychomotor retardation in patients with BD treated with ADs (21.5% vs. 17.6%, respectively) [12]. In a different study, patients with unipolar depression treated with ADs with a manic/hypomanic switch were compared to those with not having experienced this switch [41]. Manic/hypomanic switch was most frequently observed between 2 and 3 weeks after an increase of the ADs dose. Patients from the switch group included a greater proportion of male individuals and had a higher frequency of family history of BD compared to the non-switch group, which suggested a biological susceptibility in certain individuals [41]. In depressed bipolar patients, the AIHM during the first month following a new AD therapy was found in 4.8% of cases and was associated with lifetime manic, depressive, and total mood episodes, and with past AIHM. A higher score on the items of the Montgomery–Asberg depression rating scale related to pessimistic and suicidal thoughts was significantly associated with AIHM. The two most common factors associated with AIHM were the presence of past AIHM and the number of previous manic episodes, with an association between having presented more than four past manic episodes with a 2.84-fold increased risk of AIHM [45]. The STEP-BD study also explored variables associated with AIHM within the first 12 weeks after having started an AD

in patients with BD and found that a shorter duration of illness (odds ratio [OR] 1.02, 95% CI: 1.01–1.04) and a history of multiple AD trials (OR 1.73, 95% CI 1.38–2.16) were more likely to report a history of switch than other patients [46]. Other factors that have been associated with AIHM are earlier age at onset, the depressive polarity of the first affective episode, history of previous hospitalizations, lower rate of responses to ADs, and substance abuse [42, 47].

Evidence from genome-wide association studies (GWAS) on manic switch following bipolar depression in BD type I, defined as a manic episode occurring within 8 weeks of remission from an acute depressive episode, found the top SNP rs10262219 on chromosome 7 as the strongest allelic association with manic switch, which was however not significantly replicated. The research group observed in logistic regression analysis that the CC genotype of rs10262219 (odds ratio 3.0; 95% CI: 1.7–5.2) and AD treatment (OR 2.3; 95% CI: 1.4–3.7) significantly increased the risk of manic switch with a joint effect (odds ratio 5.9; 95% CI: 3.7–9.4), concluding that both factors jointly increased the risk of manic switch after bipolar depression [48].

Other reports showed that the risk of manic switch in monotherapy was significantly higher than combination treatment with antipsychotics or mood stabilizers and that patients with a history of manic switch were more likely to receive ADs for no more than 3 months ($Z = 3.298$, $p < 0.001$) [49]. This study suggested that the risk of the manic switch is especially prominent in the first months of AD use and that in the long term, the addition of mood stabilizers to ADs may decrease the risk of switches [49]. In young patients (ages 6–18 years) with BD, both AD monotherapy and polytherapy exhibited higher risk of manic switch within 6 weeks than SGA monotherapy, mood stabilizer monotherapy, or SGA-mood stabilizer polytherapy (AD monotherapy vs. SGA monotherapy, hazard ratio [HR] 2.87 [95% CI: 1.10–7.49]; AD monotherapy vs. mood stabilizer monotherapy, HR 1.41 [95% CI: 0.52–3.80]; AD polytherapy vs. SGA-mood stabilizer polytherapy, HR 1.61 [95% CI: 0.90–2.89]), although only the comparison between AD monotherapy and SGA monotherapy was statistically significant [50]. This supports the recommendation of being cautious in clinical practice regarding AD prescription in BD.

Specific AD classes confer a higher risk for a manic switch than others. For instance, selective serotonin reuptake inhibitors and bupropion represent the lowest risk [42]; in contrast, serotonin and norepinephrine reuptake inhibitors are associated with a high risk [16, 18]. Tricyclic ADs also seem to display a higher risk for manic switch compared to other ADs [42, 51]. The STEP-BD study found in patients who had never switched to mania/hypomania a significantly increased risk in those taking tricyclic ADs (OR 7.80, 95% CI: 1.56 to 28.9), even though risk also existed with serotonin reuptake inhibitors (OR 3.73, 95% CI: 1.98 to 7.05), or bupropion (OR 4.28, 95% CI: 1.72 to 10.6). The switch was less common during treatment with electroconvulsive therapy or monoamine oxidase inhibitors compared to other ADs [46].

27.6 Antidepressants and Rapid Cycling

Bipolar depression is the major clinical challenge in the treatment of BD. Manic switch and rapid cycling are some of the risks associated with AD treatment in BD. Rapid cycling is defined as the presence of at least four mood episodes in the previous 12 months that meet the criteria for manic, hypomanic, or major depressive episode and are demarcated by partial or full remission for at least 2 months or a switch to an episode of opposite polarity [52]. For individuals with rapid cycling, they do not seem to be helpful for the treatment of bipolar depression and may accelerate cycles [53]. In fact, rapid cycling is a risk factor for AIHM, and special prevention is needed when other factors, such as mixed features or substance abuse, are present.

The STEP-BD study evaluated rapid cycling as a response in patients randomized to continue vs. discontinue AD treatment over 3 years, after an initial response for an acute major depressive disorder [54]. From the group who continued on ADs, rapid cycling patients experienced 268% more total episodes per year, and 293% more depressive episodes per year, compared to nonrapid cycling patients ($p = 0.03$). In contrast, no such differences were found between patients with and without rapid cycling who had discontinued AD treatment. When both rapid cycling groups were compared, a higher mean number of episodes per year was found in those who continued the AD treatment, but the difference was not statistically significant [54].

A meta-analysis aimed at collecting the available evidence for efficacy, acceptability, and tolerability of treatments in patients with rapid cycling BD showed that the only ADs suggesting significant depression benefits were fluoxetine combined with olanzapine, citalopram, and venlafaxine [55]. Most of these effect sizes were from only one trial per treatment. Venlafaxine had the highest effect sizes but most safety concerns, while selective serotonin reuptake inhibitors had moderate efficacy and safety, and bupropion was reported to be both effective and safe. However, this meta-analysis did not analyze manic switch rates, or the number of episodes throughout long follow-up periods, although it noted reduced cycling with bupropion and increased risk with venlafaxine compared to other ADs.

Even though ADs worsen rapid cycling in people with BD, it is worth considering the clinical profile, the type of AD, the treatment duration, and the combination administered, since an AD paired with an antimanic agent can promote longer periods of euthymia [55].

According to a systematic review focused on the treatment of rapid cycling, the most recommended treatments are aripiprazole, olanzapine, and valproate for acute manic or mixed episodes, and quetiapine for acute depressive episodes. Regarding prophylactic treatment, aripiprazole and lamotrigine are recommended [56]. Lithium has been found to be as efficacious in rapid and nonrapid cycling patients [56]. There is a consensus not to use ADs in BD and rapid cycling, although the evidence is inconclusive. For patients presenting with an acute depressive episode, NICE guidelines recommend the use of an olanzapine-fluoxetine combination, lamotrigine, or quetiapine [57]. For relapse prevention, they recommend lithium, and if insufficient, adding valproate [57].

27.7 Antidepressants and Suicidal Behavior

Even though ADs are known to confer some risk of a manic switch, they are often used in bipolar depression with suicidal ideation. However, AD use in BD has been associated with an increased risk of suicidal behaviors [58]. In fact, the new onset of suicidal thoughts after the introduction of an AD in patients with a major depressive episode should raise the clinician's suspicion of the likelihood of an underlying bipolar illness [58].

Reports from a 27-year longitudinal study examined the risk of suicidal behavior associated with ADs in BD and major depressive disorder [59]. This study found that more severely ill participants were more likely to initiate AD treatment. Patients with BD type I had a significant reduction in risk of suicidal behavior by 54% (HR 0.46; 95% CI: 0.31–0.69; $t = -3.74$; $p < 0.001$) during periods of AD exposure compared to matched unexposed intervals. Similarly, the risk was reduced by 35% (HR 0.65; 95% CI: 0.43–0.99; $t = -2.01$; $p = 0.045$) in BD type II. This suggested that AD treatment protected patients with BD from suicidal behavior [59].

Nevertheless, agitated or mixed depression often responds to AD drugs with increased agitation and insomnia, with a higher risk of presenting with psychotic symptoms, and a higher risk for suicidal ideas and impulses [25]. Increased energy and impulsivity characteristics of agitated depression and mixed features also may increase suicide risk. In other cases, without psychic or motor agitation, this can appear after AD initiation, with the most rapid triggering seen with selective serotonin reuptake inhibitors [25]. Thus, in cases of agitated depression or mixed clinical features, treatment with atypical antipsychotics, anticonvulsants, and benzodiazepines might be indicated, and ADs should not be used. In patients with suicide risk, lithium use should be prioritized, given its association with suicide prevention [60]. Ongoing management in patients at risk of suicidal behavior should involve monitoring for suicidal ideation, substance use disorders, assessment of depressive symptomatology, treatment adherence, the identification of adverse effects, and psychotherapeutic treatment [52].

27.8 Antidepressants and Bipolar Disorder Type II

Some literature supports the use of ADs in BD type II, especially in those individuals with depressive predominant polarity [61, 62]. Indeed, a large genome-wide association study showed that BD type II is more strongly correlated with major depressive disorder than BD type I [63]. A comparative study including patients with BD type I and BD type II showed that the second group was more likely to have more initial depression and less hypomania, higher intake depression and anxiety ratings, and less mood-switching with ADs, as well as a greater proportion of time depressed and less hypomanic, and more depressive predominant polarity [61]. In clinical practice, they are more likely to receive AD and benzodiazepine

treatment compared to BD type I [61]. However, as in BD type I, in depressive episodes with mixed features, ADs are not recommended. Hence, even though pharmacological treatment should be individualized, for patients with BD type II for whom depression is the main source of burden, the presence of hypomanic episodes should be assessed, which might allow to identify those patients in whom AD use might entail a lower risk for hypomanic switch [62]. In these cases, they should be combined with mood-stabilizing treatment. Evidence regarding the use of AD monotherapy in BD type II is still limited. However, a recent meta-analysis showed the short-term efficacy of venlafaxine and sertraline in bipolar depression without significantly increased switch rates. Thus, there is an urgent need for randomized controlled trials investigating the safety of AD monotherapy in BD type II [64].

Other evidence has shown antidepressant effects in some antipsychotic treatments. Lumateperone is an antipsychotic with a potent serotonin 5-HT_{2A} receptor antagonism that also acts as a serotonin reuptake inhibitor and, adjunctive to lithium or valproate, has shown efficacy in the treatment of bipolar depression in a randomized controlled trial [65]. The antipsychotics lumateperone, quetiapine, olanzapine/fluoxetine combination, lurasidone, and cariprazine are approved for the treatment of bipolar depression in BD type I, and lumateperone and quetiapine are approved for the treatment of bipolar depression in BD type II [65].

27.9 Novel Antidepressant Treatments in Bipolar Disorder

Clinical heterogeneity and complex neurobiology of BD pose significant challenges to drug development, with scarce therapeutic options existing particularly for bipolar depression. Therefore, novel molecular mechanisms and treatment approaches are being investigated. The involvement of inflammation in BD pathophysiology is increasingly consensual, with the immune system and neuroinflammation playing a key role in the course of this illness, pointing out inflammation as a novel therapeutic target for BD. One of the novel treatments under study is trimetazidine, which is currently used to treat angina pectoris for its cytoprotective and metabolic effects (improved glucose utilization for energy production). Bipolar depression has been associated with the presence of mitochondrial dysfunction, inflammation, and oxidative stress. In this line, preclinical and clinical literature strongly supports trimetazidine's potential to treat bipolar depression, since it exerts anti-inflammatory and antioxidant effects while normalizing mitochondrial function when it is compromised. Further, trimetazidine has demonstrated proper safety and tolerability, which supports the recommendation for testing its efficacy in bipolar depression in future clinical trials [66].

Other evidence has identified an implication of dysfunctional signaling of gamma-aminobutyric acid (GABA) in the etiology of major depression. Zuranolone (SAGE-217) is an oral neuroactive steroid and a positive allosteric modulator of GABA-A receptors that has found positive effects in major depressive disorder and has been recently approved by the FDA for postpartum depression [67], with an

acceptable profile of adverse effects. Its antidepressant effects arise from its ability to enhance inhibitory GABAergic signaling by increasing synaptic and extrasynaptic GABA-A activity and regulation of GABA-A receptor expression. Future research should determine the potential efficacy of this treatment in bipolar depression, especially in bipolar postpartum depression [68].

Among the innovative options for the treatment of major depressive episodes, trace amine-associated receptor 1 (TAAR1) has been identified as a potential target [69]. The potential suggested mechanisms underlying their beneficial effects are ion-homeostatic, metabolic, neurotrophic, and anti-inflammatory enhancements in the limbic system [69]. Notably, TAAR1 activity is associated with antidepressant-like effects, attention enhancement, and response inhibition; it also reduces compulsive reward-seeking and has shown positive hedonic and cognitive effects [69]. Growing evidence supports the potential utility of TAAR1 as a therapeutic target also for BD due to a number of mechanisms, such as its interaction with the dopamine D2 receptor, the enhancement of glucose uptake and storage, and ATP synthesis, thus reducing oxidative stress and neuroinflammation, and its role in immune cell activation [70]. The available evidence also suggests that TAAR1 activation might confer neuroprotective effects through the inhibition of NF κ B-mediated transcription and also through brain-derived neurotrophic factor (BDNF) [70]. However, further studies involving participants with BD are needed to assess the potential efficacy of TAAR1 agonists.

In spite of receiving antidepressant treatments, some BD individuals with bipolar depression present a poor response to the available treatments and are finally diagnosed with treatment-resistant bipolar depression (B-TRD). Esketamine, an S-enantiomer of ketamine, a glutamatergic drug with NMDA agonism, has recently been approved for treatment-resistant depression (TRD), but the evidence in B-TRD is scarce. A comparative study with 35 B-TRD subjects and 35 TRD patients treated with esketamine nasal spray showed a significant reduction in depressive symptoms at 1 and 3 months of follow-up in both groups, with no significant differences in response or remission rates between them. This improvement was not associated with a treatment-emergent affective switch [71]. Recently, arketamine, an R-enantiomer of ketamine, has also shown rapid and sustained antidepressant effects in TRD [72]. However, further evidence is needed to assess the efficacy and the risk of AIHM in patients with bipolar depression treated with esketamine and arketamine.

Other novel antidepressant agents, including GABAergic drugs, new-generation antipsychotics with 5HT-7 and 5HT-2 antagonism, and adjunctive dopaminergic agents, including pramipexole and modafinil, are promising options as monotherapy or add-on therapies. Also, newer dual-action ADs (e.g., milnacipran) may have good efficacy. However, the risk of AIHM as monotherapy or add-on treatments should be assessed in further studies [73]. A systematic review and meta-analysis focused on melatonin receptor agonists suggested their potential to prevent relapse due to depression in patients with BD, although the scarcity of studies included in the review limited their conclusions [74].

Psilocybin, a psychedelic compound, has evidence for rapid-acting antidepressant effects that were investigated in bipolar II depression in a 12-week open-label nonrandomized controlled trial, which suggested the efficacy and safety of psilocybin together with psychotherapy in treatment-resistant depression [75].

Other agents under study for their potential benefits in bipolar depression are: cannabidiol, an exogenous cannabinoid, bifeprunox, a partial agonist of the dopamine D2 receptors and the serotonin 5HT-1 receptors, GSK1014802 and riluzole, which are sodium channel antagonists [73, 76]. Other strategies that have been proposed for bipolar depression are a ketogenic diet and mitochondrial modulators, such as N-acetylcysteine [77, 78]. However, there are currently no adequately powered randomized controlled trials to support the use of the mentioned alternatives in bipolar depression.

27.10 Antidepressants for Relapse Prevention in Bipolar Disorder

Antidepressants are used to treat acute depression in patients with bipolar I disorder, but their effect as maintenance treatment after the remission of depression has not been well studied. Yatham and Cols. investigated the potential role of ADs in relapse prevention in a double-blind trial, with some patients assigned to continue AD treatment for 52 weeks and others to switch to placebo at 8 weeks [79]. Whereas 12% and 6% had mania or hypomania, respectively, 17% compared to 40% had a recurrence of depression [79], which indicates a potential preventive efficacy of bipolar depression. This evidence supports the use of ADs, in combination with mood-stabilizing treatment, in specific individuals, especially those with depressive predominant polarity and BD type II, and those with previous history of depressive relapse after AD discontinuation. However, evidence including the use of long-term antidepressant treatment for relapse prevention is still limited.

27.11 Clinical Tips

- Despite AD use being common in BD, particularly in bipolar depression, it is not recommended as a first-line option.
- Even considering the different risks of ADs, their risk/benefit ratio varies among individuals, and no absolute contraindications have been posed.
- Antidepressant monotherapy should be avoided whenever possible in BD since mood stabilizers and SGA should be considered before their use in bipolar depression.

- Antidepressant use should be avoided in patients with mixed features, psychomotor agitation, rapid cycling, and substance use since they have been associated with an increased risk of manic or hypomanic switch.
- Patients with BD type I are at higher risk of switching than BD type II.
- In the case of prescribing ADs, clinicians should consider first bupropion and selective serotonin reuptake inhibitors before serotonin and norepinephrine reuptake inhibitors and tricyclic ADs, since the first are associated with a lower risk for manic and hypomanic switch.
- Ongoing management in patients at risk of suicidal behavior treated with ADs should involve monitoring suicidal ideation, substance use disorders, depressive symptomatology and potential mixed symptoms, treatment adherence, and adverse effects.
- As maintenance treatment, ADs might be considered as add-on therapy in cases in which depressive relapses occur after stopping AD therapy and in those with a depressive predominant polarity.
- After an AD prescription in BD, patients, caregivers, and clinicians should be aware of the potential risks and close follow-up should be provided.

27.12 Future Perspectives

The effectiveness of ADs in bipolar depression, whether prescribed as monotherapy or as an adjunctive treatment to mood stabilizers or SGA, is still unproven. The understanding of the risks and benefits underlying the relationship between BD and ADs is an ongoing area of research. The identification of biomarkers or specific profiles of patients might guide toward the identification of a population that can benefit from AD use with a low risk of AIHM. Future development of tools that account for key clinical factors, including previous history, substance abuse, predominant polarity, and characteristics of the current episode, might serve clinicians towards the individualization of the risk of manic switch regarding the use of AD during acute mood states or as prophylactic treatment. In addition, the development of specific tools might allow us to identify those patients at high risk of rapid cycling and those at high risk of suicide.

Yatham and Cols. showed a significant reduction in depressive recurrences in the long-term AD treatment [79]. Other long-term longitudinal studies assessing the potential benefits of ADs in the prevention of bipolar depression, especially in those patients with depressive predominant polarity, can help unravel the safest treatment combinations to treat acute mood episodes and prevent future relapses.

Future research should also elucidate specific mechanisms underlying novel treatments and the potential risks and benefits of novel ADs in the BD population, either as monotherapy or as add-on treatments, through the design of a greater number of randomized controlled trials and naturalistic studies.

In addition, future studies should focus on the identification of new molecular targets that allow the development of new drugs with greater efficacy, tolerability,

and speed of action, with mood-stabilizing properties and thus low risk of manic switch. Biological studies focusing on the specific mechanisms that lead to clinical response or remission in BD can provide valuable insights into potential strategies that should be explored for the development of targeted interventions.

27.13 Conclusion

Figure 27.1 summarizes the clinical aspects emphasized in this chapter. The role of ADs in the treatment of bipolar depression and as a prophylactic treatment continues to be a controversial topic since they have been demonstrated to increase the risk for manic or hypomanic switch, rapid cycling, and, in some cases, suicidal behavior. Clinicians should be trained to identify cases of agitated depression or depressive episodes with mixed features since the use of ADs might worsen the characteristics of the acute mood episode and also impair the course of illness in these cases.

Short and long-term studies are needed to find the most efficacious combination treatments and also to identify the specific profiles of patients in which ADs might be beneficial and entail low risks. Given their strong and complex association, randomized controlled trials and naturalistic studies should be performed in populations with BD. The development of novel AD treatments could cover current clinical needs and should be specifically studied in BD populations.

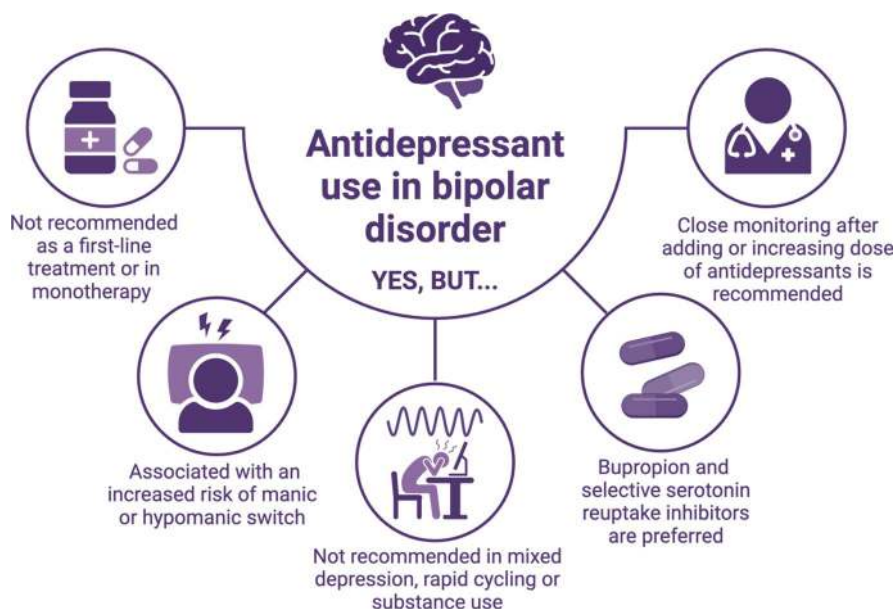


Fig. 27.1 Antidepressant use in bipolar disorder. Clinical recommendations according to specific clinical profiles and risks associated with their use are represented

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Chapter 28

Repurposed Drugs of Abuse (Stimulants, Ketamine, and Psychedelics): Focus on Risks



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28.1 Introduction

Research into repurposing drugs of abuse, such as serotonergic psychedelics, psychostimulants, and dissociative drugs has increased significantly over the past two decades [1]. Concerns over the use of such drugs for the treatment of mental health conditions create major roadblocks—including legal intervention by governing bodies—on the research path for drugs like methamphetamine, ketamine, and lysergic acid diethylamide (LSD). This situation limits scientific advancement in the already narrow field of treatment alternatives for bipolar disorders (BD) [2]. These concerns are mostly centered on the possible potential for abuse of these drugs and have been especially directed toward the theoretical risk of mood destabilization for individuals with BD [3]. The reemergence and repositioning of drugs of abuse may help correct what seems like an excessively conservative approach, sustained in the face of scarcely available evidence with regard to the actual risks, benefits, and potential of these drugs for BD.

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Scientific discussion on methamphetamines and their associated risks has taken place between mental health researchers, particularly those directed to bipolar disorder, for some decades [4, 5]. Psychiatric use of amphetamine has been marketed since 1937, when the bronchodilator benzedrine sulfate was approved with a main emphasis on general medicine but was also prescribed for psychiatric individuals diagnosed with mild depression [6]. In the 1940s, stimulants started popularizing themselves as diet pills for weight loss, though not approved by the American market for this purpose. Concerns over their abuse potential emerged mostly in the post-war period since their sales were, up until that point, over the counter. Starting in Japan, governments started imposing restrictions on their availability, which was done in the USA in the 1960s. Available in the United States without a prescription up until 1951, amphetamine tablets are estimated to be used by 0.3% to 1.1% of the world population [7]. As evidence of possible risks for those with BD, misuse of amphetamine-related substances has been increasing in the United States as hospital admissions soared by more than 500% between 1992 and 2002 [8].

Initially prescribed as a dissociative anesthetic [9], ketamine is used as a pharmacological model of psychotic behavior in animals [10], described as a transient psychotomimetic phenomenon, which has been a cause for concern over its use in individuals with psychotic and/or bipolar disorders [11]. Since the first results of rapid antidepressant effects [12], research on this drug rose substantially, resulting in low-dose ketamine being approved by regulation entities both in the United States and Europe as an adjuvant for unipolar treatment-resistant depression [13]. A blockade of N-methyl-D-aspartate receptors and a surge of glutamate are thought to underlie ketamine's dissociative and schizophrenia-like states [14]. These symptoms can worsen with high doses, resulting in loss of awareness and out-of-body experiences labeled as "k-hole" in contexts of drug abuse [15]. Like the other substances that will be reviewed in this chapter, ketamine's recreational use has been reported since the 1960s, and although current nonmedical use is not clearly mapped, population use rates are around 1% [16].

Lysergic acid diethylamide (LSD), in its turn, was first synthesized in 1938, concurrent with the rise of amphetamine use globally [17]. Research on LSD reached its peak by 1950, with around 40,000 people being administered LSD for multiple mental health conditions up until 1965 [18]. Due to its abuse as a recreational drug, LSD was the aim of government intervention around the 1970s and 1980s in the United States, which resulted in a near halt in research development. Drugs of abuse are an especially concerning topic for individuals with bipolar disorder, given that alcohol and drug use disorders are 14% and 6% higher in individuals diagnosed with BD when compared to the general population, with a 61% risk of having any substance use disorder for the bipolar I subtype and 48% for the bipolar II subtype. This risk is even higher for individuals with mania, who are six times more likely to exhibit a substance use disorder when compared to the general population [19].

The repurposing of drugs of abuse for the treatment of bipolar disorder thus faces what seems like major concerns with regard to both individual and societal risks. The following sections of this chapter focus on the repositioning of different drugs

of abuse to the treatment of bipolar disorder, weighing on their associated risks and benefits, describing known mechanisms of pathophysiology and their relation to stimulants and hallucinogens, while critically assessing the available evidence.

28.2 Stimulants

28.2.1 *Comorbidities to Take into Account When Treating Bipolar Patients with Psychostimulants*

28.2.1.1 Comorbidity with Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder comprising three basic characteristics: attention deficit, hyperactivity, and impulsivity, with an estimated prevalence of around 7.6% in children and 5.6% in teenagers [20]. Manifestations may include a lack of self-control, impulsive behaviors, and excessive activity, impairing social interactions and onerating personal and educational life [21]. Manifestations vary between sexes, with boys exhibiting more externalized symptoms (e.g., impulsivity), while girls generally express more internalized symptoms (e.g., inattentiveness and low self-esteem). The inward direction of suffering puts girls with ADHD at high risk for depression (including bipolar depression), anxiety, and eating disorders [22].

Mood lability occurs in around 38% of children with ADHD, that is, ten times more than the population rate [23]. Several pathophysiologic explanations have been raised about this overlap, including both “bottom-up” and “top-down” mechanisms. Evidence also suggests network dysfunctions involving central regions for emotional stimuli processing and emotional regulation, including the amygdala, ventral striatum, and orbitofrontal cortex [23]. Issues in controlling emotions in children with ADHD can make the differential diagnosis of this disorder with pediatric bipolar disorder rather challenging [24]. Rates of the comorbidity pediatric BD-ADHD, thus, vary greatly in literature, ranging from 4% to 94% (with a mean prevalence of 48%) [25].

Considering all age groups, individuals with mood disorders, particularly BD, experience ADHD more frequently than the general population [26]. Supporting this association, genetic studies indicated that relatives of bipolar I patients are at an increased risk for ADHD (27% for offspring and 30% for siblings), while relatives of ADHD patients have a greater risk for bipolar I disorder (6.8% for offspring, 5.9% for siblings, and 5.1% for parents), as reported by [27]. A recent systematic review and meta-analyses involving 71 studies and 646,766 across 18 countries, found that about one in 13 adults with ADHD also received a BD diagnosis (7.95%; 95% CI: 5.31–11.06), and nearly one in six adults with BD had ADHD (17.11%; 95% CI: 13.05–21.59%) [28]. Nonetheless, there is an ongoing debate regarding

whether this comorbidity might be artifactual, potentially reflecting subtypes of BD marked by an early-onset ADHD-like prodromal phase, or whether it represents a genuine comorbidity, possibly arising from a common diathesis [29]. This discussion will be explored in greater detail in the specific chapter (see Chap. 11).

The presence of ADHD in patients suffering from BD is associated with higher rates of other comorbid psychiatric conditions and of suicide attempts, also earlier onset of mood episodes, greater severity and frequency of affective episodes, as well as greater likelihood of engaging in interpersonal violent behavior [30, 31]. The evidence thus suggests that BD combined with a history of childhood ADHD (irrespective of symptom persistence in adulthood) may represent a distinct early-onset phenotype of BD, with the potential for greater life-long impact and poorer global functioning. Given all these negative outcomes, effective therapeutic options are fundamental. Nevertheless, ADHD remains untreated in patients with mood disorders as it tends to be misrecognized or underestimated. This is corroborated by earlier research indicating that only 9% of patients with BD-ADHD had been appropriately diagnosed and treated for ADHD [32].

Subjects with comorbid ADHD and mood disorders often do not receive adequate ADHD treatment due to a clinical emphasis on mood-related symptoms [32]. Additionally, there is heightened concern regarding the risk of mood destabilization in patients with BD I or psychosis in patients using stimulants [33]. Also, it is necessary to caution those with co-occurring substance use disorders and eating disorders [3]. Despite these concerns, limited research has been conducted on the effectiveness, safety, and tolerability of psychostimulants in individuals with this comorbidity.

28.2.1.2 Comorbidities with Eating Disorders and Obesity

Another important aspect regarding drug abuse in individuals with BD involves their utilization for weight management and for addressing eating disorders (ED). Stimulants, recognized for their appetite-suppressing properties, may hold considerable importance in treating ED [34], which might be extended to the context of BD. The association between BD and obesity is well documented [35] and rates of ED are higher within BD patients than in the general population. Binge-eating disorder (BED) stands as the most prevalent ED co-occurring with BD, followed by bulimia nervosa (BN) [36, 37].

A study evaluating adjunctive lisdexamfetamine dimesylate (LDX) effects on anthropometric and metabolic parameters in adults with BD I/II demonstrated significant benefits on body weight, body mass index, and various metabolic aspects, coupled with favorable safety and tolerability [38]. In 2015, LDX was the first pharmacologic agent to be approved by the US Food and Drug Administration for the treatment of moderate or severe BED in adults [39].

No randomized controlled trials have specifically targeted treating individuals with both ED and BD. However, McElroy and colleagues conducted a trial in 2015 that shed light on this area [40]. While the primary aim was to demonstrate LDX's superiority over a placebo in reducing depressive symptoms in bipolar depression,

secondary objectives included assessing LDX's effectiveness in alleviating associated symptoms like food cravings, binge eating, and metabolic abnormalities. In this 8-week trial, adjunctive LDX didn't outperform placebo in improving clinician-rated depressive symptoms. Yet, it was superior in reducing self-reported measures of depressive symptoms, excessive daytime sleepiness, fatigue, and binge eating, along with enhancing certain metabolic factors. Additionally, except for one possible case of misuse, LDX demonstrated a generally good safety profile. Furthermore, a case report highlights a young woman with bulimia nervosa, bipolar I disorder, and other comorbidities who found sustained relief from bulimia and improved ADHD symptoms by adding methylphenidate after successful treatment of her other conditions [41].

Given the well-known weight-related effects of LDX and other stimulants within the general population, there's a notable risk of individuals misusing these medications with the explicit purpose of weight loss [42]. This behavior seems to be fairly common, particularly among young women. While vigilance in monitoring stimulant misuse is essential, most trials examining their use in eating disorders indicate a low likelihood of misuse. Besides the previously mentioned potential case of misuse [42], other trials investigating LDX for BED or BN, involving over a thousand patients, reported no instances of misuse [43, 44]. Notably, the study reporting the instance of potential misuse involved bipolar patients.

28.2.2 *Methylphenidate*

Methylphenidate's (MPH) mechanism of action involves blocking norepinephrine and dopamine reuptake—as well as acting as a weak 5HT1A agonist. Increasing these neurotransmitters' concentrations in the synaptic cleft entails stimulant effects, acting mainly in the prefrontal cortex. Unlike selective serotonin reuptake inhibitors (SSRIs), stimulants' mechanism of action relies primarily on catecholaminergic effects. Compared to other phenethylamine derivatives (i.e., amphetamines), MPH seems to increase neuron firing rates. It is approved by the Food and Drug Administration of the United States (FDA) for treating ADHD in patients above 6 years old, as well as a second-line treatment for narcolepsy in adults [45].

28.2.2.1 **Methylphenidate in the Treatment of Pediatric Patients with Comorbid Attention-Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorders (BD)**

A recent systematic review of pharmacotherapy for children and adolescents with comorbid ADHD and BD investigated the efficacy and safety of MPH in this scenario. Methylphenidate did not increase the risk of manic switch or psychotic symptoms when used along with a mood stabilizer in this study, and the authors state that it should be used in first-line treatment for cases of simple comorbidity

between BD and ADHD. The authors also propose the use of atomoxetine as an alternative in cases of intolerance, ineffectiveness, or comorbidity with anxiety, oppositional defiant disorder, conduct disorders, tic disorders, or substance use disorders [24].

Short-term efficacy and safety were later demonstrated by Findling et al. [46], in an RCT ($n = 16$) with euthymic BD-I patients (aged 5–17 years old) with comorbid ADHD. Patients were in current use of mood stabilizers (lithium or valproate), and placebo or MPH—at doses of 5, 10, and 15 mg, twice daily—were added over a 1-week interval in a crossover design with randomized treatment order. MPH improved ADHD symptoms (with a large effect size), as well as psychiatric symptomatology in general (measured through the Clinical Global Impressions—Severity Scale, CGI-S). Clinical improvement with MPH use was not counterbalanced by any significant negative effects over the following 4 weeks, including manic switch [46]. Another study with a similar design [47] and the same follow-up period added MPH (0.3–0.7 mg/kg per day) to the treatment regimen of ADHD-BD patients aged 8–17 years old ($n = 14$) previously stabilized with aripiprazole. Participants in the MPH group had a significant decrease in patient-reported depressive symptoms relative to placebo in a secondary analysis, yet not significantly improving from ADHD symptoms. Though two patients were excluded—one in the MPH group due to a mixed episode, though the patient did not comply with the medication use in the week before; and one loss of follow-up in the placebo group—no between-group difference was found regarding manic symptoms, reinforcing MPH's safety in this population.

28.2.2.2 Methylphenidate in the Treatment of Adult Patients with Comorbid Attention-Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorders (BD)

Less studies have been conducted with MPH treatment for this comorbidity in adult patients, and evidence supporting its use comes mainly from studies with children and adolescents, as discussed in the previous topic. Concerns over the risk of the manic switch with MPH use are supported by a previously published nationwide study with adult BD patients in Sweden ($n = 2307$) showing a statistically significant increased risk of mania within 3 months in patients with comorbid ADHD in MPH monotherapy [HR 6.7 (95%CI: 2.0–22.4)] [48]. The association of MPH with a mood-stabilizing treatment—either lithium, valproate, or atypical antipsychotics (i.e., aripiprazole, olanzapine, or quetiapine)—significantly reduced this risk in the same trial, reinforcing the need to adequately address mood symptoms prior to stimulant treatment initiation.

28.2.2.3 Methylphenidate in the Treatment of BD (as Augmentation for Treatment-Refractory Bipolar Depression)

Even in the absence of comorbid ADHD to “justify” introduction, stimulants have been studied as augmentation agents for bipolar depression in a review published in 2014 [49]. Three open-label studies provided preliminary support for the use of MPH in “pure” BD patients [4, 50, 51]. The first of them was a prospective study ($n = 14$), with BD I and II patients in acute depressive episodes, in which the combination of MPH (5–10 mg twice daily) + mood stabilizer resulted in significant improvement in depressive and global psychiatric symptoms within 1 week and over 12 weeks of follow-up—mainly due to five patients that responded to treatment. Three patients withdrew from the study for increased anxiety, agitation, and hypomania, respectively, and one BD II patient relapsed into ethanol abuse [50]. The second study had a retrospective design ($n = 8$, 3 patients in MPH, 5 in AMPH) in BD I and II patients with residual symptoms and/or medication-induced sedation. The mean treatment duration was 18 months and the MPH dose ranged from 20 to 40 mg daily. Patients exhibited moderate clinical improvement in residual symptoms, as well as substantial improvement of overall BD symptoms, with no evidence of treatment-induced hypomania, mania, or substance abuse—in spite of prior substance abuse/dependence among the patient sample. Lastly, a prospective study ($n = 50$; 44 in MPH, 6 in dexamphetamine) with treatment-resistant unipolar ($n = 23$) or bipolar depression ($n = 27$) treated subjects with either stimulant monotherapy (28%) or as adjunctive treatment to antidepressants (72%). 64% of the sample reported either complete or some level of improvement. In this study, one BD patient had a severe manic episode following MPH use, while three had transient “highs,” and two reported transitory feelings of being “jazzed up” (representing 12% of the BD sample) [51].

Only two randomized controlled trials (RCT) for MPH use in major depression were identified—including only unipolar depression—and both failed to demonstrate the superiority of augmentation treatment with MPH over antidepressant monotherapy [52]. Significant results of the latter were limited to positive stimulant effects on fatigue and apathy.

28.2.3 Amphetamines

Similar to MPH, amphetamines inhibit the reuptake of both dopamine and norepinephrine. Additionally, the pumps exhibit reversible functionality, facilitating the active diffusion of these neurotransmitters in the synaptic cleft. Moreover, amphetamines directly occupy the substrate site of catecholamine transporters (DAT and NET), and intracellular amphetamines also decrease dopamine metabolism by inhibiting the vesicular monoamine transporter (VMAT-2).

FDA-approved indications for commercially available amphetamines include:

- Mixed amphetamine salts (MAS): Narcolepsy and ADHD in adults and children ages 3–16 years. MAS are a mixture of equal parts of: dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate capsules.
- Dextroamphetamine sulfate (D-amphetamine): Narcolepsy and ADHD. D-amphetamine is the dextro isomer of amphetamine sulfate.
- Lisdexamfetamine (LDX): ADHD in patients ages 6 and above, maintenance treatment in adults with ADHD, and binge-eating disorder. LDX is a prodrug of D-amphetamine and has a longer duration of action than dextroamphetamine sulfate.

A recent review by the FDA found that nonmedical stimulant use has remained relatively stable over the past two decades. The highest prevalence was observed among young adults aged 18–25 (4.1–7.5%), college students (4.3%), and individuals with attention-deficit/hyperactivity disorder (ADHD) (14–32%). The primary motivation for nonmedical use was perceived improvement in work or academic performance. Nonmedical use was typically infrequent, with 50–75% of users using the stimulants no more than once per month.

Amphetamines have been studied as a human model of mania, producing effects such as increased happiness, alertness, energy, thought speed, light-headedness, and restlessness. The Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline classifies amphetamines as one of the pharmacological agents with the highest risk of inducing manic episodes during treatment, similar to tricyclic antidepressants (TCAs). Nevertheless, there are some studies using amphetamines in patients with BD as an option for the treatment of bipolar depression or comorbid ADHD, like MPH.

28.2.3.1 Amphetamines in the Treatment of Adult Patients with Bipolar Disorder

The effectiveness and safety of LDX in treating bipolar depression among adults were investigated in a small RCT. A group of 25 participants with BD type I or II, who didn't respond adequately to mood stabilizers or antipsychotic therapy, were randomly divided to receive LDX or a placebo over 8 weeks. The results showed that both LDX and the placebo led to similar improvements in depressive symptoms, as assessed by the MADRS. However, LDX exhibited superior effectiveness compared to the placebo in addressing self-reported depressive symptoms, excessive daytime sleepiness, fatigue, and binge eating. It also showed positive effects on certain metabolic variables. In terms of safety, there were no instances of inducing mania or psychosis. Only one participant was excluded due to the problematic use of LDX.

An open-label study involving 40 patients with ADHD-BD using LDX adjunctive revealed improvement in both ADHD symptoms and residual depressive symptoms. In terms of safety, there were no manic switches, although the follow-up period was only 4 weeks.

A chart review reported cases of eight patients with bipolar depression who used adjunctive stimulants (either methylphenidate or amphetamine). In a long-term follow-up, lasting at least 2 years, there was improvement in symptoms such as sedation, weight gain, low energy, and fatigue. Additionally, the stimulants were well-tolerated. In another chart review from a specialized BD service, 25% of the sample had prior stimulant treatment for ADHD or bipolar depression. Twenty-one patients used methylphenidate, 17 used amphetamine, and 6 used modafinil. Less encouragingly, this study demonstrated a stimulant-associated mania/hypomania rate of 40%. However, unlike previous studies, 43% of the patients using stimulants were not on mood stabilizers.

28.2.3.2 Amphetamines in the Treatment of Pediatric Patients with Bipolar Disorder and Comorbid ADHD

There was an RCT involving pediatric patients diagnosed with either bipolar disorder I or II and ADHD. The study aimed to evaluate the safety and effectiveness of mixed amphetamine salts in treating ADHD symptoms. The inclusion criteria specified that patients should demonstrate responsiveness to divalproex sodium following a recent mixed, manic, or hypomanic phase. A total of 30 patients were randomly assigned to receive MAS or placebo, maintaining a stable divalproex sodium dosage. It was a 4-week crossover trial. MAS were superior to placebo in effectively treating ADHD symptoms. Following that, a group of 23 patients was monitored in an open-label trial for an additional 12 weeks, utilizing the combination of divalproex sodium and MAS. Only one patient demonstrated a manic exacerbation after 4 weeks of using the MAS. The manic symptoms in this particular case resolved within 4 weeks following the discontinuation of the MAS.

28.2.4 Modafinil and Armodafinil

Modafinil and armodafinil, the R-enantiomer of modafinil, are wakefulness-promoting agents that exert stimulant-like effects. Unlike traditional stimulants, they exhibit low affinity for the dopamine transporter (DAT) and demonstrate selectivity for brain regions involved in regulating wakefulness. This reduced interaction with the nucleus accumbens contributes to their lower addictive potential compared to traditional stimulants.

In a previously mentioned review, the authors highlighted the preferable use of newer stimulant alternatives—modafinil and armodafinil—which may exhibit the same benefits as older, dopaminergic stimulants, yet with fewer abuse potential risks in depression augmentation treatment [49]. They had the most robust evidence with six RCTs, though one of them had negative findings and another one was interrupted due to two reports of suicidal ideation in the modafinil group, both including only unipolar depression [53–58]. Only two studies were focused on BD: one with modafinil 100–200 mg/day ($n = 85$) [58] and one with armodafinil 150 mg/day ($n = 257$) [54]. These studies demonstrated significant group differences—using the Inventory of Depressive Symptomatology (IDS) scale as the primary outcome—favoring adjunctive treatment of modafinil/armodafinil along with mood stabilizers, as well as no between-group difference in treatment-emergent hypomania or mania.

28.2.5 Key Clinical Considerations Regarding the Use of Psychostimulants in Bipolar Disorder

- The CANMAT and International Society for Bipolar Disorders (ISBD) guidelines for the management of BD [59]: the CANMAT task force recommendations for the management of patients with mood disorders and comorbid ADHD and the European Consensus Statement on Diagnosis and Treatment of Adult ADHD emphasize the importance of achieving mood stability prior to initiating ADHD treatment and maintaining concurrent use of optimal-dosing antimanic medications.
- All of these guidelines underscore the efficacy of stimulants in addressing attention symptoms, along with their established safety in clinical trials with regard to the theoretical risk of manic switch [59].
- MPH and MAS exhibit level 3 evidence, categorizing them as second-line treatments for adults with BD-ADHD, in conjunction with mood stabilizers. For patients deemed to be at low risk for manic switch, these medications might be considered as first-line interventions.
- LDX possesses level 4 evidence for managing the comorbidity of BD and ADHD and is advocated as a third-line treatment.
- Regarding the use of psychostimulants for the treatment of bipolar depression, CANMAT recommends only modafinil (level 2 evidence) and armodafinil (level 4 evidence), categorizing them as third-line interventions [59].
- We must, as clinicians, individualize treatment decisions considering individual patients' risk of mood destabilization, as well as adequate treatment to clinical context in terms of mood phase (e.g., acute treatment of manic episodes, treatment of residual ADHD symptoms in euthymic patients).

28.3 Psychedelics

28.3.1 *Ketamine*

Ketamine was initially approved by the FDA in 1970 as a rapid-acting general anesthetic. In 2000, Berman and colleagues published the first study demonstrating ketamine's antidepressant properties and, since then, accumulating evidence has supported its promising therapeutic potential in psychiatry. Efforts culminated in the FDA approval, 2019, of intranasal esketamine as the first rapid-acting antidepressant (RAAD) for major depressive disorder (MDD) patients [13]. In 2020, this approval was extended to MDD patients with acute suicidal ideation and behavior.

Due to ketamine's distinct mechanism of action, different from classic serotonergic psychedelics (SPs), debates arise over its classification as such an agent. Though targeting different neurotransmitter systems, both ketamine and SPs induce rapid and transient psychoactive states. Evidence even suggests some possible shared downstream mechanisms between them, including mechanistic targets of rapamycin complex 1 (mTORC1) signaling and changes in neuroplasticity [60, 61]. Nevertheless, research on these latter drugs is in its early stages, especially when compared to the extensive and growing body of research conducted on ketamine.

28.3.1.1 Ketamine in the Treatment of BD

While emerging clinical evidence suggests that ketamine holds promise as an adjunctive therapeutic modality for managing bipolar depression [62], the current body of research on the efficacy of a single intravenous racemic ketamine infusion for bipolar depression is limited to only three randomized controlled trials (RCTs) targeting depressive symptoms [63–65]. Notably, only one of these trials compared ketamine to an active comparator (midazolam) [64]. This paucity of data underscores the need for further research into the therapeutic potential of ketamine in managing bipolar depression episodes.

The pioneering RCT investigating ketamine's efficacy in bipolar depression was conducted by Diazgranados et al. [63], who documented a marked alleviation of depressive symptoms, commencing 40 min following intravenous ketamine infusion. A substantial proportion of subjects (71%) exhibited a response to ketamine, while only 6% responded to a placebo at some point during the trial. Interestingly, manic symptoms emerged in one subject receiving ketamine and one receiving a placebo. Overall, ketamine was well-tolerated, with dissociative symptoms being the most commonly reported adverse effect.

Building upon their previous work, the same research group conducted a secondary analysis of three independent samples of subjects with treatment-resistant depression. This analysis revealed a paucity of data to support the occurrence of manic-like symptoms following single ketamine infusions, underscoring the need for further investigation into this potential adverse effect [66].

Zarate et al. [65] corroborated the findings of Diazgranados et al. in a randomized, double-blind, placebo-controlled crossover trial involving 15 patients diagnosed with bipolar disorder types I or II, who were concurrently receiving lithium or divalproate. The study protocol involved administering a single intravenous infusion of either ketamine (0.5 mg/kg) or placebo to each participant, with infusions repeated at 1-week intervals. A substantial improvement in depressive symptoms and suicidal ideation was perceptible from 40 min post-infusion. A remarkable 79% of patients in the ketamine group met response criteria to treatment at some point during the trial, compared to none of the placebo group. Additionally, the incidence of switching to mania (or hypomania) was lower in the ketamine group than in the placebo group. These findings suggest that ketamine may be an effective treatment for bipolar depression, with a favorable safety profile [63, 65].

Grunebaum et al. [64] aimed to evaluate the feasibility of ketamine versus midazolam infusion on suicidal ideation in bipolar depression. Sixteen participants were randomized and assessed for suicidal ideation, neurocognition, and blood biomarkers. The results showed that ketamine was feasible and well-tolerated. In addition, suicidal thoughts were lower after ketamine than after midazolam at a trend level of significance, although this was a trial that failed to meet its primary endpoint.

Lally et al. [67] investigated the effects of ketamine on anhedonia in 36 treatment-resistant patients with bipolar depression. In a randomized, double-blind crossover study, participants received a single dose of intravenous ketamine or placebo. Anhedonia scores were assessed using the Snaith–Hamilton Pleasure Scale (SHAPS). Positron emission tomography (PET) imaging was also conducted to evaluate changes in brain glucose metabolism. The results of the study showed that ketamine rapidly reduced anhedonia scores, even in the absence of a significant reduction in depressive symptoms. This suggests that ketamine may have a specific effect on anhedonia, which is a core symptom of bipolar depression. PET imaging revealed that the anti-anhedonic effects of ketamine were associated with increased glucose metabolism in the anterior cingulate cortex and putamen. These brain regions are involved in reward processing and motivation, suggesting that ketamine may improve anhedonia by modulating these neural circuits.

The findings of Lally et al. [67] provide further evidence for the role of the glutamatergic system in the treatment of bipolar depression and anhedonia. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may exert its therapeutic effects by modulating glutamate signaling in these brain regions. Overall, this study highlights the potential of ketamine as a novel treatment for anhedonia in patients with bipolar depression. Further research is needed to investigate the long-term efficacy and safety of ketamine for this indication.

While a standardized protocol for ketamine maintenance treatment in bipolar depression remains under investigation, Zheng et al. [68] conducted a study involving 97 patients with unipolar or bipolar depression, administering six repeated ketamine infusions. The authors observed a notable response rate of 14.4% and 68% at 24 h following the first and sixth infusions, respectively. These findings suggest that repeated ketamine infusions can enhance therapeutic outcomes in patients with bipolar depression. Further research is warranted to establish a standardized

maintenance protocol for ketamine and to elucidate its long-term efficacy and safety profile. Noteworthy, all ketamine trials for bipolar depression to date used racemic ketamine.

Though esketamine—with its strong affinity for the NMDA receptor and substantial anesthetic potential—is recognized as the active isomer of ketamine [9, 69], studies on animal models of major depression have suggested that arketamine may exhibit antidepressant effects, with a safer adverse event profile [70]. As of today, only preliminary evidence regarding arketamine is available in treatment-resistant depression and bipolar depression.

An open-label trial has assessed the safety and tolerability of arketamine in treatment-resistant depression, demonstrating rapid antidepressant potential [71], followed by negative results in a pilot randomized controlled clinical trial [72]. Regarding bipolar depression, only one pilot open-label trial to date testing two different doses of arketamine pointed out the feasibility and safety of this molecule with rapid-acting antidepressant effects [73]. Further evidence is needed to determine if arketamine might be a potential novel therapeutic agent for a major depressive episode in bipolar disorder types I and II.

28.3.2 *Classic Psychedelics (LSD, Psilocybin, MDMA)*

Interest in the value of psychedelics in psychiatry first arose in the early twentieth century, exploring mescaline and peyote's capacity to induce psychosis-like effects, coining the term “psychotomimetics” (psychosis-mimicking). Over time, these drugs' potential to contribute to the understanding of the underlying basis for psychiatric disorders gained attention. Investigations proceeded, evolving into a possible role for psychedelics as adjuncts to psychotherapy, and this became the main focus after the discovery of LSD in 1943. Scientific efforts had to be suspended in the 1960s when the U.S. government—under President Nixon—initiated the “drug war” and imposed restrictions on new studies. After decades of prohibition, clinical research was gradually re-established over the last years. More recently, the preferred term adopted has been psychedelics, referring to substances with agonist or partial agonist effects at serotonin 5-HT_{2A} receptors (e.g., LSD, mescaline, and psilocybin) [74].

28.3.2.1 **Psychedelics in the Treatment of BD**

Modern clinical trials with psychedelics have excluded individuals diagnosed with bipolar disorder, mostly due to the major serotonergic activation reported in psychedelic use and the possible risk of an affective switch [75]. This means that the lack of available evidence precludes the planning of future clinical trials and also inhibits what could be productive psychoeducation between clinicians and their patients. Psilocybin, for example, is a serotonin transporter inhibitor and partial 5-HT_{2A}

receptor antagonist, which reflects its serotonergic mechanisms of action that are theoretically linked to affective switches for those with BD. In line with the ongoing debate over the real risks of possible affective switches in bipolar disorder, scientific reports of treatment with classic psychedelics are largely limited and still consist of single-patient case reports [75] or descriptive surveys from recreational users [76].

A systematic review [75] found a total of 17 case reports, dating back to 1966, which describe mania, psychosis, or a combination of these symptoms emerging after the use of LSD, psilocybin, dimethyltryptamine (also known as DMT), and ayahuasca. Cases differ between single or multiple substance use, single or multiple dosages before symptoms, known family history of BD, and time before symptoms are resolved. Another study, an international web-based survey completed by 541 people and aimed at exploring psilocybin use in individuals with a self-reported diagnosis of BD, found that one-third (32.2%) of respondents described increasing symptoms after psilocybin use [76]. Despite manic symptoms being prominently reported, together with difficulty sleeping and anxiety, use of emergency medical services was rare (3.3%), and responses indicate that psilocybin use was more helpful than harmful.

Data on the use of atypical psychedelics for BD is even more scarce. Two reports on ibogaine, an alkaloid of the shrub commonly referred to as iboga used to treat substance-related disorders [77], show conflicting results arising from distinct methods. A 3-patient case series focuses on temporal associations between ibogaine ingestion and consequent manic-like symptoms [78], while a case report of ibogaine microdosing for a woman with type II BD describes symptomatic improvement at 15 and 90 days post-treatment [79].

The paucity of reliable evidence regarding the use of both classic and atypical psychedelics for bipolar depression is clear, and further research is necessary. Although no clear pattern emerges from the analysis of adverse symptoms after the use of typical and atypical psychedelics, a cautionary tale can be derived from the scarcely available evidence. An ongoing clinical trial of psilocybin therapy for BD type II (NCT05065294), designed to recruit 14 participants, is expected to offer a clearer picture of the real risks and possible benefits for this population.

28.3.3 Key Clinical Considerations Regarding the Use of Psychedelics in Bipolar Disorder

- Reliable and reproducible evidence on the possible use of psychedelics for BD is severely lacking, given that there are no randomized clinical trials assessing the risks and benefits in the short or long term.
- Data on possible risks associated with the recreational use of psychedelics in individuals with BD is also limited, mostly due to confounding caused by the relatively common use of multiple drugs of abuse by a single person and reliance on measures of self-report.

- The safety of concomitant use of psychedelics with well-established pharmacotherapies for BD, such as mood stabilizers, is also unclear, which further hinders precise assessment of risks and benefits in clinical settings and clinical trials.

28.4 Future Perspectives

The recent approval of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for PTSD in Australia, and the recognition by the FDA of MDMA-assisted therapy for PTSD as a breakthrough therapy are encouraging developments. Further research may help elucidate critical points for the field of mental health, such as mechanisms of action, long-term safety concerns, and real-world effectiveness, potentially opening the path for other psychedelics.

28.5 Conclusion

Despite the recent tendency to reposition drugs that until very recently were used exclusively for recreational purposes, such as classic psychedelics, or drugs that were usually contraindicated in bipolar disorder, such as psychostimulants and drugs that until a few years ago had no indication in psychiatry, such as ketamine, we must maintain caution in the large-scale use of these drugs in people with BD. We need to wait for more consistent studies on such medications and only prescribe them in unequivocal situations where they are indicated for off-label use. Furthermore, we must highlight that in several countries some of these drugs are still illegal.

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Part IV
Psychosocial Interventions

Chapter 29

Psychoeducation in Bipolar Disorder



J. Huang, Howard C. H. Khoe, and Cyrus S. H. Ho

29.1 Introduction

Psychoeducation is a systematic, didactic psychosocial intervention that provides patients and their families with knowledge about mental illness to enable patients to better cope with illness. This is typically done as a part of a complex psychosocial intervention, usually in combination with drug therapy. The rate of use of psychoeducation as a formalised intervention is somewhat limited, varying between 7 and 50% [1]. For psychoeducation to be more widely adopted in the clinical management of bipolar disorder, there needs to be a better understanding of its utilisation and benefits.

The concept has its roots that can be traced back to an approach formulated by Anderson et al. [2] as a form of family treatment for adult patients with schizophrenia, which aimed to provide them with an educational intervention to increase their knowledge about the illness and the ability to react appropriately. Although initially developed for the treatment of schizophrenic patients and continuing to be a crucial element in the management of this disorder, it quickly gained traction in bipolar patients as well.

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29.2 Elements of Psychoeducation

There has been much literature regarding the key elements of psychoeducation. Bauml et al. [3] identified essential psychotherapeutic elements within psychoeducation, including a focus on the therapeutic interaction, clarification of knowledge and enhancing coping competence, which included the involvement of family members as ‘co-therapists’ and as a source of support. Similarly, Sarkhel [4] identified four primary goals in psychoeducation, namely to (A) provide knowledge to participants, (B) provide insight into illness, (C) encourage relapse prevention, and (D) equip stakeholders with crisis management skills. The long-term treatment goal of these interventions is to prevent further relapses of mood episodes and avoid suicidal acts [5], as well as decrease the severity and psychosocial consequences of each relapse and improve functional status and quality of life (Table 29.1).

Symptoms in bipolar disease, particularly during manic episodes, such as grandiosity and hypersexuality, are generally viewed negatively, with patients being perceived as unpredictable and aggressive [6, 7]. It is no wonder that bipolar disorder is associated with stigmatisation, similar to that of other debilitating disorders such as schizophrenia [8]. The stigma associated with the use of antipsychotics in bipolar treatment can increase the risk of treatment nonadherence and subsequent relapses [9]. Stigma is also associated with concealment, social withdrawal and reduction of social support networks, which is associated with depressive relapses and worsened clinical outcomes [6]. Psychoeducation thus serves as an avenue of sharing knowledge and increasing understanding of disease to reduce stigma and promote help-seeking behaviour.

Loss of insight is common in bipolar disorder, particularly in the manic phase [10–12]. This is likely due to the greater presence of psychotic symptoms during the manic phase. Lower levels of insight into treatment are associated with worse treatment compliance and a higher risk of adverse clinical outcomes in bipolar disorder [13]. Therefore, a meaningful treatment opportunity exists in using psychoeducation to improve the patient’s insight into bipolar disorder.

Table 29.1 Core elements of psychoeducation

Essential elements of psychoeducation [4]	Psychotherapeutic elements within psychoeducation [3]
1. Briefing patients about their illness	1. Therapeutic interaction (relationship level)
2. Problem-solving training	2. Clarification (causal attribution)
3. Communication training	3. Enhancement of coping competence (control attribution)
4. Self-assertiveness training	

29.3 Adherence to Treatment

The importance of medication adherence in bipolar disorder cannot be further emphasised. Nonadherence to medications is linked to increased risks of relapse, increased rates of recurrence, decreased likelihood of remission and recovery, and hospitalisations in patients with bipolar disorder [14, 15]. A longitudinal study done on 158 bipolar patients [16] showed a four times decrease in suicide risk in treated individuals vs untreated individuals. Nonadherence to lithium maintenance treatment in patients with bipolar I was also shown in another study [17] to result in a 5.2 times increased risk of suicide. Patient nonadherence to medications has also been shown to be linked to an increase in relapses, an increase in time being symptomatic, and an increased risk of hospitalisations and functional impairment. Unfortunately, there is a high level of nonadherence to medications, averaging between 40 and 50% [14, 18].

With regards to determinants of medication adherence, it has been increasingly recognised that demographic and clinical factors play a less significant role than the patient's attitudes and beliefs towards bipolar disorder and its management, leading to a shift from an illness-centred to a patient-centred approach [19, 20]. Lack of awareness towards disease and negative attitudes towards medications seemed to play a role in nonadherence. A lack of understanding of the disease and denial of having it can lead to nonadherence to medications [20–22]. Negative attitudes towards treatment, such as doubts about its efficacy, can also lead to nonadherence. A European study done in 2004 [1] reported worries regarding medications and their adverse effects on health, and the risk of dependence was present in a significant proportion (37%–66%) of their respondents. Some stopped their medications to achieve the pleasurable feeling of hypomania or perceived medications as a loss of freedom. Even for those whose condition is well controlled, patients might feel that their condition is no longer active and hence do not need medications, eventually resulting in relapses [18, 23]. Psychoeducation, through its provision of knowledge about bipolar disorder and its management, has been shown to improve treatment attitudes, which in turn leads to better adherence and symptom reduction [18]. Studies have also shown that the treatment attitudes of family members influence that of the patient [18], which justifies the involvement of family members in psychosocial interventions to improve adherence.

Adherence to medications should not be seen as a homogenous concept, and psychoeducation might need to be adjusted to target different aspects of adherence. In a paper written in 2005 [24], Colom identified various forms of nonadherence seen in bipolar disorder. Late nonadherence occurs when, after a period of adherence, patients start to discontinue medications. Selective nonadherence describes patients who are selectively adherent to medications depending on the phase of the disease (acute treatment vs. maintenance treatment) or type of medication. Intermittent adherence describes a pattern of medication adherence where patients do not follow their regime consistently, opting to abandon their treatment for

specific periods, such as before an important meeting. With such heterogeneity in the patterns and causes of medication nonadherence, psychoeducation needs to be tailored to address the specific concerns of patients.

29.4 Therapeutic Alliance

Therapeutic alliance has been an essential consideration in the management of patients with bipolar disorder. Pharmacological treatment for bipolar disorder requires time for titration to find an optimal medication regime that is both efficacious and tolerable to patients. This process requires a degree of trust between patient and clinician to persist with treatment [23]. While therapeutic alliance has been shown to promote better clinical outcomes in other mental illnesses such as psychosis [25] and depression [26], more research is needed to prove the link between therapeutic alliance and clinical outcomes in bipolar disorder [27], though its association with medication adherence through an improvement in health attitudes has been well established [28]. The establishment of therapeutic alliance, hence, has been an important component in psychoeducation.

29.5 Relapse Prevention

While bipolar disorder has a strong biological basis, with medications being the mainstay of treatment, it is known that psychosocial factors are likely to affect the course of illness for bipolar disorder. It has been thought that high levels of stress were associated with a higher likelihood of relapse [29], and patients most commonly report adverse life events before acute mood episodes, whether manic or depressive [30–33]. A recent review, however, has shared that literature regarding stressful events as a trigger for relapses might be contradictory [34]. Nonetheless, stress management techniques have been an integral component in some psychoeducation programmes [35, 36], not only for relapse prevention but also to improve mental well-being.

Ehlers hypothesised [37, 38] in the social zeitgeber theory that changes in cues that affect one's biological clock, such as social demands, people or physical factors like light, also known as zeitgebers, can disrupt circadian rhythm and trigger depression in vulnerable individuals. Similar findings have been found in bipolar disorder, where a disruption in social rhythm and circadian rhythm was found to be associated with subsequent manic episode onset [34, 39]. The maintenance of circadian rhythm to prevent relapse has hence been an essential target in bipolar disorder treatment, whether through pharmacological means like lithium or psychosocial interventions such as interpersonal and social rhythm therapy [40].

Multiple studies have identified prodromal symptoms before depressive and hypo/manic episodes in bipolar disorder, with most patients experiencing at least

one prodromal sign [41]. The ability to recognise and respond to prodromal symptoms or early warning signs can lead to a reduction in rehospitalisation among bipolar patients [42]. Early warning signs will also allow for early treatment and better management of risk, such as suicide or dangerous behaviour associated with disinhibition in manic episodes. Hence, it has become a key component in psychoeducation for bipolar disorder patients to include identification and education about prodromal symptoms and an action plan for the corresponding symptoms [35, 43]. A Cochrane review [44] evaluating the efficacy of interventions to recognise early warning signs showed favourable results with a statistically significant increase in time to first recurrence and specifically to depressive episodes and a decrease in hospitalisation rates. There was also increased time to manic/hypomanic episodes, but it did not reach statistical significance.

29.6 Timing of Psychoeducation

To the authors' best knowledge, there have not been studies investigating the optimal phase of illness in which psychoeducation should be conducted in clinical practice. Most studies of the efficacy of psychoeducation in bipolar disorders have been done on populations who were euthymic at the time of intervention [45], likely due to ease in recruitment and due to insight being more intact during euthymic states, which will likely yield better results. Early intervention seems to be preferred, with adherence to maintenance therapy being more effective early in the course of illness as opposed to later. A history of multiple episodes also confers a worse prognosis, suggesting the importance of early treatment to prevent recurrent episodes [46]. While it is intuitive for psychoeducation to be conducted early in the course of illness, there might be benefits with further psychoeducation for long-term patients due to issues of late nonadherence towards medications. During periods of remission, patients are often tempted to stop taking medications, with studies showing 28% of psychiatric patients citing an improvement of symptoms [47] and 26.7% citing recovery as a cause of nonadherence [48]. Psychoeducation during such symptom-free periods might hence help to reduce nonadherence to maintenance therapy. Hospitalisations and periods of acute illness might also be good opportunities for family-focused psychoeducation due to the increased family involvement to reduce rehospitalisation [49].

29.7 Types of Psychoeducation

Formal psychoeducational interventions can be classified based on the format in which they are delivered. It can be provided to patients directly in a one-to-one fashion or in a group setting with other patients. It can also involve the patient and their family members and caregivers or just the caregivers alone (without the

patient). In addition, technological advancements have allowed psychoeducation to be delivered in various media forms, e.g., written, audio, video, online (app-based), or through a virtual reality medium.

29.8 Individual Psychoeducation

In individual psychoeducation, a one-to-one approach is employed, with the patient having the individual attention of the mental health practitioner. One of the more recognised types of psychoeducation comes from an adaptation of Colom and Vieta's manual of psychoeducation for bipolar disorder [50]. In the following referenced randomised trials, psychoeducation sessions were typically carried out by final-year psychology students [51–54], psychologists [55, 56], psychiatry trainees [57] or psychiatrists [56]. Typically, 6–12 psychoeducation sessions were carried out (except for Pelligrini et al. [56] who carried out 16 sessions and Gumus et al. [58] who carried out four sessions), each lasting between 50 and 90 min and carried out weekly or twice weekly. The common themes covered include teaching individuals to identify prodromal symptoms of both depressive and manic relapse and to come up with an action plan once those symptoms are recognised. It also covers the biological nature of the disorder and the importance of adherence to pharmacological treatment while attempting to reduce stigma.

Patients who were given individual psychoeducation in addition to routine treatment presented with a lower incidence of new manic episodes and longer time to manic relapse [55, 57], improved depressive symptoms [51, 52, 54, 57] and depressive relapses [57], fewer hospitalisations [57], regulation of sleep and social domains [52, 55], improved medication compliance [57], and global clinical impression in the clinician and patient's point of view [56]. The benefits of psychoeducation on bipolar depression are significant because most of the morbidity associated with bipolar disorder occurs during the depressive episodes rather than relapsing manic features [59, 60] because of the increased frequency and longer duration of time spent during depressive relapses [59–61]. Interestingly, a randomised trial by Wiener et al. [51] demonstrated that psychoeducation-induced biochemical changes in the form of increased neurotrophic factors, which are small secretory proteins that regulate the development and differentiation of neurons. Glial cell line-derived neurotrophic factor, a trophic factor known for its neuroprotective properties, was increased in patients who underwent psychoeducation in addition to medication therapy. Other benefits of individual psychoeducation include flexibility in session scheduling to better cater to the individual patient's schedule [62]. Individual psychoeducation tends to be more well accepted by patients due to perceptions of privacy being preserved and empowerment as owners of their session. Bipolar patients might also perceive it as more comfortable, especially with the high rates of comorbid social anxiety.

However, while there is evidence of the clinical benefit of individual psychoeducation in patients, several studies presented conflicting information. Some showed no statistically significant benefits in time to first depressive relapses or symptoms

[55, 56], manic relapses and symptoms [51, 54, 56], regulation of biological rhythm [54] and quality of life [53, 56]. There has yet to be a meta-analysis that seeks to reconcile the differences in results, likely due to the heterogeneity of studies on this topic. Nonetheless, most studies still show evidence of clinical benefit in individual psychoeducation.

29.9 Group Psychoeducation

In group psychoeducation, people with bipolar disorder received psychoeducation together in a group setting. One of the more recognised types of group psychoeducation comes from Colom and Vieta's manual of psychoeducation for bipolar disorder [35, 50], though other programmes such as Bauer and McBride's [63] Life Goals Programme have also been used. Group psychoeducation sessions were usually carried out by psychiatric nurses [64, 65], psychologists [36, 65–68], or psychiatrists [65, 69] with a group size of 5–16 individuals. Typically, 6 [66, 68, 69] or 21 [64, 67, 70, 71] psychoeducation sessions were carried out (except for Kessing et al. [65] who delivered 12 sessions), each between 45 and 120 min long and carried out weekly or twice weekly. The common themes covered include illness awareness, adherence to treatment, lifestyle regularity, and early detection of prodromal symptoms and recurrences.

Patients who underwent group psychoeducation in addition to regular treatment had a longer interval between mood episodes [36, 65, 70], fewer depressive or manic relapses [36, 70, 72] and spent fewer days acutely unwell. They also spent less time hospitalised [67, 70] and had a lower frequency of hospital admissions [65, 67]. Some of these benefits were sustained up to 5 years after the initial follow-up in one study [70]. The benefits of group psychoeducation extend to patients with bipolar disorder and comorbid personality disorders; group psychoeducation in this group of patients led to a lesser likelihood of relapse, a longer period well before relapsing and overall fewer relapses [50]. Another study [66] also showed improvements in clinician-rated anxiety and subjective mood fluctuations sustained at 6 months follow-up. Group psychoeducation results in higher adherence to pharmacological treatment [65, 66, 68, 69, 72], with one study showing a subgroup of patients who were on lithium having significantly higher and more stable lithium serum levels in those who received group psychoeducation compared to patients on pharmacological treatment alone [71]. Younger adults (18–25 years old) who received both group psychoeducation and pharmacological treatment also adhered to mood stabilisers and antipsychotics more in contrast to those treated with pharmacological treatment alone [65]. Group psychoeducation has been shown to provide beneficial functional outcomes, as evidenced by higher scores on the functioning levels using the bipolar disorder functioning scale [64]. In group psychoeducation, other patients also become a source of support as patients identify with one another and empower individuals to help others in their group [73]. Group psychoeducation might be more feasible and cost-effective than individual psychoeducation [74]. A

small study involving 85 bipolar patients found a significantly longer time to hospitalisation when they were given group as opposed to individual psychotherapy [62]. However, more research would need to be done to reach more definitive conclusions on the relative efficacies of group and individual psychoeducation.

Group psychoeducation interventions were not associated with an increase in health-related quality-of-life [66, 68]. However, these studies were limited to a six-month follow-up, which might be inadequate given that symptom recovery usually precedes functional recovery. A study by Petzold et al. [68] showed that despite six weekly group psychoeducation sessions followed up with 54 weeks of computer-based self-charting or diary (to report mood, sleep, life events, weight, menstrual data and psychiatric medication use), the intervention arm did not have any superior benefits in terms of mood episodes, time to recurrence, quality of life, self-efficacy expectations, or perceived involvement in care. The authors postulated that the lack of benefits seen might be due to their participants' characteristics, where 68% of patients had six or more previous bipolar disorder episodes, adding support to the notion that psychoeducation may be more efficacious at earlier stages of the disease. A study [74] which found the dropout rate in group psychoeducation (20.2%) to be higher than in individual psychoeducation (9.7%) sheds light on how one may choose which patients may benefit more from individual psychoeducation over group psychoeducation. Patients with comorbid social anxiety symptoms or performance anxiety may have their symptoms exacerbated in group psychoeducation. Patients felt that individual psychoeducation resulted in better privacy preservation, a greater sense of being unique, and a stronger feeling of empowerment as owners of the sessions. Patients who report a stronger need to express themselves and require more time given to them may also benefit from attending individual psychoeducation instead. This is juxtaposed against group psychoeducation, which may be more feasible to conduct based on limited resources available and more cost-effective in clinical settings.

29.10 Family-Focused Psychoeducation

In family-focused psychoeducation, people with bipolar disorder and their immediate family members (sometimes extended relatives) receive psychoeducation together as a family. Bipolar disorder, besides its debilitating effects on patients, also contributes to family burden in the form of disruptions in household routine, strained familial relations, family finances and emotional burden [75]. High-expressed emotion, a concept first studied in families of schizophrenic patients to describe critical comments, hostility, or emotional over-involvement by family members, has been shown in bipolar disorder to affect the course of illness negatively [75]. Family psychoeducation allows families to talk more freely about their loved one's illness. It brings about positive change in the family, helping the patient

and family cope better with their illness [76]. One of the more recognised types of family psychoeducation comes from family-focused psychoeducational treatments for bipolar disorder by Miklowitz et al. [77–79]. This covers psychoeducation, communication enhancement training, and problem-solving skills training. The objectives of family-focused psychoeducation are to integrate the experiences associated with episodes of bipolar relapses, accept vulnerability to future episodes, accept the necessity of medications for symptom control, distinguish between the patient's personality and symptoms of bipolar disorder, recognise and cope with stressors that may trigger relapses, and re-establishing functional family or marital relationships after an illness episode.

Those who received family-focused psychoeducation had fewer relapses [80], rehospitalisation [80], more rapid episode recovery, more significant reductions in mood symptoms overall, and better medication adherence [77, 78] over 1–2 years. Other benefits include improvements in global functioning and Clinical Global Impression Scale ratings over 1 year [81], significant improvements in social functioning, and caregivers showing decreases in burden relatives' subjective and objective burden [82]. In a study [49] which compared family-focused psychoeducation to individual psychoeducation, family-focused therapy led to a reduced risk of relapse (28% versus 60%) and rehospitalisation (12% versus 60%). This difference was postulated to be due to skills that patients and family members develop through family participation-focused therapy and family members taking a more active role in managing the illness, including a greater knowledge of bipolar disorder and effective communication and problem-solving skills. Family members could rely on the tools they developed in family treatment, such as early symptom identification, appropriate use of mental health resources, and problem-solving. This was further supported by the fact that amongst participants who had symptomatic relapses during the 2-year study, just over half of the patients in family treatment were rehospitalised, whereas almost 90% of patients in individual treatment were rehospitalised. This benefit was not attributed to differences in medication adherence in both groups, as there were none. A shorter 4-month family-focused therapy was administered to adolescents and young adults at high risk for bipolar disorder (i.e. with bipolar disorder not otherwise specified, major depressive disorder, or cyclothymic disorder who had a first-degree relative with bipolar disorder I or II and active mood symptoms) [83]. Youths who received combined treatment had a more rapid recovery from their initial mood symptoms, more weeks in remission, and a more favourable trajectory of Young Mania Rating Scale scores over 1 year than youths who underwent just 1–2 sessions of education (control group). The treatment effect was more significant among youth in families with high-expressed emotions (versus low-expressed emotions). Therefore, when family intervention is administered early in the high-risk period, it may prevent, delay or mitigate the onset or severity of bipolar disorder in children and adolescents. However, studies with longer follow-ups are required.

29.11 Caregiver-Focused Psychoeducation

In caregiver-focused psychoeducation, the target participants are the caregivers of people with bipolar disorder, and patients are not required to attend the groups. Due to the patient's poor insight, especially during manic relapses, caregivers play a significant role in identifying warning signs and helping with medication adherence. Caregiver-focused psychoeducation can be part of a more extensive family therapy programme, including communication and family problem-solving training [84]. Reinares et al. developed a programme [85] with 12 weekly 90-min group psychoeducation sessions given to caregivers focused on knowledge of bipolar disorder, the nature of the illness, skills training for its management, and coping skills. An emphasis on reducing feelings of guilt and highlighting the role of the family as allies were made. The themes covered were similar to those of other individual, group and family-focused psychoeducation programmes. Additional information taught included the role of the family in enhancing compliance, prevention and management of family stress through communication skills training (e.g. using role-playing) and problem-solving, the importance of caregivers looking after themselves, and other issues such as suicidal thoughts, hospitalisation, pregnancy, genetic risk, social resources, and legal aspects. Patients were then followed up for 1 year post-intervention, and it was found that caregiver-focused psychoeducation led to a reduction in the percentage of patients with hypomanic/manic recurrence and longer relapse-free intervals. Unfortunately, there were no differences in preventing depressive and mixed episodes nor significant differences in medication compliance. The authors attributed the discrepancy in results between manic and depressive relapses to the fact that manic prodromes are more distinct and easily detectable compared with depressive prodromes [41] and more challenging to teach how to monitor and cope.

In terms of benefit for the caregivers themselves, Madigan et al. [86] conducted a randomised trial with caregivers undergoing either a multifamily group psychoeducation programme (MFGP), solution-focused group psychotherapy (SFGP), or treatment as usual (pharmacotherapy). MFGP had benefits in terms of carer knowledge, carer burden, carer psychological distress, quality of life, and almost global functioning. MFGP and SFGP are similarly effective in improving caregiving burden. The findings of improvements in caregiving burden were also replicated by Hubbard et al. [87] who carried out a briefer psychoeducation programme (two sessions only) directed at caregivers in a group setting with additional benefits of increases in bipolar disorder knowledge and self-efficacy. These improvements were sustained or increased during the one-month follow-up. No significant change was observed on the Depression, Anxiety, and Stress Scale that assesses depression, anxiety, and stress symptoms in the carers themselves, possibly because these symptoms in caregivers were not specifically targeted in the intervention provided. These findings suggest that even a brief group psychoeducation programme directed at caregivers was effective in increasing caregivers' bipolar disorder knowledge and confidence in caregiving while reducing the burden experienced.

29.12 Bipolar Disorder and Comorbid Substance Use Disorder

Bipolar disorder is found to be associated with other comorbid psychiatric disorders, including substance use disorder [88], with a meta-analysis by Hunt et al. [89] estimating the pooled lifetime prevalence of substance use disorder to be 35.7% in bipolar I and 28.1% in bipolar II individuals. While this might be explained by shared neurobiological pathways and genetic risk factors between bipolar disorder and substance use disorders, a probable explanation is also due to the use of substances as a form of self-medication [90], with a study concluding that the prevalence of self-medication with substances was as high as 41% in bipolar I and 35% in bipolar II disorder [91].

Bipolar disorder is known to worsen functional outcomes, including cognition, and this is further exacerbated when there is comorbid substance use [92, 93]. There is also a correlation between comorbid substance use and suicidality [94]. Substance use disorders also seem to increase the recurrence of bipolar episodes, whether directly or indirectly, through the contribution of poor treatment adherence and increased psychosocial stressors [95]. As such, avoiding substance abuse has been an essential goal in psychoeducation to provide knowledge of the potential impact of substance use on disease progression and morbidity [35]. The relationship between substance use disorder and bipolar disorder is further explained in Chap. 11.

29.13 Bipolar I Versus Bipolar II Disorder

Bipolar disorder is a heterogeneous disease with varied presentations. Patients with bipolar I disorder who suffer from manic episodes experience more psychotic symptoms than patients with bipolar II disorder and have higher rates of hospitalisation [96, 97]. Patients with bipolar I experience higher levels of stigma than bipolar II disorder patients as well [98], possibly due to hospitalisations and disruptive behaviours during manic episodes. As such, a single psychoeducation programme might not suit all patients. Most studies on psychoeducation for bipolar disorder have excluded bipolar II disorder in their analysis or analysed it together with bipolar I disorder [45], with only a few having analysis specifically on bipolar II. However, there are some studies which show the benefit of psychoeducation for patients with bipolar II disorder in improving medication adherence [99] and reducing rates of disease recurrence [100]. Patients with bipolar II disorder had a higher frequency of depressive episodes [101]. Individuals may also transit across the different spectrums between bipolar I and II disorder, and depending on the predominant type of bipolar disorder the individual presents with, a flexible, tailored form of psychoeducation should be administered. For example, patients with bipolar II disorder will benefit from a tailored psychoeducation programme that focuses on

techniques to target depressive relapses and depressive symptoms while having less emphasis on psychotic symptoms, which is less common in bipolar II disorder [100].

29.14 Future Directions

In recent times, there has been growing interest in incorporating technology for psychoeducation in bipolar disorder. With the widespread usage of mobile hand-phones due to their convenience and scalability, mobile and web applications are promising avenues to increase therapeutic reach. The self-directed nature of such apps may also help to promote patient empowerment [102]. There have been multiple programmes [103–106] which have incorporated psychoeducation into applications. However, the results have not shown convincing benefits in patient outcomes [102]. While able to provide some information about bipolar disorder and symptom monitoring, most mobile applications are not based on evidence-based psychoeducation manuals, nor do they comprehensively address the main psychoeducation domains [107], with some mobile and web applications using self-reported questionnaires that are not clinically validated [102]. These technologies have not been widely incorporated into clinical practice, and doing so will likely require more convincing evidence, as well as addressing limitations in personal data protection and alerting healthcare services when there is a duty of care to do so.

With technological advances and decreasing virtual reality (VR) costs, VR has been increasingly used in psychiatry. Through the provision of a realistic and immersive experience, it serves as a promising avenue to engage patients in psychological interventions. It also potentially can provide individualised therapy while being judicious in manpower requirements. Small sample studies have been conducted investigating the use of VR in psychiatric disorders such as anxiety, depression, and posttraumatic stress disorder with mixed results [108]. VR has not been implemented in bipolar disorder psychoeducation and would be an exciting research direction moving forward.

To summarise, the areas that can be further explored would include:

1. How should psychoeducation differ based on the various clinical presentations of bipolar disorder?
2. How can we better incorporate technology (such as mobile/web applications and virtual reality) into psychoeducation?
3. What is the most efficient way of allocating resources for psychoeducation in terms of
 - (A) Best time in the disease course for psychoeducation
 - (B) Patient group that will benefit the most in psychoeducation—including the effectiveness of psychoeducation in subgroups such as those with comorbid personality or substance use disorder.

29.15 Conclusion

Psychoeducation is a psychosocial intervention that has become an integral part of the management of bipolar disorder, whether done formally as part of a structured programme or informally during clinical encounters. Psychoeducation has a significant role in the management of bipolar disorder, mainly due to several aspects of the disease. Its chronic course makes therapeutic alliance important. The recurrent mood episodes with worsening prognosis with each relapse make relapse prevention a vital therapeutic goal. In contrast, the psychosocial contribution of relapses makes psychoeducation a viable strategy for reducing recurrences. Bipolar disorder patients are also known to have high rates of medication nonadherence and poor insight, leading to high rates of relapse, contributing to society's healthcare burden. Hence, psychoeducation is a cost-effective intervention that can improve clinical and functional outcomes.

In summary, in its various formats, psychoeducation has wide-ranging benefits that should not be overlooked. The following main benefits from each form of psychoeducation are summarised as follows: fewer relapses of manic episodes (individual, group, family-focused, and caregiver-focused); longer time to manic relapse (individual, group, and family-focused); improvement in manic symptoms (family-focused), fewer relapses of depressive episodes (group and family-focused); longer time to depressive relapse (individual and group); improvements in depressive symptoms (individual and family-focused); fewer days unwell with mood symptoms with more rapid recovery (group and family-focused); fewer median number of days in hospital (group); fewer hospitalisations (individual, group, and family-focused); improvements in medication adherence (individual, group, and family-focused); improvements in global clinical impression (individual, family-focused, and caregiver-focused); decreased caregiving burden in relatives (family-focused and caregiver-focused), improved regulation of sleep (individual) and social domains (Individual and family-focused).

Moving forward, a potential direction could be to study disease and patient factors influencing the efficacy of psychoeducation to optimise its content and delivery to each patient further. Incorporating technology into psychoeducation is a promising area that can improve its efficacy and scalability.

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Chapter 30

Cognitive Behavioral Therapy for Bipolar Disorder



Luciano Dias de Mattos Souza, Evelin Franco Kelbert, and Karen Jansen

30.1 Introduction

In the 1960s, Aaron T. Beck pioneered cognitive behavioral therapy (CBT) for major depressive disorder, which later evolved into a cornerstone of psychotherapy. The efficacy of CBT in treating depression paved the way for its exploration in bipolar disorder (BD), initially focusing on negative thoughts and beliefs [1]. By the 1980s, CBT had expanded its application to bipolar symptoms, scientifically demonstrating its potential [2, 3].

Over the decades, diversified research collaborations have adapted CBT for distinct phases and stages of life, showcasing its efficacy and flexibility [4]. Although evidence-based manualized interventions exist for CBT in BD, the practice of this psychotherapeutic approach presents numerous challenges. It demands the integration of diverse knowledge areas and the establishment of a strong therapeutic alliance with the patient, considering their individual context [5–7].

This chapter delves into CBT applications, ranging from very early-onset symptoms in children to challenges faced by older adults. Emphasis is placed on what we consider important topics derived from both research and clinical practice, highlighting satisfactory outcomes. The goal is to present a step-by-step exploration of

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the main CBT protocols for BD treatment, providing strategies for practitioners and individuals navigating the complexities. This aims to chart the evolution of CBT as a tailored therapeutic approach across the lifespan.

30.2 Considerations About BD and CBT Treatments Throughout the Life Cycle and Stage of Illness

Bipolar disorder can manifest at any stage of the life cycle. Studies suggest that the onset of BD follows a trimodal distribution: early onset (mean = 17.3 years; 45% of the sample), intermediate onset (mean = 26.0 years; 35%), and late onset (mean = 41.9 years; 20%) [8]. This proposed classification facilitates the categorization of BD onset based on distinct life stages. Notably, early life onset is linked to a more severe and remitting course [9], accompanied by comorbidities such as anxiety disorders and substance abuse [10]. Consequently, the impact on the therapeutic plan may vary, contingent upon the specific life stage at which BD initiates.

Various factors, including age of onset, frequency of mood episodes, duration of illness, and the presence of concurrent mental health disorders, are intricately connected to a poorer prognosis of BD [11]. A considerable proportion of individuals with BD exhibit cognitive impairments that persist even after the remission of mood symptoms, particularly in those who undergo multiple episodes [12]. Additionally, functional deterioration may progress in nearly half of the patients, marked by a higher number of relapses, higher number of hospitalizations, more pronounced neurocognitive impairment, and increased severity of depressive symptoms [13]. These factors can act as indicators, signaling either a deterioration or acceleration of the disease, delineating a progressive course of BD for a subset of individuals affected by the disorder.

The concept of illness staging is widely applied across various medical fields to forecast the course or prognosis and optimize treatment. The BD staging models operate under the assumption that psychopathology unfolds along a predictable trajectory: from an at-risk or latency stage, through a prodrome progressing to a first clinical threshold episode, and then one or more recurrences with the potential to revert or progress to late or end-stage manifestations. The BD staging model encompasses progressive biochemical, neuroimaging, and cognitive changes, along with potential stage-specific variations in response to pharmacological and psychosocial treatments. Moreover, staging models advocate for the implementation of stage-specific treatment approaches that not only aim at symptom reduction but also hinder the neuroprogression of the illness [14].

A preliminary study including individuals with sub-threshold presentations who are probably at risk of developing bipolar or other major mental disorders assesses an intervention that includes strategies for problem-solving, reducing sleep–wake cycle disturbances, self-management of rumination, and that addresses the needs of individuals with “sub-threshold” and showed a relatively high benefit-to-risk ratio, promising levels of engagement with the therapy modules, and the therapy appears

to be acceptable to a wide range of help-seeking youth with early expressions of BD [15].

A comprehensive evaluation of the disorder's trajectory in each patient is crucial for effective treatment planning. Assessing cognitive and functional conditions at the initiation of treatment is particularly important for individuals with BD in the late stages of the disease. The incorporation of targeted pharmacological strategies and functional remediation could prove beneficial for bipolar patients in the late stages [16].

Psychosocial intervention proposals based on CBT were structured and scientifically tested according to the life cycle stage of BD patients. Especially among subjects with BD, it is necessary to adapt treatment models not only to the life cycle stage but also to the stage of neuroprogression of the disease.

30.3 CBT for Children with BD Diagnoses or at Risk for BD

The early diagnosis of BD is a topic both controversial and highly relevant. Challenges arise from the limited autonomy of diagnosed patients, variations in parental styles, and notable gaps in evidence-based treatment approaches. Clinical work with children diagnosed with bipolar disorder becomes both challenging and fraught with ethical dilemmas due to these factors [17]. Mental health professionals should recognize that interventions for childhood BD not only improve immediate mood regulation and overall functioning but also function as preventive measures against potential long-term impairments linked to the natural course of the illness. The described protocol below has demonstrated satisfactory outcomes for children diagnosed with BD, reducing mood symptoms and prevalent comorbid manifestations associated with BD [18]. Additionally, it may prove valuable in addressing mood swings and behaviors in children [19].

Child- and Family-Focused Cognitive Therapy (CFF-CBT or RAINBOW therapy) [19] serves as an adjunctive psychosocial intervention for children aged 7 to 13 with bipolar spectrum disorders and their families. This innovative pediatric treatment is specifically designed to address the unique needs of these children. It requires active involvement from parents or caregivers to establish an effective parenting coping system and aims to integrate psychoeducation and interpersonal techniques into the CBT approach through a tailored intervention. The protocol is grounded in three research areas: dysfunctional affective circuitry in pediatric BD, developmentally specific symptoms of pediatric BD, and the impact of BD on the psychosocial and interpersonal functioning of children.

This intervention comprises six pivotal components encapsulated by the acronym RAINBOW (**R**outine; **A**ffect regulation; **I** can do it!; **N**o negative thoughts and live in the now; **B**e a good friend and balanced lifestyle for parents; **O**h, how can we solve the problem?; **W**ays to find support). These components are systematically organized in a 12-session protocol designed to unfold weekly over a span of 3 months (Table 30.1). In its family-individualized format, each session lasts

Table 30.1 RAINBOW 12-session protocol for children diagnosed with BD and their families

Session	Participants	Main topics	Main component
1	Child and parents	Treatments introductions, goals and concepts; engagement issues; relationship-building with the child	Nonspecific factors as contract and therapeutic alliance
2	Child and parents	Psychoeducation about pediatric bipolar disorder; mood charts for child	Affect regulation
3	Parents only	Affect regulation and establishing routines; identifying difficult feelings; anger management	Routine and affect regulation
4	Child only	Affect-regulation skills; labeling emotions recognizing difficult feelings; triggers	Affect regulation
5	Child only	Coping skills, problem-solving; positive thinking	I can do it!; no negative thoughts; and oh, how do we solve this problem?
6	Parents only	Positive thinking; mantras; reframing negative thoughts; mindfulness	I can do it!; and no negative thoughts;
7	Child only	Communication skills (<i>BEME</i> skill = Back straight; eye contact; mouth to speak clearly; ears to listen) and interpersonal problem-solving	Be a good friend
8	Parents only	Promoting social competence; help child problem-solve and cope effectively; behavior management; balanced life and self-care	Be a good friend and balanced life for parents
9	Child, parents, and siblings	Family coping and problem-solving	Oh, how do we solve this problem?
10	Child and parents	Social support for parents and for children; drawing the “support tree”	Ways to find support
11	Child and parents	Reflection on RAINBOW experience and review of skills	All
12	Child and parents	Celebration, highlight strengths and positive qualities and discuss follow-up plan and maintenance plan	All

approximately 75 min. The RAINBOW protocol has been thoughtfully adapted for group application, extending the duration of each session accordingly while preserving its foundational structure.

Each session strictly adheres to a structured framework based on the principles of CBT. This framework incorporates key components, including concise summaries, mood assessments, agenda setting, assigned homework, and subsequent review. The comprehensive materials required for each session are detailed later in this chapter. Importantly, we suggest that therapists and/or families have the flexibility to create tailored materials as needed. This adaptability enables a dynamic and personalized application of the intervention, ensuring coherence for patients and their families while maintaining ease of comprehension. As with any psychotherapeutic process, flexibility in implementation is a crucial feature. However, it is important to note that adherence to the essential elements remains a predictive factor for achieving satisfactory therapeutic outcomes.

The **“Routine”** component aims to enhance affect regulation and reduce the manifestations and intensity of bipolar symptoms. Sleep disturbances are prevalent in children with BD and may contribute to a more severe clinical presentation of BD [20, 21]. Additionally, nutritional behaviors might play a role in exacerbating symptoms [22]. These two aspects are emphasized throughout the treatment. Therefore, the more balanced the circadian rhythm of a child with bipolar disorder, the fewer potential stressors occur to initiate or intensify BD symptoms.

Certainly, planning routines should encompass engaging in enjoyable activities both in the child’s life and in the lives of the parents, both separately and together. Scientific literature indicates that physical activity and a sense of social cohesion play a protective role in the mental health of children throughout their development, particularly for those with serious mental disorders [23, 24].

Another important factor involves establishing routines regarding adherence to pharmacological treatment. This is a common element of all psychosocial interventions for bipolar disorder since pharmacological treatment protects the child and family from future mood episodes and their various harms [18]. Poor medication adherence is a significant issue in children with BD, exacerbated by comorbid attention-deficit/hyperactivity disorder and parents’ mental disorders. Identifying and treating this comorbidity is crucial for improving medication adherence and prognosis [25, 26]. We highlight the need for constant monitoring of parents and their responsible attitude in administering this aspect of treatment. We also suggest addressing parents’ concerns about their child’s illness and treatment in any part of the protocol as well as exploring potential challenges related to adherence.

The **“Affect Regulation”** component is driven by the children’s and family members’ understanding of bipolar disorder, from the pathophysiological explanations associated with BD to its symptomatic manifestations. Beyond its psychoeducational focus, this component strives to empower parents with behavioral management techniques, fostering a more consistent and less stressful environment. Effective parental supervision mitigates stressful situations, avoids disproportionate or inconsistent punishments, and discourages disruptive parental conduct. The child is instructed in recognizing emotions, monitoring mood functionality, preventing emotional dysregulation, and responding in an emotionally regulated manner as part of their education. Beyond achieving immediate improvements in mood and enhancing communication with parents, these interventions may also diminish the likelihood of developing highly detrimental personality traits [27].

Early diagnosis of bipolar disorder in children can carry a potentially strong and harmful social stigma [28]. Self-esteem and self-efficacy significantly influence the assimilation of early experiences and emotional reactions [29, 30]. For these reasons, the I Can Do It component includes techniques to increase self-efficacy and self-esteem for both children and parents. Parents are urged to adopt an effective parenting style centered on trust, empathy, setting clear and firm boundaries, assertive and calm communication, and positive reinforcement of desirable behaviors. Children are also encouraged to observe the open, empathetic, and supportive behavior of their parents during their upbringing. They are guided to direct attention to their own qualities, cultivate self-affirming statements, and engage in collaborative behavior.

The following component's name elucidates two fundamental concepts within the treatment: **"No Negative Thoughts and Live in the Now."** Decreasing negative thinking through the identification of its contents, the cognitive distortions associated, and its impact on life functionality is the first goal of this step. Traditional CBT techniques adapted to the child's level of development, especially cognitive development, are used to differentiate helpful and unhelpful thoughts and reframe attitudes to life situations, collaborating with the improvement of coping strategies and problem-solving. Children and parents are encouraged to concentrate on the present moment, emphasizing coping strategies to enhance well-being and improve overall functioning from that perspective [31]. After thorough in-session learning, we recommend the collaborative use of applications involving both parents and children, featuring brief guided meditations to exercise essential cognitive functions for healthy development, as well as the use of positive mantras to deal with stressful events.

The component **"Be a Good Friend and Balanced Lifestyle for Parents"** involves enhancing children's social skills to foster the establishment and maintenance of friendships, particularly with peers, thereby expanding their social support network. Parents are encouraged to seek opportunities for their child to engage in activities with peers, promoting the development of new skills and friendships through activities like sleepovers, play dates, and supervised group activities. As noted, the Routine component of the protocol incorporates the importance of a balanced lifestyle for children diagnosed with BD. At this stage, parents are prompted to integrate balanced lifestyles into their daily routines. Parents of children with BD often experience both objective and subjective stress and burden, with the potential to influence the deterioration of the illness course [32]. We assert that this element of the protocol holds particular significance in enhancing the learning potential proposed in the treatment, given the evident reliance on parental participation throughout its implementation. Committed and well-informed parents act as role models for their children.

The objective of the **"Oh, How Can We Solve the Problem"** component is to involve parents and children in a collaborative and effective problem-solving process. Encouraging empathetic communication from problem identification to developing creative solutions, considering the advantages and disadvantages of each solution, and selecting the best approach to implement, along with a method for evaluating outcomes. This entire component is devoted to instructing problem-solving techniques, given their considerable potential to alleviate family conflicts and safeguard the development of crucial cognitive functions [33, 34].

In order to increase social support, the last component is **"Ways of Get Support."** Isolation, shame, and limited access may hinder parents of children with BD from connecting with friends, family members, or even health professionals who can offer respite and support. The emphasized techniques underscore the importance of identifying and actively seeking out individuals who can assist the child and/or their parents in managing challenging situations. In this step, children and their parents individually draw a tree with the names of people in their lives who may be able to

help them. School involvement and teacher participation can be beneficial during this phase. Teachers' access to support materials generated throughout the treatment should be taken into consideration [35]. After this component, booster sessions might be encouraged for maintenance treatment.

In a randomized clinical trial comparing RAINBOW with treatment as usual (TAU) for pediatric BD, adjunctive to pharmacotherapy, children who received RAINBOW exhibited greater improvement in mania, depression, and global functioning. RAINBOW can impact children's mood and functioning by improving parenting and coping skills, family flexibility, and positive family reframing. Furthermore, parenting and coping skills, family flexibility, and positive family reframing have shown promise as mediators of children's mood symptoms and global functioning in the treatment of pediatric BD [36]. All therapeutic endeavors strive to extend periods of euthymia; however, individuals diagnosed with TB commonly experience mood swings. Effectively addressing children and family frustrations arising from relapses or minor dysregulations becomes crucial.

30.4 CBT for Youths with BD Diagnoses

The onset of BD occurs before the age of 25 for two-thirds of diagnosed individuals [8]. The distribution of BD by age of onset throughout life and specific developmental contexts has important implications for the therapeutic plan. Different responses may occur due to varied contexts, emphasizing the need for age-specific therapeutic strategies.

Tailoring treatment must consider family support level and dynamics, education development, and social relationships. Specifically, parenting skills, coping family flexibility, and family-positive reframing showed promise as mediators of child mood symptoms and global functioning [36]. A CBT protocol selection between the RAINBOW or any CBT for adults with BD has to be made.

Preliminary evidence indicates that RAINBOW is acceptable and an important complement to pharmacological treatment for adolescents with BD. RAINBOW for pediatric BD, adapted from children (7–12 years) to adolescents (13–18 years), applied in a multifamily format, was effective in developing parents' skills and knowledge for coping with pediatric BD, increasing adolescents' psychosocial functioning, and improving family climate [37]. The results of this study suggest that RAINBOW is a valuable adjunctive treatment for adolescents with BD.

Nonspecific factors, especially regarding to age-related topics, must be taken into account in CBT practice with BD patients. Self-esteem, body image, sedentary, eating and sexual behaviors, drug use, engaging in work and educational activities and family or social communication are important life aspects to be discussed in the practice of CBT protocols with adolescents to focus on the course of life and the formation of themselves and identities [38]. By addressing age-specific challenges, mental health professionals optimize CBT outcomes.

30.5 CBT for Adults with BD Diagnoses

CBT stands out with substantial evidence supporting its effectiveness and represents an important clinical treatment for early interventions for BD [39]. The scientific literature suggests that adults with BD who undergo CBT treatment experience fewer episode recurrences and greater stabilization of depressive symptoms. This treatment approach may yield even more favorable outcomes with the involvement of a family member [40]. For treatment-resistant BD patients, adjunctive CBT treatment may provide alleviation from symptoms of mania, depression, and anxiety within 6 months. Furthermore, improved adaptation to daily life is observed post-treatment, with the potential for sustaining all these benefits up to 5 years after treatment completion [41].

There are two CBT protocols for bipolar disorder with wide clinical use worldwide and evidence-based [42, 43]. The first protocol was intentionally tested with flexibility, encompassing 12 to 18 weekly sessions lasting 1 h each, conducted individually, and supplemented by two reinforcement sessions over the subsequent 6 months [42]. Building upon the foundation of CBT for depression, this protocol presents the emphasis on the diathesis-stress model underlying the necessity of a combined approach (medication and psychotherapy). It uses CBT techniques for mood monitoring, with a focus on recognizing prodromes and modifying behaviors to prevent the progression of these moments into full-blown episodes. Another crucial aspect of this treatment involves customizing sleep strategies and routine management to promote a stable lifestyle, aiming to mitigate common stress triggers associated with mood episodes. Therapists are oriented to actively seek behaviors compensating for impairments from previous episodes. The protocol may also address extreme exertion attitudes as part of the therapeutic process.

This approach integrates proven CBT strategies with specific elements flexible and tailored to BD, addressing not only mood monitoring and stabilization but also the unique daily challenges associated with this condition. The reinforcement sessions contribute to the sustainability and application of learned skills over an extended timeframe.

Another structured CBT protocol was developed for individuals with BD [43] to unfold on a weekly basis, comprising 20 sessions, each lasting approximately 50–60 min (Table 30.2). Additional monthly sessions to assess the sustainability of therapeutic progress may be clinically recommended. This protocol is organized into five modules and ideally involves the engagement of family members.

The primary mode focuses on psychoeducation. During the initial session, an introduction to CBT is provided, establishing specific therapeutic contracts delineating responsibilities for each participant. The second session focuses on key BD definitions, exploring their manifestations influenced by both biological and psychosocial factors. The third and fourth sessions delve into essential pharmacological treatments, considering mechanisms of action, potential side effects, associated biases, and overall clinical management. It is crucial to emphasize the neuroprotective effects of pharmacological intervention. Session 5 addresses symptoms

Table 30.2 CBT protocol for adults diagnosed with BD

Session	Content	Main procedures	Main component
1	CBT's general view	Familiarize participants with CBT; Review treatment plans; Review the objective of homework assignments and psychoeducational material.	Psychoeducation
2	What is BD?	Feedback from homework readings; Address about the definition of BD; Provide reading material for homework.	Psychoeducation
3	Mood stabilizers	Review homework; Assess adherence to treatment; Discuss about mood stabilizers medications; Provide reading material for homework.	Psychoeducation
4	Antidepressants	Review homework; Assess adherence to treatment; Converse about antidepressants medications; Provide reading material for homework.	Psychoeducation
5	BD symptoms	Feedback from homework readings; Inquire participants about the impact of BD on their daily lives.	Psychoeducation
6	Self-monitoring	Introduce mood chart utilization; Plan a chart that aligns better with a specific description of the patient's BD symptoms.	Psychoeducation
7	Adherence to treatment	Feedback on self-monitoring charts; Introduce CBT model of adherence.	Adherence to treatment
8	Cognitive bias	Assess beliefs and attitudes about diagnosis and therapeutic plan; Compare the therapeutic plan with the patient's true behaviors; Evaluate and resolve obstacles to the therapeutic plan; Provide reading material for homework.	Cognitive and behavioral techniques
9	Depressive cognitions	Feedback from homework readings; Evaluate treatment adherence; Define cognitive errors and bias; Identify potential depressive cognitions; Introduce to automatic thoughts record (ATR); Provide material for homework.	Cognitive and behavioral techniques
10	Cognitive restructuring	Evaluate treatment adherence; Feedback on the ATR exercise; Evaluate the supporting and conflicting evidence for the depressive thoughts; Elaborate alternative explanations Identify its impact in emotional responses.	Cognitive and behavioral techniques

(continued)

Table 30.2 (continued)

Session	Content	Main procedures	Main component
11	Maniac cognitions	Evaluate treatment adherence; Feedback on the ATR and their socratic analysis; Evaluate the supporting and conflicting evidence for the hypomanic thoughts; Elaborate alternative explanations; Instruct weighing pros and cons techniques and the process of setting goals; Homework.	Cognitive and behavioral techniques
12	Depressive behavioral management	Evaluate treatment adherence; Feedback on the mood charts and ATR; Describe graded task assignment to increase activities and pleasurable moments; Present lethargic cycle of depressive episodes.	Cognitive and behavioral techniques
13	Maniac behavioral management	Evaluate treatment adherence; Feedback on the mood charts and ATR; Analyzing the rationale for implementing goal setting; Comparing mastery and pleasure experiences in euthymic states to altered mood states; Homework	Cognitive and behavioral techniques
14	Psychosocial problems	Evaluate treatment adherence; Feedback on the mood charts and ATR; Identify psychosocial challenges associated with the condition. Homework	Psychosocial problems
15	Psychosocial functioning	Evaluate treatment adherence; Feedback on the mood charts and ATR; Evaluate interpersonal relationships quality; identify current psychosocial stressor and social support sources	Psychosocial problems
16	Problem-solving technique	Evaluate treatment adherence; Select a specific psychosocial problem and apply problem-solving technique	Psychosocial problems
17–20	Applying problem-solving	Enhance the utilization of problems-solving methods in patients' lives.	Psychosocial problems
21–24	Follow-up sessions	Verify the presence of mood changes and the risk of episodes, along with assessing the effectiveness of learning related to the protocol techniques.	Maintenance treatment

associated with BD, while Session 6 revolves around monitoring these symptoms. The focus is on distinguishing between altered mood episodes and euthymic moments, along with identifying the connection between daily life experiences and manifestations of BD. This phase involves constructing and using mood charts to aid patients and their families in these endeavors.

The second module incorporates a session on treatment adherence, focusing on understanding the cognitive-behavioral model and identifying potential obstacles to treatment compliance. This stage delves into challenges related to pharmacological treatment, distorted perceptions of the diagnosis and disease course, social and interpersonal stressors, as well as difficulties with healthcare professionals. Pros and cons analysis might help patients in making important decisions to prioritize their euthymic mood.

The third module introduces cognitive-behavioral interventions. Session 8 aims to reinforce the understanding of the significance of thoughts in mood states and assists the patient in identifying distorted thoughts linked to mood changes. Session 9 concentrates on thoughts and cognitive distortions associated with depressive symptoms. Session 10 involves teaching patients the Socratic questioning technique to evaluate the validity of their thoughts and develop alternative thoughts that are adaptive to stressful situations. Session 11 reviews the types of thoughts that may serve as indicators for the onset of mania. Training patients, and particularly their families, to identify changes associated with mood swings can be essential for preventing future episodes. Cognitive restructuring techniques can also assist in addressing hypomanic distortions. Techniques focused on reevaluating plans, such as projecting into the future, aid in managing such symptoms. A dedicated emphasis on impulsive and compulsive behaviors is crucial to prevent situations that may pose risks to patients' mood and social functioning. Sessions 12 and 13 are designed to identify behavioral problems associated with depression and mania, respectively. During these sessions, forms of behavioral mood management are discussed. Reorganizing daily activities, regulating leisure tasks, and seeking feedback from others can be helpful during these moments.

Psychosocial problems are the focus of the fourth module in the protocol. Session 14 involves an open discussion on life challenges stemming from BD. Facilitating dialogue and enhancing social and communication skills can be beneficial. Session 15 aims to enhance social functioning by identifying interpersonal strengths and weaknesses and working on goal setting to help in dealing with them. Session 16 is dedicated to instructing the patient in the problem-solving technique through practical application. The subsequent sessions (17 to 20) in this module focus on addressing the psychosocial challenges identified in earlier sessions.

The last module focuses on maintenance treatment. This phase comprises 1 to 4 monthly sessions dedicated to reviewing mood monitoring and reinforcing the application of cognitive-behavioral techniques. It is advised to conduct a thorough review and refinement of the knowledge acquired through the protocol during these sessions.

It is not entirely clear which techniques contribute to the effectiveness of CBT in BD. Interventions proven effective for unipolar depression, such as psychoeducation, mood monitoring, behavioral activation, and cognitive restructuring, may potentially improve the mood of individuals with bipolar depression. While there is no evidence suggesting the efficacy of cognitive restructuring on manic or hypomanic manifestations, behavioral techniques focused on regulating the circadian rhythm may contribute to reducing the presence of these symptoms [44]. Additional clinical trials are necessary to comprehend the mechanisms of change that significantly contribute to improved health outcomes in BD.

As mentioned earlier, it is crucial to take into account the patient's overall clinical context and the potential impairments linked to neuroprogression before commencing a CBT intervention. A greater number of episodes over a lifetime is correlated with reduced effectiveness of CBT treatment [45, 46]. Considering that an earlier onset of BD symptoms carries the potential for general and cognitive deterioration it is anticipated that CBT may exhibit lower efficacy in such instances.

In these cases, other learning-based interventions may be useful as adjuncts or substitutes. Functional remediation (FR) can also be an alternative intervention adjunct to the treatment of BD. It aims to improve general functioning in individuals affected by bipolar disorder. The sessions focus on training the use of neurocognitive skills, such as attention, memory, and executive functions, for application in daily routines to enhance overall functional outcomes [47]. FR program comprised 21 sessions, weekly administered, each lasting 90 min. Most techniques involve paper-and-pencil tasks and group activities. All the protocol content is rooted in ecological tasks designed for the clinic and the home settings. Patients undergo training with exercises targeting memory, attention, problem-solving, reasoning, multitasking, and organization to enhance their functional outcomes. The majority of techniques involve paper-and-pencil tasks and group activities [48].

Research results indicated efficacy in improving functional outcomes [49] and sustaining these improvements after 1 year [50]. In the first session, introductory explanations about FR are offered, discussing the family's role, the relevance of practice, and reinforcement. The second session explores myths and realities about cognitive dysfunctions in individuals with bipolar disorder. The third meeting focuses on cognitive impairment. Sessions 4 and 5 are centered on attention, providing both psychoeducational content and crafting strategies and exercises to enhance it. Next, sessions 6, 7, 8, and 9 emphasize memory, incorporating similar technical strategies for real-life applications. Session 10 is dedicated to reading and recalling content. Session 11 aims to retrieve past information. Executive functions take the spotlight in a block of sessions (from 12 to 16), introducing self-instruction and self-monitoring techniques, activity planning, priority setting, time management, and problem-solving strategies. Session 17 highlights stress management, while sessions 18, 19, and 20 focus on communication skills, autonomy, and interpersonal relationships. The final session involves a review of key topics and the consolidation of learning [48]. Considering the neuroprogression linked to BD and the potential advantages of FR, we recommend healthcare practitioners to contemplate referring individuals for a neuropsychological

assessment and incorporating neuropsychological rehabilitation or FR techniques in a tailored manner into the CBT protocol based on the observed functional vulnerabilities.

30.6 CBT for the Elderly People with BD Diagnoses

The decreased prevalence of manic episodes and the rise in general medical clinical issues often diminish the relevance of BD in the elderly. However, these very characteristics contribute to a more intricate treatment perspective for this population [51]. These patients are typically categorized based on the age of the first episode featuring manic manifestations. Those experiencing their initial manifestation before the age of 40 are termed as having early-onset bipolar disorders (EOBD), while those with manifestations at 40 years of age or later are classified as having late-onset bipolar disorders (LOBD) [52].

The clinical presentations of these two groups seem to exhibit differences. Individuals with EOBD have a higher risk of mood disorders among their first-degree relatives, presenting a more severe phenotype. This is characterized by atypical symptoms in their initial manic episode, a higher occurrence of psychotic symptoms, and rapid cycling. On the other hand, those with LOBD more commonly report BD type II, with less pronounced manic symptoms and fewer complications related to neurological disorders, cognitive decline, and somatic conditions [53–55]. Therefore, a meticulous evaluation of neurocognitive functionality is crucial for older adults with EABD to steer clear of psychosocial treatments with limited potential for effectiveness and minimize unwarranted stress.

Few clinical trials have been conducted to assess the effects of cognitive-behavioral therapy (CBT) in older adults with BD. Oliveira [56] compared the efficacy of group CBT protocol [43] adapted for the elderly [57, 58] as adjuncts to standard pharmacological treatment. Patients in the CBT group exhibited significant reductions in manic symptoms and irrational belief patterns scores post-intervention, whereas no significant changes were observed in the psychoeducational and only medication groups. CBT may contribute to prolonged stability, emphasizing the need for comprehensive and personalized treatment approaches for this population. These findings underscore the potential benefits of incorporating CBT into standard pharmacological treatments for elderly BD.

The innovative approach of medication adherence skills training (MAST) also includes CBT techniques in its protocol [59]. Beyond its explicit emphasis on medication adherence and the intricacies of bipolar disorder, this treatment strives to tailor itself to the specific challenges encountered in old age, encompassing clinical comorbidities, cognitive impairments, and related factors. This is a comprehensive multicomponent intervention comprising 12 weekly group sessions, striking a balance between thoroughness and the desire to limit participant burden. The sessions, each lasting 1.5 h, are divided into four components: education, motivational training, medication management, and symptom management. It is recommended to

dedicate a minimum of three sessions to each component as necessary. Each session followed a structure similar to CBT, incorporating mood checking, bridging with the previous session, an interactive psychoeducation segment, agenda setting, and homework tasks [60].

The educational component has the objective of this segment is to enhance participants' understanding of the symptoms and treatment of BD. A comprehensive education on the diagnosis, symptoms, and trajectory of illness is recommended, alongside an exploration of the personal impact of the illness. The educational component includes instruction on maintaining mood charts, a practice that continues throughout the intervention, with participants submitting these charts weekly to the therapist. Additionally, participants receive printed materials summarizing the purpose, dosages, and characteristics of mood stabilizers, antipsychotics, and antidepressants, along with general factors influencing medication effectiveness. This enables individuals to tailor the provided information to their specific circumstances.

The motivational training component aims to heighten participants' awareness of the personal advantages and challenges associated with medications, offering practical coping strategies to monitor and mitigate the impact of side effects. Participants engage in a decisional balance activity, assessing the benefits and drawbacks of medication use, a technique commonly employed in motivational interviewing. Subsequently, a personalized plan is developed to address chronic side effects through behavioral techniques such as problem-solving.

Next, the medication management component focuses on enhancing participants' skills in managing medications, specifically in tracking, organizing, and using behavioral cues to remember their medications. It also aims to improve participants' ability to communicate effectively with healthcare providers. The component addresses personal practical barriers to medication adherence, facilitating goal-setting to overcome these challenges. Finally, participants engage in a role-play scenario, practicing how to discuss treatment preferences and report side effects to a healthcare professional.

The final component of MAST is symptom management. This segment aims to enhance participants' skills in coping with distress, particularly focusing on residual depressive symptoms. The goal of this component is not to provide practice in cognitive-behavioral therapy but to identify simple and/or existing coping strategies for managing day-to-day stressors based on this approach. Participants are introduced to practical methods for dealing with distressing thoughts and feelings related to the treatment of BD. Cognitive techniques emphasizing acceptance, Socratic questioning, and self-instruction are frequently employed during this stage. Additionally, participants are introduced to behavioral methods, encouraging engagement in activities and the setting of personal goals, all tied to being active and consistent participants in their treatment.

The outcomes of this protocol were promising, indicating positive adherence and acceptance from participants and high levels of satisfaction with the intervention. Self-report measures further suggest enhanced skills in medication management, reduced intensity of depressive symptoms, and improved quality of life across

various domains, with effect sizes ranging from small to moderate. However, it is important to highlight that the average age of the participants was 60 years old [59]. This factor may have played a role in the inclusion of individuals with less neuroprogression damage in the study sample.

Likewise, Tahghighi et al. [61] designed an educational program focusing on medication adherence for elderly individuals with bipolar disorder. The authors incorporated a two-session motivational interview component, commonly utilized in CBT protocols and a learned-based therapy. This program consists of five components: (1) Review and documentation of medication administration; (2) Attention from the patient and caregiver to the undesired side effects of medications that may contribute to discontinuation; (3) Review and documentation of the reasons for medication withdrawal. This is a comprehensive multicomponent intervention comprising 12 weekly group sessions, striking a balance between thoroughness and the desire to limit participant burden; (4) Education on the importance of treatment and correction of reasons for medication withdrawal identified in previous components; and (5) Use of motivational interview.

The motivational interview sessions aimed to induce behavioral change in patients through intrinsic reasons facilitated by their family caregivers. The focus was on fostering a deeper understanding of potential issues associated with medication consumption and addressing any reluctance the patient may have had in adhering to the prescribed medication regimen. Collaborating with the family caregiver, the program successfully extended the patient's duration of consistent and regular medication use. Over two training sessions, efforts were made to shift the patient's perspective regarding the drawbacks of nonadherence and underscore the advantages of regular and continuous medication use. Despite being a challenging task, these endeavors held promise for yielding positive effects, emphasizing the critical importance of enhancing medication adherence in this patient population. The experimental study results indicated that the motivational-educational program exhibited a noteworthy improvement in the mean medication adherence score compared to the control group. Based on the outcomes of these programs, we recommend incorporating motivational interviewing techniques into CBT treatments for elderly individuals with BD in nonadvanced stages of neuroprogression.

In a similar perspective, recovery-focused therapy (RFT) also emerges as a CBT treatment adapted for BD patients [62], relying on the collaboration of individuals living with BD [63] that presents promising results for elderly people, like better outcomes regarding time to relapse and mood symptoms [15]. RfT is designed individually to assist clients in identifying meaningful, personal goals that enable them to lead fulfilling lives alongside their experiences with bipolar disorder. Whether symptom-related or centered around aspects like relationships, social engagement, or work, the therapist collaborates with the client during initial sessions to create a shared understanding of recovery. Establishing an individualized case formulation is a crucial aspect of the process, ensuring that the therapy aligns with the person's specific needs. RfT underscores the significance of maintaining a flexible approach to therapy engagement, giving importance to rapport-building and considering the

timing, duration, and frequency of sessions. In their experimental study with elderly individuals, this protocol was tested using 14 therapy sessions, with six or more sessions considered an appropriate therapeutic dose.

30.7 Clinical Tips

- CBT practice should be tailored according to the stage of the life cycle, considering the stages of neuroprogression and social aspects of each patient.
- CBT for pediatric BD may also serve as preventive action against potential long-term impairments associated with the natural course of the illness.
- Consider social age-specific life aspects when applying CBT for adolescents or young adults with BD.
- The integration of family members in CBT increases its benefits also for all ages.
- Consider CBT as an effective intervention for elderly individuals with late-onset BD.
- CBT for BD may not be effective when patients present an advanced stage of neuroprogression, as well as during crisis situations, hospitalizations, or psychotic manifestations.
- Explore tailored CBT protocols and adjunct neurocognitive interventions for older adults or adults in late-stage BD.

30.8 Future Perspectives

Cognitive-behavior therapists should consider the integration of new technologies into psychotherapeutic procedures. The use of applications, wearable devices, ease of information sharing, and the increasing familiarity with virtual behaviors suggest the use of hybrid strategies to enhance patients' and their families' understanding of the disorder. This includes access to self-monitoring of behaviors, emotions, and thoughts, identification of prodromes, implementation of action plans to deal with episodes, as well as greater consistency in the social support network [64–68]. Moreover, a hybrid intervention, therapist-led, incorporating cognitive remediation therapy and a computerized program, has shown feasibility for individuals with bipolar disorders. This approach holds the potential to improve cognition and overall functioning [69].

Regarding the psychotherapeutic techniques used, established CBT protocols can increase benefits from incorporating techniques found in third-wave CBT, especially for better emotional regulation in cases of psychiatric comorbidity associated with BD [70, 71]. Similarly, specific techniques from cognitive rehabilitation or remediation can be applied preventively, considering early impairments in BD and their potential impact on symptoms and the expansion of cognitive reserve.

30.9 Conclusion

Clinical and research evidence underscores the effectiveness of CBT as a supplementary treatment modality alongside pharmacotherapy for individuals diagnosed with BD. Protocols that strategically focus on enhancing patients' and their families' understanding of the illness, fostering awareness regarding the significance of drug treatment and a healthy lifestyle, establishing personalized techniques for early identification of TB manifestations in patients' daily lives, delineating preventive strategies and episode management actions, and addressing functional and social losses resulting from prior episodes tend to yield favorable outcomes.

It is crucial to note that the aforementioned benefits may not be guaranteed for individuals experiencing advanced neuroprogression of the illness. Therefore, we emphasize the importance of early application of existing CBT interventions, extending their reach to populations at a heightened risk of BD development. Furthermore, there is a recognized necessity to devise psychosocial interventions utilizing the tools inherent in the CBT approach to forestall the progression of neurodegeneration within this specific population.

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Chapter 31

Specific Management for Patients with Suicidal Ideation



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31.1 Introduction

According to the World Health Organization (WHO), suicide is an alarming global concern, standing as the fourth leading cause of death among 15–29-year-olds in 2019. Every year, 703,000 people take their own lives, and there are many more who attempt suicide [1]. More than 90% of individuals who die by suicide had a diagnosis of psychiatric illness, and bipolar disorder has the highest rate of suicide of all psychiatric conditions, approximately 20–30 times that of the general population [2]. Suicide is one of the leading causes of death in bipolar disorder, with approximately 6%–7% of identified patients with bipolar disorder dying by suicide [3]. This demonstrates the importance of frequent monitoring of suicidal ideation by clinicians. A more in-depth discussion of the epidemiology of suicidal behavior in

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bipolar disorder was previously explored in the chapter entitled “Evidence-Based Clinical Guide to Suicide Risk and Prevention in People with Bipolar Disorders.”

The management of patients with suicidal ideation involves a complex approach, which includes pharmacological interventions as well as nonpharmacological measures such as psychosocial actions, along with other therapeutic strategies. The aim of the present chapter is to review the main evidence-based strategies used in the management of patients with suicidal ideation with a focus on psychosocial and preventive interventions since the pharmacological approach was already discussed in a prior chapter.

31.2 Clinical Evaluation

During the clinical evaluation of a patient with bipolar disorder, it is important to assess signs and factors that may indicate a heightened risk of suicide. Patients may not always reveal or express their intentions during clinical consultations. Therefore, we must be attentive to signals given by the patient, and in the case of suicidal ideation, investigate possible methods and plans already devised, such as the type of weapon to be used, whether by hanging, car accident, or drowning, for example. The clinician should inquire about previous attempts, lethality, circumstances involved, and the impact on the patient and their family after the attempt.

Some warning signs may also be present in the assessment of a patient with suicidal ideation, among them a decreased sense of purpose for living and a higher score on scales measuring lifetime aggression and impulsivity. Predicting which patients will attempt suicide remains a complex task. Generally, suicide attempts can be divided into planned and impulsive categories, with the latter being more challenging to anticipate.

Various well-described risk factors for suicide exist in bipolar disorder, and they were already discussed in the chapter entitled “Evidence-Based Clinical Guide to Suicide Risk and Prevention in People with Bipolar Disorders.” From a clinical history perspective, the main one is a history of previous attempts. Recent hospital discharge is another important factor to consider, especially after early discharges with persistent ideation. Other factors include the number of previous hospitalizations,

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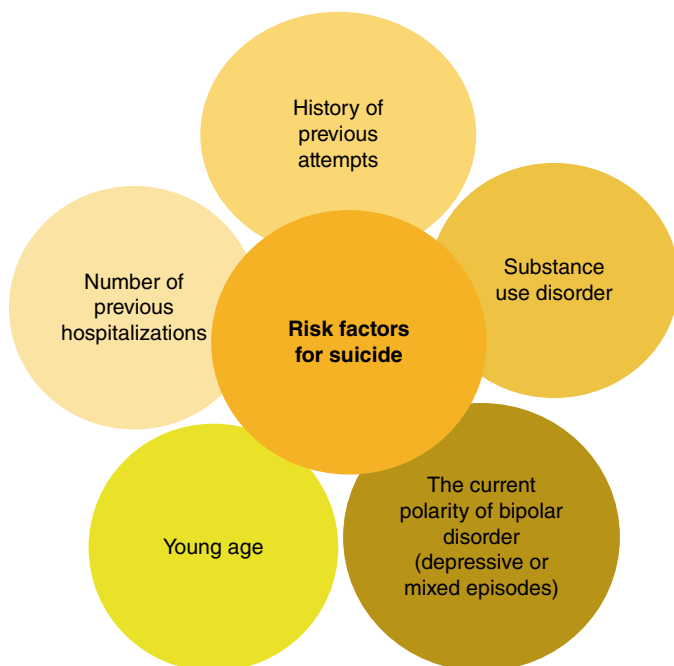


Fig. 31.1 Risk factors that should be included in the clinical evaluation

young age, a short time since the diagnosis of mood disorder, and personality traits (Fig. 31.1). Individuals with more impulsive, aggressive personalities or marked by hopelessness and low frustration tolerance have an elevated suicide risk. Occupational history is also important, with recent dismissals increasing the risk, especially when linked to debt and financial issues. Poor sleep quality and high body mass index also seem to be involved [4]. The current polarity of bipolar disorder is relevant, with individuals in depressive or mixed episodes presenting a higher risk, while manic episodes may act as a protective factor. In comparing mixed and depressive episodes, it appears that individuals with some degree of manic symptoms, such as irritability and dysphoria, may have higher rates of suicide attempts, but studies are not unanimous.

The Columbia Suicide Severity Rating Scale (C-SSRS) is a tool developed by researchers at Columbia University to evaluate and measure suicidal ideation. While the complete protocol is ideally administered by trained professionals, its screening version, comprising six succinct “yes” or “no” inquiries, allows the use by a broader audience, including family members and other professionals. Encompassing a spectrum from passive contemplations to concrete attempts, this scale not only serves as a reliable measure of suicidal ideation but also proves invaluable in uncovering previously undetected thoughts of self-harm during clinical assessments.

31.3 Psychosocial Interventions

The psychosocial approach represents one of the dimensions involved in the assessment and management of patients with suicidal ideation. It encompasses various nonpharmacological strategies that work in conjunction with other therapeutic approaches.

31.3.1 *Cognitive-Behavioral Therapy*

Psychoeducation appears to be efficacious and is a core element of more elaborate and intensive psychotherapies [5]. Psychoeducation can be administered to an individual patient and family, or to a group of patients and families. The main pillar of psychoeducation is to enhance the patient's understanding of their illness, contributing to the reduction of guilt and stigma, while also combating misinformation. The purpose is to transform guilt into responsibility and hopelessness into active self-care [6].

Cognitive-behavioral therapy occupies a central place in psychosocial treatment. A randomized study showed that a relatively brief cognitive therapy intervention was effective in preventing suicide attempts for adults who recently attempted suicide. The study included 120 individuals who had attempted suicide and underwent medical or psychiatric assessments within 48 h of the incident. The therapy applied cognitive and behavioral strategies to address identified thoughts and beliefs, guiding participants in developing adaptive coping mechanisms for stressors. Specific vulnerability factors addressed included hopelessness, poor problem-solving, impaired impulse control, treatment noncompliance, and social isolation. Results revealed a significantly lower reattempt rate in the cognitive therapy group compared to the usual care group. The hazard ratio was 0.51 (95% CI, 0.26–0.997), indicating that participants in the cognitive therapy group were 50% less likely to attempt suicide during the follow-up period than those in the usual care group [7]. A meta-analysis showed that CBT, encompassing cognitive-behavioral and problem-solving therapy demonstrated a lower likelihood of individuals engaging in repeated self-harm at both the 6-month (odds ratio 0.54, 95% CI 0.34–0.85; 12 trials; $n = 1317$) and the 12-month follow-up (0.80, 0.65–0.98; ten trials; $n = 2232$). Additionally, noteworthy enhancements were observed in secondary outcomes, including reductions in depression, hopelessness, suicidal ideation, and improved problem-solving skills [8].

31.3.2 *Dialectical Behavior Therapy*

Dialectical behavior therapy (DBT) is an outpatient treatment offered through four modalities, which include individual psychotherapy, group skills training, out-of-session coaching, and therapist consultation team meetings. The treatment usually

lasts for 1 year. This technique has been demonstrated to reduce self-directed violence in clinical trials, according to a meta-analysis that included 18 controlled trials of DBT [9].

A recent randomized clinical trial aimed to determine whether DBT for adolescents with bipolar spectrum disorder could be more effective than the current standard of care (SOC) in reducing suicide attempts within 1 year [10]. This study is relevant because the early onset of bipolar mood disorder can imply an increased risk of suicide. In this study, participants aged 12–18 years were randomly assigned to 36 sessions of DBT ($n = 47$) or SOC ($n = 53$). It is important to note that all participants received medication management during the follow-up period.

Suicide attempts during the 1-year period, mood states (mania or depression), and measures of signs and symptoms were the primary outcomes. Secondary analyses included the effect of DBT on individuals with a history of suicide attempts and improvements in emotional dysregulation.

At the beginning of the study, participants in both groups reported similar numbers of suicide attempts according to the Adolescent Longitudinal Follow-Up Evaluation (ALIFE). The mean number of attempts for the DBT group was 2.0, and 1.8 for the SOC group. Another scale used was the C-SSRS, in this scenario, the DBT group had a slightly higher number of suicide attempts than the SOC group, with means of 1.4 and 0.6 attempts, respectively ($p = 0.02$) [10].

After being evaluated quarterly for 1 year, the DBT group showed fewer suicide attempts, as assessed by ALIFE (mean of 0.2 vs. 1.1) and C-SSRS (mean of 0.04 vs. 0.1; $p = 0.03$ for both measures). The reduction in incidences of suicide attempts was 0.32 for ALIFE and 0.13 for C-SSRS, indicating more favorable outcomes with DBT compared to standard care, although both groups showed improvements in mood signs and symptoms and mood episodes during the study period.

One focus of DBT is reducing emotional dysregulation. For patients with baseline dysregulation, DBT may help reduce suicide attempts by providing better emotional control strategies. It is emphasized that more studies are needed to support the amplification and generalization of the results found, given the lack of diversity in the studied population (predominantly female and 74% white) [10]. However, the therapeutic focus of DBT on distress tolerance, social skills, and emotional regulation appears to be an important therapeutic strategy for reducing suicide attempts.

A meta-analysis reviewed the impact of DBT on outcomes associated with suicide; however, it did not specifically focus on the population with bipolar disorder. Suicide-related outcomes were categorized into three groups: self-directed violence (i.e., suicidal and nonsuicidal self-injurious behavior), accessing psychiatric crisis services (i.e., inpatient psychiatric care and presentation to the emergency department), and suicidal ideation. Random effects meta-analyses demonstrated that DBT reduced self-directed violence (Cohen $d = -0.324$, 95% CI = -0.471 to -0.176) and reduced frequency of accessing psychiatric crisis services ($d = -0.379$, 95% CI = -0.581 to -0.176). There was not a significant pooled effect of DBT with regard to suicidal ideation ($d = -0.229$, 95% CI = -0.473 to 0.016) [9]. Nevertheless, it is important to highlight that the average impact of DBT, when combined across

all studies, was relatively moderate. As a form of psychotherapy, DBT constitutes a component of comprehensive suicide prevention strategies within clinical populations and should be taken into account alongside concurrent initiatives aimed at reducing the risk of suicide through means such as safety measures [11].

31.3.3 *Mindfulness-Based Intervention*

A 2020 systematic review aimed to assess the impact of mindfulness-based interventions on reducing suicidal behaviors. This technique is rooted in training individuals to maintain attention in the present moment, without judgment and in a nonreactive manner. Various interventions share this common starting point. The authors found evidence regarding mindfulness-based cognitive therapy. Among the ten studies reviewed, nine reported a reduction in suicide-associated risk factors, such as impulsivity and depressive symptoms. However, despite promising results, this research field still requires further studies [12].

31.4 Pharmacological Treatments

Pharmacological treatment for patients with suicidal ideation remains a field of ongoing discovery, and the specification of suicidal ideation in the context of patients with bipolar disorder further narrows the scope of knowledge. Within this branch, lithium stands out as the medication option with the greatest potential to prevent suicide for several years, although the debate about its real efficacy in this aspect still exists. In 2013, a meta-analysis coordinated by Cipriani and colleagues included 48 clinical trials aimed at comparing lithium with a placebo or other medications used for mood disorder treatment (antidepressants and antipsychotics, among others). The primary outcomes sought were completed suicide, self-harm episodes, and all-cause mortality. The sample involved patients with unipolar depression, bipolar depression, or schizoaffective disorder [13].

The results of this meta-analysis reaffirmed that lithium, compared to placebo, was able to reduce the risk of suicide (OR 0.13; 95% CI 0.03 to 0.66) and decrease the risk of all-cause mortality (OR 0.38; 95% CI 0.15 to 0.95). However, when patients with unipolar or bipolar disorder were evaluated separately, sensitivity analysis showed that the results were not significantly altered [13]. This study sets the initial benchmark for comparison for subsequent studies.

A more recent meta-analysis, published in 2022 by Rible and colleagues, aimed to study the role of lithium in preventing suicides in adults with major depressive disorder or bipolar disorder [14]. In the included studies, a reduction in the likelihood of suicide was observed in patients treated with lithium compared to placebo

(OR 0.30, 95% CI 0.09–1.02, $P = 0.05$); however, the results did not reach statistical significance [14]. In light of the aforementioned studies, some limitations of systematic reviews and meta-analyses of randomized clinical trials become evident, as the number of suicides in the lithium-treated and comparator groups is often low.

The first randomized, double-blind, placebo-controlled clinical trial was conducted by Katz and colleagues, aiming to measure the efficacy of lithium in preventing or delaying the recurrence of suicide-related events in participants with bipolar disorder or depression who survived a recent event. The groups, consisting of a population of U.S. war veterans, were randomized into a placebo group and a lithium group. The primary outcome was the time of a suicide-related event (suicide death, nonfatal suicide attempt, hospitalization to prevent suicide, and interrupted suicide attempt). As stated in the initial study design, a futility analysis would be conducted when half of the sample was reached; however, the committee opted to anticipate this evaluation. After conducting the futility analysis, it was found that due to the low number of primary outcomes, the probability of rejecting the null hypothesis would be less than 10%, and the study was recommended to be stopped.

As the objective of this chapter is to provide information focused on bipolar disorder, it is important to note that the study did not have sufficient participation of patients with bipolar disorder to test whether the outcomes could differ from the unipolar depression group. In light of the above, lithium appears to have evidence in suicide prevention; however, there is still difficulty in establishing which patient profile it exerts this function and at what point in the treatment it can modify the outcomes.

Other medications seem to have evidence regarding reducing the risk of suicide, but in other populations, such as clozapine for patients with schizophrenia and schizoaffective disorder [15]. Studies on ketamine are being conducted but without emphasis on the bipolar disorder population.

31.5 Other Treatments

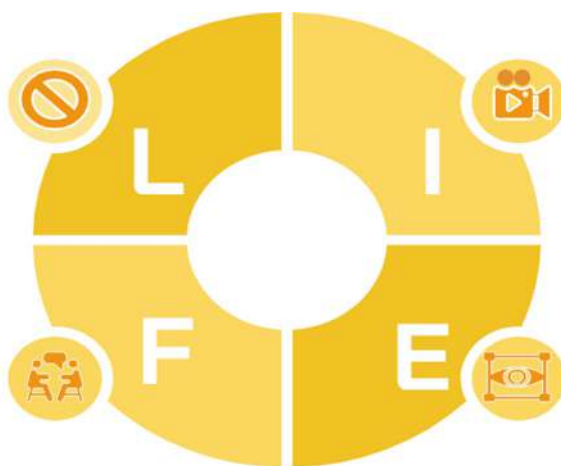
In addition to psychotherapeutic and pharmacological interventions, some studies point to the use of neuromodulation techniques such as electroconvulsive therapy (ECT). Most studies addressing the role of ECT in suicidality are based on populations with unipolar depression. Some studies have included assessments of patients with bipolar disorder among patients with other diagnoses. A recent population-based study carried out in Denmark with 10,000 individuals diagnosed with mental disorders (unipolar depression, bipolar disorder, psychotic disorder, or personality disorder) showed that among 2692 participants with bipolar disorder, there was a 73% reduction in the number of incidents of self-harm/suicide attempts when comparing the month leading up to and the month following initiation of ECT [16].

Another recent population-based study conducted in Sweden showed that among 1178 patients with depression symptoms (980 with unipolar depression and 198 with bipolar depression) and suicidal ideation, 75.64% ($N = 891$) exhibited no SI at the end of treatment. Among patients with bipolar depression, there was a 75.30% response rate. There was no statistical difference in response rate compared to patients with unipolar depression [16]. There is insufficient data in the literature to indicate other neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) for patients with bipolar disorder and suicidal ideation.

31.6 Prevention

Several suicide prevention measures have been reported. We can initially divide these strategies into measures to be implemented at the individual and population levels. The first is implemented for patients at risk in a focused manner, while the second requires multisectoral collaboration between all relevant stakeholders.

Regarding population-level measures, we highlight the WHO's "LIVE LIFE" approach, which, under the acronym "LIFE" (Fig. 31.2), presents four approaches with proven effectiveness at the population level [17].



Limit access to means of suicide
Interact with the media on responsible reporting
Foster life skills of young people
Early identify and support everyone affected

Fig. 31.2 The World Health Organization (WHO) recommends that suicide prevention interventions be implemented at the national level, rather than solely at the individual level. The acronym LIFE encompasses four evidence-based strategies that can be applied

1. Limit access to means of suicide:

- Making lethal means of suicide less easily available gives persons in distress time for acute crises to pass before taking fatal action;
- Some of the examples given by the document include banning highly hazardous pesticides, restricting firearms, installing barriers at “jump sites,” limiting access to ligature points, or taking other measures to make it more difficult to access the means of suicide;
- In this strategy, it is also possible to consider individual measures for patients at risk, such as restricting access to knives, medications, windows, poisons, and weapons. This involves recruiting the assistance of family members or other individuals close to the person.

2. Interact with the media on responsible reporting

- Widely disseminated stories of death by suicide are often followed by more suicides in the population, while stories of overcoming a suicidal crisis can lead to fewer suicides. Thus, the WHO document “Preventing Suicide: A Resource for Media Professionals” outlines recommendations, presented as “Dos” and “Don’ts,” when reporting on suicide [18].

Dos
Do provide accurate information about where and how to seek help for suicidal thoughts and suicidal crises
Do apply particular caution when reporting celebrity suicides.
Do educate the public with the facts about suicide and suicide prevention based on accurate information.
Do report stories of how to cope with life stressors and/ or suicidal thoughts and the importance of help-seeking
Do apply caution when interviewing bereaved family members or friends or persons with lived experience of suicide
Do recognize that media professionals may themselves be affected when covering stories about suicide

Don'ts
Don't use sensational language in headlines
Don't describe the method used
Don't name or provide details about the site/location
Don't report the details of suicide notes
Don't oversimplify the reason for a suicide or reduce it to a single factor
Don't use photographs, video footage, audio recordings, or digital or social media links
Don't use language/content which sensationalizes, romanticizes or normalizes suicide, or that presents it as a viable solution to problems
Don't position suiciderelated content as the top story and don't unduly repeat such stories

3. Foster life skills of young people

- Adolescence is undeniably a pivotal phase for acquiring socioemotional skills, yet it is also a time of risk for mental health conditions due to various factors. The WHO’s Helping Adolescents Thrive (HAT) guidelines advocate for programs that embrace a positive mental health approach, steering away from explicit emphasis on suicide. Furthermore, the guidelines recommend implementing initiatives in schools, such as anti-bullying programs, along with appropriate guidance for parents regarding mental health and risk factors [19].

4. Early identify and support everyone affected

- Intended to ensure that people who are at risk of suicide, or who have attempted suicide, receive the support and care that they need.

The importance of training and guidance for non-psychiatrist physicians regarding risk factors, identification, and appropriate management for patients at risk of suicide is emphasized. This is particularly significant, as individuals prior to the suicide crisis may go to non-psychiatrist physicians [20–22]. When addressing adolescent mental health, school-based interventions have demonstrated promising outcomes in reducing both suicidal ideation and behavior. However, additional studies in this area are necessary for a more comprehensive understanding [23]. A recent systematic review of elderly suicide prevention programs indicated that there is evidence suggesting interventions targeting loneliness and improving social support through group activities or telephone outreach may help reduce suicide mortality [24].

Safety planning-type interventions are a very important measure in the prevention of suicide. A recent meta-analysis revealed that safety planning-type interventions were linked to a 43% reduction in suicidal behavior, although no impact was observed on suicidal ideation [25]. The goal of safety planning-type interventions is to lessen the imminent risk of suicidal behavior by collaboratively creating a personalized plan with the patient. This plan incorporates a specific set of coping strategies and sources of support and consists of six fundamental components detailed below, all designed to resonate meaningfully with the individual [26].

1. Recognition of Warning Signs

- Include recognizing personal situations, thoughts, moods, or behaviors that immediately precede suicidal crises, such as feeling irritable, depressed, hopeless, or having thoughts like “I cannot take it anymore,” or changing behaviors and spending increased time alone.

2. Internal Coping Strategies

- This strategy is crucial as it helps individuals build self-efficacy by enabling them to find ways to distract themselves from crises and prevent the escalation of suicidal ideation. Examples include taking a shower, going for a walk, reading, engaging in a hobby, and exercising.

3. Socialization Strategies for Distraction and Support: utilizing social contacts as a means of distraction from suicidal thoughts

- In this step, the goal is to socialize with friends or family without explicitly revealing the suicidal crisis. The aim is to distract from problems and suicidal thoughts, based on the idea that patients will feel more connected to these individuals, thereby enhancing their sense of belonging. Patients can identify individuals or places where socialization occurs naturally, such as coffee shops and workplaces. They should be encouraged to avoid environments where alcohol or other substances may be present.

4. Social Contacts for Assistance in Resolving Suicidal Crises: contacting family members or friends who may help to resolve the crisis

- From this step on, there is a shift that involves sharing the suicidal crisis with others. Here, patients may choose to inform family members or friends about the crisis. It is crucial to carefully consider and select someone for the plan, assessing the likelihood of reaching this individual and whether they could provide assistance or potentially exacerbate the crisis.

5. Professional and Agency Contacts to Help Resolve Suicidal Crises

- It involves identifying and listing professionals or support locations that can assist the patient during a crisis. The list should include names, contact information, and, when applicable, addresses of these individuals and facilities. Among these, it is recommended to include a 24-h emergency facility or national support services capable of receiving emergency calls. As with the

previous steps, this should be used if the earlier strategies have not proven effective in resolving the crisis.

6. Means Restriction: reducing the potential use of lethal means

- This step is essential, as the risk of suicide intensifies when the plan involves an available and lethal method. Its significance persists even in patients who do not have a specific plan involving lethal methods. As previously mentioned, some useful strategies include the safe storage and dispensing of medication and restricting access to firearms or knives. The support of family members and friends may be necessary. This step is listed after the others because, following the identification of ways to cope with suicidal feelings, the patient may be more open to discussing the possibility of removing or restricting access to these lethal means.

31.7 Future Perspectives

Suicide is not exclusive to individuals with bipolar disorder; however, suicidality is more prevalent within this group [27]. Future perspectives include the necessity for interventions specifically targeting the risk factors unique to individuals with bipolar disorder. A greater volume of research exploring genetic and neurobiological aspects is necessary to enhance inferences regarding the specificities of this population [28].

An increasing body of evidence within the field of genetics associated with suicide in bipolar patients is emerging. However, there is still a paucity of genetic studies, and findings exhibit low replicability. While several structural brain imaging studies have identified correlates of suicide attempts within exclusive bipolar disorder samples, replication of these findings is currently unavailable [28]. A modest selection of studies on suicide attempts or deaths in bipolar disorder did not yield significant replicated peripheral marker findings. As the ongoing development of neurobiological models for suicide risk remains an active area of study [3, 21, 29–31], it is crucial to emphasize the reporting of additional data specific to bipolar disorder whenever possible. This emphasis is necessary for the advancement of understanding in this significant but still underdeveloped field [27].

Another issue is the limited generalizability of findings regarding suicidality and bipolar disorder since the majority of the existing literature comes from European and North American studies. Additionally, studies involving patients with suicidal ideation and suicidal behavior present technical limitations, as the allocation to a control group of patients with a significant risk of life in randomized clinical trials carries ethical implications. There is a current trend in research to increasingly select patient samples with the aim of demonstrating improved outcomes for the proposed interventions. However, on the other hand, the exclusion of severely ill patients limits the applicability of the findings.

In addition to new technologies, a challenge for the future is to implement on a larger scale the well-established knowledge, in an effort to provide access to measures (for instance, lithium and ECT) for the treatment and prevention of suicide.

Future perspectives encompass possibilities that may seem distant and less applicable at the moment; however, the long-term vision, coupled with curiosity and a desire for new resolutions, is what motivates the research endeavor. In this context of innovation, integration with technological advancements, such as the analysis of digital data through machine learning techniques, may prove to be an ally in predicting potential suicide risks. Future interventions may involve remote monitoring and real-time interventions through digital supports, extending beyond the techniques of care currently provided.

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Chapter 32

Interpersonal and Social Rhythm Therapy (IPSRT) for Bipolar Disorders



Holly A. Swartz and Danielle M. Novick

32.1 Introduction

Interpersonal and social rhythm therapy (IPSRT) is an evidence-based psychotherapy for bipolar disorder. Developed in the 1990s by Dr. Ellen Frank at the University of Pittsburgh as a treatment for bipolar I disorder [1], IPSRT involves three integrated elements: interpersonal psychotherapy, social rhythm therapy, and psychoeducation. Over the course of IPSRT treatment, therapists help patients resolve interpersonal difficulties, optimize the regularity of daily routines, and understand their illness. The goal of IPSRT is to achieve symptom remission by improving interpersonal functioning, establishing regular social rhythms, and supporting medication adherence [1].

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32.2 Rationale

32.2.1 Relationships and Mood

IPSRT is considered an adaptation of interpersonal psychotherapy (IPT), an evidence-based treatment for depression [2]. Originally developed as a treatment for unipolar depression, IPT builds on empirical evidence demonstrating reciprocal connections between mood symptoms and interpersonal relationships [3, 4]. IPT focuses on helping patients improve problematic interpersonal relationships or life circumstances associated with the current mood episode, thereby bringing about symptom reduction. As in IPT, the IPSRT therapist selects one or perhaps two individual problem area(s) as the focus of the IPT component of therapy, which may include a role transition, role dispute, grief, interpersonal deficit, and/or grief for the lost healthy self. Iteratively, improvement in the IPT problem area leads to improvement in symptoms, which in turn leads to further improvements in interpersonal functioning.

32.2.2 Circadian Rhythms

The social rhythm therapy (SRT) component of IPSRT helps individuals establish regular daily schedules to promote circadian rhythm stability which in turn improves mood. It is based on evidence showing that disturbances in circadian biology are central to bipolar disorder [5] and that individuals with bipolar disorder are especially vulnerable to circadian rhythm disruptions [6]. Circadian processes exert control over core features of depressive and manic episodes, including mood, energy, sleep, and concentration [7], therefore stabilization of circadian rhythms offers a pathway to stabilizing mood disorders.

32.2.3 Circadian Rhythms and Bipolar Disorder

Understanding the relationship between circadian rhythms and mood is central to the rationale for IPSRT. Thus, it is important for IPSRT therapists and their patients to have at least a rudimentary understanding of circadian biology:

Circadian rhythms are approximately 24-h cycles found throughout the plant and animal kingdom [8]. Honed through evolution to help species optimally adapt to their environment, circadian rhythms are entrained by intrinsic internal biologic processes that maintain an approximately 24-h rhythm and external factors such as daylight that can modify the circadian period or cycle. Circadian rhythms enable

nocturnal animals such as owls and mice to stay awake at night when their preferred prey is accessible and fall asleep during the day when they would be less likely to find food. Similarly, they enable diurnal animals, including humans, to be alert during daylight hours, i.e., sleep-wake patterns that increase chances for successful food acquisition and survival. When seasons or day length change, the circadian system adapts to fluctuating light conditions, ensuring alignment between cycles in the external world and internal biological processes.

The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, is the central pacemaker for the circadian system. Genes within the SCN control numerous biological processes, causing them to run on an approximately 24-h cycle. Physiologic processes with circadian periodicity (i.e., repeating patterns within a 24-h period) include the sleep-wake cycle, core body temperature, cortisol levels, autonomic function, memory, psychomotor performance, concentration, elimination, and feeding patterns [9]. Thus, many key biological processes are under circadian control.

The SCN receives information about changes in light (e.g., lengthening days, moving across time zones with new light-dark schedules) via a direct connection between the retina and the hypothalamus, the retinohypothalamic pathway. The SCN is also connected to circadian pacemakers located throughout the body that control diverse physiologic functions, including feeding-fasting behaviors, blood pressure, and body temperature [10]. These peripheral pacemakers both receive information from and send information to the SCN. Thus, circadian function is modulated not only by light but also by behaviors that affect peripheral oscillators such as mealtimes, blood pressure fluctuations (e.g. positional changes related to getting in and out of bed), and body temperature changes (e.g., exercise). These external inputs to the SCN—including light/dark cycles, feeding patterns, sleep-wake patterns, and exercise—entrain circadian rhythms [10], thereby ensuring alignment between external and internal clocks.

Current evidence from animal models, biomarkers, and physiology studies suggests that circadian system abnormalities are common in bipolar disorder and are likely both etiologic and caused by the disease itself [7, 11]. Individuals with mood disorders have baseline irregularities in biological rhythms as measured by actigraphy [12], the social rhythm metric [13, 14], assessments of diurnal preference [15], and melatonin secretion profiles [5]. Furthermore, genetic association studies have indicated that certain clock gene variants may confer vulnerability for mood spectrum disorders [16]. This biological vulnerability to circadian misalignment contributes to the genesis of mood episodes in individuals with bipolar disorder [17]. When in the midst of a mood episode, bipolar pathology disrupts important circadian phenomena, including the sleep-wake cycle, energy fluctuations, and appetite. SRT mitigates circadian disruption by helping individuals develop behaviors to entrain an easily perturbed circadian system.

32.2.4 *Zeitgebers and Zeitstörers*

Circadian researchers refer to exogenous environmental factors that set the circadian clock as *zeitgebers*, or “time givers.” Examples of *zeitgebers* include the light-dark cycle, changing seasons, and feeding activity. Research shows that perturbations in these *zeitgebers* can cause mood symptoms in biologically vulnerable individuals [6] and that *zeitstörers*—physical, chemical, or psychosocial events that disturb the biological clock—can provoke full-scale affective episodes in individuals with mood disorders [18].

The most potent *zeitgeber* in the pre-industrial era was the rising and setting of the sun. Our ancestors typically got up when the sun rose and went to sleep when the sun set. Similarly, our ancestors fed when prey was available and fasted when it was not. In the Modern era, however, circadian rhythms have become increasingly divorced from these geophysical *zeitgebers* [19]. With omnipresent light at night and easily accessible food sources, humans increasingly rely on social *zeitgebers*—i.e., personal relationships, social demands, or tasks that help entrain biological rhythms. Examples of social *zeitgebers* include getting up at the same time every day to go to work, exercise routines, communal meals, and childcare activities. By identifying and regularizing an individual’s social *zeitgebers* or social anchors, SRT helps individuals entrain dysregulated circadian rhythms, thereby stabilizing mood [20].

32.2.5 *Psychoeducation*

Psychoeducation is a mainstay of psychotherapy for bipolar disorder [21]. Group and individual psychoeducational interventions are efficacious as maintenance and acute depression treatments [22]. Elements of psychoeducation are incorporated into most bipolar-specific psychotherapies, including IPSRT, contributing to their efficacy [23]. In IPSRT, psychoeducation focuses on providing information about bipolar disorder (e.g., course, outcomes, symptoms), circadian rhythms (i.e., the rationale for SRT), and the role and importance of medications in illness management.

Figure 32.1 illustrates the components of IPSRT and the goals of treatment.

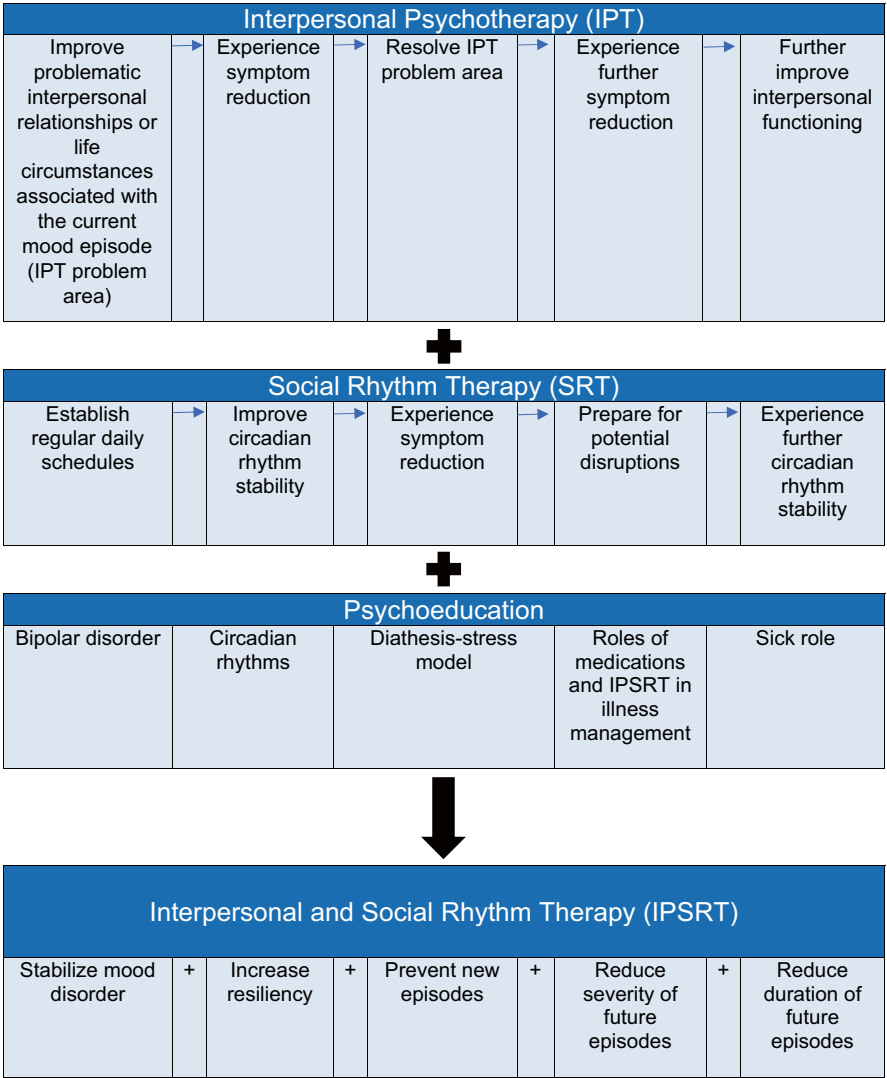


Fig. 32.1 Components of interpersonal and social rhythm therapy

32.3 Empirical Evidence

32.3.1 Maintenance Treatment

The efficacy of IPSRT has been demonstrated in randomized controlled clinical trials. The first study of IPSRT, conducted by Frank and colleagues at the University of Pittsburgh, compared IPSRT to an intensive clinical management (ICM)

approach in patients with bipolar I disorder [1]. One hundred and seventy-five acutely ill participants (in a current depressive, manic, or mixed episode) meeting criteria for bipolar I disorder who were treated with medication were randomly assigned to either IPSRT or ICM. Once stabilized, participants were reassigned to either IPSRT or ICM (in conjunction with the medication regimen that led to stabilization) for 2 years of monthly maintenance treatment. Participants assigned to IPSRT in the acute treatment phase survived significantly longer without a new affective episode during the 2-year maintenance phase ($p = 0.01$; hazard ratio = 0.35), irrespective of maintenance treatment assignment. The researchers also found that participants assigned to IPSRT had significantly higher regularity of daily routines at the end of acute treatment ($p < 0.001$), and the ability to increase regularity of daily routines during acute treatment was significantly related to reduced likelihood of recurrence during the maintenance phase ($p = 0.05$), demonstrating that social rhythm stabilization mediated positive outcomes. Also, participants assigned to IPSRT in the acute phase demonstrated significantly more rapid improvement in occupational functioning than did participants assigned to ICM [24].

Another maintenance study, conducted in a routine practice setting in Italy, randomized stable patients with bipolar I or II disorder ($n = 44$) to either IPSRT or treatment as usual, assessed at 3- and 6-month follow-up. The primary outcome measures included anxiety symptoms, manic symptoms, depressive symptoms, global functioning, and the Affective Morbidity Index. Compared to the control condition, those assigned to IPSRT had significantly greater improvement in all symptom and functioning measures over time [25].

32.3.2 Acute Depression Treatment

IPSRT was first evaluated as a treatment for acute bipolar depression in the context of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). In this trial, 293 depressed participants with either bipolar I or bipolar II disorder were randomly assigned to one of three intensive psychotherapies (IPSRT, family-focused therapy, or cognitive-behavioral therapy) or to a control condition called comprehensive care (CC). Over a 9-month period, 65% (40/62) of those assigned to IPSRT achieved “recovered” status (defined as ≤ 2 moderate symptoms for ≥ 8 weeks) compared to only 52% (67/130) of those assigned to CC. The median time to recovery for participants assigned to IPSRT was shorter than for participants assigned to CC [26]. Patients receiving intensive psychotherapy also had better total functioning, relationship functioning, and life satisfaction scores over 9 months compared to those assigned to CC [27]. Note that this study was not designed or adequately powered to compare the active psychotherapies to each other.

32.3.3 IPSRT as Monotherapy for Bipolar II Disorder

IPSRT has been tested as monotherapy (i.e., not in combination with medication) for individuals with bipolar II disorder [28]. This approach has not been tested in, nor should it be considered for, individuals with bipolar I disorder. In an initial study, unmedicated individuals ($n = 25$) meeting DSM-IV criteria for bipolar II disorder, currently depressed, were randomly assigned to weekly sessions of IPSRT or quetiapine. Both groups showed statistically significant declines in depression and mania scores over time (for both $p < 0.05$), but there were no differences in outcomes between groups over 12 weeks in this small study [29]. In a follow-up study, individuals with bipolar II depression ($n = 92$) were randomly assigned to either IPSRT plus pill placebo or IPSRT plus quetiapine for 20 weeks. Both groups improved significantly over time, with no between-group differences in response rates ($\geq 50\%$ reduction in depression scores). Assignment to IPSRT plus quetiapine yielded significantly faster improvement in depression scores ($p < 0.05$) but was also associated with significantly higher side effects, including increased Body Mass Index over time ($p < 0.05$). We concluded that for some individuals with bipolar II disorder, IPSRT alone suffices and may be associated with fewer risks than IPSRT plus quetiapine [30].

32.3.4 IPSRT for Adolescents and Young Adults

IPSRT has been adapted for adolescents (IPSRT-A). An open study of IPSRT-A ($n = 12$; mean age 16.6 years) was conducted in individuals with a diagnosis of bipolar spectrum disorder. Participants received 16–18 sessions of adjunctive IPSRT-A and experienced significant decreases in manic, depressive, and general psychiatric symptoms over the 20 weeks of treatment. Participants' global functioning increased significantly as well [31].

In New Zealand, a large trial ($n = 100$) of IPSRT for individuals aged 15–36 found no benefit of IPSRT compared to specialist supportive care on measures of depression and social functioning, although both groups showed significant reductions pre- to post-treatment [32]. A 3-year follow-up of this cohort found cumulative recurrence rates of 53% for IPSRT and 49% for specialist supportive care, a numeric difference that was not statistically significant [33].

More recently, an open pilot study of SRT for adolescents and young adults aged 17–24 with bipolar disorder ($n = 13$) administered primarily via a video-conferencing platform found significant improvement pre- to post-treatment in depression, mania, and suicide measures (all < 0.05). The researchers also found that increased social rhythm regularity was associated with reduced suicide propensity after controlling for mood symptom reductions [34]. Another recent randomized trial compared 12 sessions of SRT to an emotion regulation-focused intervention for adolescents and young adults aged 16–29 years ($n = 60$). SRT--but not the emotion regulation intervention--was associated with significant pre- to post-treatment improvements in

regularity of daily routines, suicide risk, anxiety, and emotion dysregulation. Improvements in rhythm regularity were associated with decreases in left amygdala responses when participants viewed fearful or emotionally ambiguous faces, which also correlated with reductions in emotion dysregulation and suicide risk [35].

IPSRT has been tested as a prevention strategy in adolescents at risk for bipolar disorder by virtue of having a parent with the illness. Participants ($n = 42$) were randomly assigned to IPSRT or a data-informed referral for care. The authors followed the youth for 6 months and found that one individual in the IPSRT condition versus two in the referral condition experienced subthreshold manic symptoms ($p < 0.05$). The authors also found a small effect on sleep, with those assigned to IPSRT experiencing significant declines in awakenings after sleep onset after treatment as measured by actigraphy (Cohen's $d = 0.28$) [36].

32.3.5 *Social Rhythm Therapy*

SRT has been operationalized as a stand-alone treatment [37] and shown to have efficacy in both bipolar disorder [38–40] and major depressive disorder [41] and has been successfully adapted for use in routine care [38, 42]. Rhythms And You [RAY], the online version of SRT, has been administered both with and without brief coaching (“CH”). In a 3-arm study comparing RAY, RAY + CH, and written psychoeducational materials as treatments for bipolar spectrum disorders, depression and health-related quality of life (HRQOL) scores improved in all groups. However, a significantly greater improvement in HRQOL scores was found in the RAY+ CH group, suggesting that adding a coach to the intervention may improve outcomes [43].

32.3.6 *Group IPSRT*

Although IPSRT was originally developed as an individual intervention, it has also been administered in a group format. At the University of Pittsburgh, we adapted IPSRT for delivery in a group format in both inpatient and outpatient settings and then demonstrated the feasibility of delivering group IPSRT in routine practice settings with reductions in depression symptoms pre- to post-treatment [42].

In a trial conducted at the Mayo Clinic in the U.S., group IPSRT was administered openly to nine individuals with bipolar disorder (out of 14 who were deemed eligible). Participants received two 60-min individual sessions followed by six 60-min group IPSRT sessions over 2 weeks. Outcomes assessed at 2- and 12-week follow-up showed significant improvements in psychosocial functioning and depressive symptoms post-treatment which were maintained at week 12 [44]. Receipt of group IPSRT was associated with high levels of satisfaction [45].

A preliminary efficacy study of group IPSRT was conducted in the Netherlands. In this trial, eligible participants first participated in weekly SRT groups, 1.5 h per week for 4 weeks to 4 months, depending on how long it took for participants to

learn about SRM completion and principles of SRT and to achieve social rhythm stability. After successful completion of the SRT group, participants were eligible for an IPSRT group that incorporated a focus on interpersonal goals. IPSRT groups were comprised of eight to ten participants with two therapists and consisted of 16 weekly sessions of 2 h duration. Twenty-seven patients were enrolled in one of three IPSRT groups, of whom 22 completed treatment. There were significant improvements in depression and SRM scores among completers, pre- to post-treatment [46].

32.3.7 Implementation in Routine Practice

IPSRT is frequently used in clinical practice. However, studies of its implementation are limited. Two studies to date have shown the feasibility and acceptability of IPSRT in routine care. One randomized trial found positive symptomatic outcomes when IPSRT was implemented in general practice in Italy [25], and another showed positive pre- to post-changes when implemented in a large hospital system in the United States [42]. Investigators in New Zealand have argued that SRT can likely be translated into clinical practice in diverse settings [38], but follow-up data is not yet available.

32.4 Techniques and Strategies

Below we describe IPSRT strategies. When delivered appropriately, the IPT, SRT, and psychoeducation components of IPSRT are variably combined within each session to meet the needs of the patient (see Fig. 32.1). For instance, when a patient is depressed, therapists may begin with IPT before introducing the SRT material, whereas therapists may initiate SRT immediately for someone who is hypomanic. The therapist has flexibility in titrating the IPSRT components within sessions, although all aspects of the treatment are delivered over time. IPSRT strategies are summarized in Tables 32.1 and 32.2.

Table 32.1 Strategies of interpersonal and social rhythm therapy used throughout treatment

Phase	Strategies	
All sessions	General therapeutic approaches	Psychoeducation
	Encourage affect Guide with open-ended questions Be collaborative, reflective, non-judgmental, and empathic Attend to cultural factors contributing to patient experiences Instill hope Assess risk	Bipolar disorder: Symptoms, course, and recovery Circadian rhythms: Basics, relationships with mood and health, zeitgebers and zeitstörers Diathesis-stress model of bipolar symptoms and recurrences: Connections among life events, social rhythm disruptions, and medication inconsistencies, if applicable Roles of medications and IPSRT in illness management Sick role: Need for increased social support, relief from some social responsibilities, responsibility to attend treatment, and work toward improved health

Table 32.2 Strategies of interpersonal and social rhythm therapy by phase and interpersonal psychotherapy (IPT) or social rhythm therapy (SRT) component

Phase of treatment (Number of Sessions)	Strategies by components	
	Interpersonal psychotherapy (IPT)	Social rhythm therapy (SRT)
Initial (3–5 weekly)	Assessment • Illness timeline • Interpersonal inventory	Assessment • Social rhythm metric (SRM)
	Treatment plan • Case formulation • Selection of IPT problem area	Treatment plan • Personalized rationale for making changes to daily rhythm
Middle(15–17 weekly)	Resolve primary IPT problem area • Role transition • Role dispute • Grief • Interpersonal deficits	Resolve secondary IPT problem area • Grief for the lost healthy self
	Use IPT techniques • Role play • Communication analysis • Decision analysis • Between session skills practice	Monitor daily routines, mood, and energy with SRM • Review patterns • Establish goals • Modify routines • Create anchors
	Identify early warning signs of relapse	Connect regularity of social rhythms to mood stability
Maintenance (3–24 monthly)	Preserve treatment gains	Maintain rhythm regularity Anticipate and problem-solve rhythm-disrupting events
Completion/termination (2–3 monthly)	Review treatment gains Develop relapse-prevention plan Normalize feelings about concluding treatment	

32.4.1 *Phases of Treatment*

IPSRT is typically administered in four phases (initial, middle, maintenance, and termination) during which IPT, SRT, and psychoeducation are seamlessly interwoven. Acute treatment (initial and middle phases) usually lasts for about 20 weeks. The maintenance phase has been studied as a 2-year intervention [20] but can continue indefinitely if needed. Sessions are administered weekly in during the acute phase and then monthly during the maintenance phase. The last phase (termination) occurs over 2–3 sessions that are spaced according to the needs of the patient.

Throughout treatment, IPSRT therapists employ general or nonspecific psychotherapeutic principles [47] such as attention to affect, use of open-ended questions, consideration of cultural factors, instilling hope, employing a nonjudgemental stance, and assessing risk (Table 32.1). The first phase (initial phase) typically lasts 3–5 sessions and focuses on assessment, psychoeducation, and selection of the IPT

problem area (Table 32.2). For instance, in the initial phase, the therapist provides psychoeducation about circadian rhythms tailored to the learning needs of the patient and initiates training in the completion of the social rhythm metric (SRM). As described below and summarized in Table 32.3, the therapist completes the Interpersonal Inventory to inform the selection of the IPT problem area and begins the IPT component of treatment. The illness history timeline is used to understand more about the patient's course of illness and build a personalized rationale for making changes in daily routines. As part of psychoeducation, the therapist assigns the patient the "sick role" in which the needs of being a patient are normalized (e.g., need for increased social support, relief from some social responsibilities, accommodation for illness) and new responsibilities are identified (e.g., to attend therapy sessions, to engage with health care providers, to track mood symptoms, etc.).

The second phase (intermediate phase) is the "workhorse" phase of treatment, lasting 15–17 sessions. In this period, the therapist collaboratively helps patients resolve the selected interpersonal problem area using IPT principles and strategies [2]. Grief for the lost healthy self, as discussed below, is addressed in the middle phase. Patients monitor their daily routines and moods using the SRM, beginning each session with an SRM check-in to review patterns and progress over the past week. In the late middle phase, therapists and patients focus on modifying those routines by establishing SRM goals and discussing broader goals (e.g., getting a new job or asking for help with childcare) to promote social rhythm stability.

The maintenance phase of treatment focuses on preserving acute treatment gains, identifying early warning signs of relapse, and using SRT strategies to anticipate and address rhythm-disrupting events. Termination focuses on reviewing treatment gains, developing a relapse-prevention plan, and planning for future treatment needs.

32.4.2 *Interpersonal Inventory and IPT Problem Area*

IPSRT therapists identify a problematic interpersonal relationship or social role that contributes to the onset or maintenance of the current mood episode with the goal of intervening with the identified interpersonal problem area to improve symptoms. The interpersonal inventory is used to help understand the interpersonal context of the patient's presenting complaint and, ultimately, to select the most relevant problem area. The inventory consists of a careful review of the important individuals in the person's life currently, as well as the family of origin. The therapist asks probing questions to evaluate the satisfying and unsatisfying nature of these relationships and attempts to determine whether these relationships are confiding, mutually satisfying, or characterized by nonreciprocal role expectations. Ideally, the therapist selects a problem area that is temporally linked to the onset of the current mood episode.

In IPT [2], the therapist chooses among four possible problem areas as the focus of treatment: grief (i.e., loss of a loved one), role transitions (i.e., change from one social role to another such as retirement, becoming a parent, or graduation), role

Table 32.3 IPSRT problem areas

Problem area	Goal	Bipolar examples
Role transition • Patient has experienced a tangible or abstract change in their social role.	Patient develops more realistic views of both the old and new roles and acquires new interpersonal skills to master the new role.	Mania-driven, inappropriate behavior may lead to unexpected job loss. Depression-associated social isolation and hypersomnia may lead to strained relationships.
Role dispute • Patient experiences different, non-reciprocal role expectations about their relationship with an important person in their life.	Patient identifies the disagreement and stage of disagreement (renegotiation, impasse, dissolution), chooses a plan of action, and alters role expectations and/or communication patterns to resolve the dispute.	Mania-driven infidelity or mixed episode-associated irritability may tax an intimate relationship.
Grief • Patient experiences the death of an important person in their life.	Patient mourns the deceased, develops a more realistic and nuanced understanding of their relationship with the deceased, and (re)establishes interests and relationships.	Loss of a primary social anchor leads to disrupted daily rhythms and a protracted episode of depression.
Interpersonal deficit • Patient's circumstances are not captured by the other problem areas • This is a focus when there is a long history of unsuccessful relationships and no clear interpersonal event associated with episode onset.	Patient develops some social support and relationships.	Lack of positive social support and interpersonal connections leads to irregular daily rhythms and frequent recurrences.
Grief for the lost healthy self • Patient experiences a change associated with developing and/or being diagnosed with bipolar disorder. • This is a primary or secondary problem area, and a sub-type of role transition.	Patient develops an understanding and acceptance of changes associated with developing and being diagnosed with bipolar disorder, including possible need for life-long medication treatment. Patient mourns the loss of the old role (living as someone without bipolar disorder) and begins to accept the new role (living with bipolar disorder).	Not applicable

disputes (i.e., conflict between the patient and a significant other), or interpersonal deficits (i.e., longstanding impoverished or contentious relationships; sometimes labeled as “interpersonal sensitivities”). In IPSRT, a fifth problem area, grief for the lost healthy self, is added to the list (see below). Typically, the therapist selects a single problem area as a treatment focus, however, in IPSRT, it is often appropriate

to address grief for the lost healthy self as a second problem area, in addition to one of the traditional IPT options. Although the therapist is responsible for selecting the problem area based on presenting material and history, the patient must agree to the selected problem area(s) for therapy to proceed. Thus, the IPSRT therapist must be prepared to present to the patient a rationale for why the proposed problem area seems most relevant to the patient's mood episode and to make the argument that this specific problem should be the focus of subsequent treatment sessions.

32.4.3 Sick Role

As part of providing psychoeducation about bipolar disorder, the therapist assigns the patient the “sick role,” a social role intended to relieve patients of responsibilities if needed (e.g., housework, job responsibilities, child care) while assigning them the responsibilities of adhering to treatment and working toward improved health [48]. The sick role is designed to absolve patients from the guilt associated with decreased function due to disordered moods. As part of assigning the sick role and providing psychoeducation in IPSRT, the therapist points out that, in addition to social stressors increasing vulnerability to mood disorders, disruptions in circadian rhythm stability may also increase the risk for mood dysregulation in an individual who is biologically predisposed to illness. Highlighting this diathesis-stress model of illness helps patients understand that bipolar disorder is not their fault, and yet they can be active participants in managing their symptoms. Discussion of the sick role also provides an opportunity to explore the patient's understanding of the role of medications in their illness self-management.

Because bipolar disorder is a chronic illness, it is important for the therapist to work with the patient to identify appropriate and realistic goals for recovery, making sure that the patient aspires to improved health without feeling overwhelmed by unattainable goals.

32.4.4 Illness History Timeline

The history of the illness is conducted during the initial phase of therapy. As with any treatment, the clinician uses this information to establish a diagnosis and inform current treatment decisions. In the case of IPSRT, however, the therapist takes a careful history of the mood disorder to develop an illness timeline that illustrates for the patient the historical connections between prior episode onset and rhythm dysregulation. This process is used to establish the rationale for IPSRT—i.e., to show the patient that previous episodes have been triggered by changes in routine or sleep-wake cycles. By using the patient's own history as “evidence,” the therapist begins to make the case for the importance of making changes in routines to promote rhythm stability.

32.4.5 *Social Rhythm Metric*

In IPSRT, the regularity of social rhythms is monitored with the social rhythm metric (SRM) [49]. The 5-item version of the SRM [50] asks patients to record the timing of five daily activities: (1) rising from bed, (2) first contact with another person, (3) starting work, school, or other daily responsibilities such as child care or housework, (4) having dinner, and (5) getting into bed for the night. The SRM also asks patients to rate their mood and energy each day, helping the patient to see the links between rhythm stability (or instability) and mood/energy states.

As part of the SRM, patients are asked to rate their mood daily on a scale of “minus 5 to plus 5.” In preparation for initiating this scale, the therapist spends some time helping the patient to understand the anchor points for the scale and the rationale for using such a metric. We have found that this scale is intuitively reasonable to individuals with classic bipolar I mood disorders but may be more confusing to individuals with more variable or spectrum bipolar mood presentations. The therapist explains that a “minus 5” represents the worst depressed mood that the patient can envision, and zero represents a “normal” or stable mood. It is helpful to elicit descriptors from the patient. In contrast, a “plus 5” is described as fulminate mania, noting that “plus” values do not necessarily denote positive or desirable mood states.

32.4.6 *SRM Goal Setting*

Over the course of treatment, the therapist works with the patient to develop more regular routines, as evidenced by more regular SRMs. The SRM form includes fields for establishing target times, which are used to gradually regularize social rhythms. Using principles of behavior therapy to set graded assignments for change, the therapist uses the SRMs to identify the most disruptive patterns of activity and to set modest goals for change. In general, the therapist will recommend that the patient alter his or her schedule by 15-min increments every few days to bring the social rhythms into increasing regular configurations. As the therapist works with the patient to achieve rhythm stability, the therapist attends to the many interpersonal factors that contribute to rhythm disruption and may interfere with the establishment of regular rhythms. Monitoring mood and energy states as the patient makes changes in the schedule gives the patient an automatic reinforcing mechanism for underscoring the importance of enhancing the regularity of rhythms.

32.4.7 Grief for the Lost Healthy Self

In IPSRT, a fifth problem area is available to the therapist. This problem area was developed specifically for patients who suffer from bipolar disorder. Because of the life-altering nature of bipolar episodes, many of these individuals divide their lives into two parts: before the onset of the disorder and after its onset. “Grief for the Lost Healthy Self” focuses on the changes that patients experience because of the illness, mourning the person they could have become had they not developed bipolar disorder and adapting to the demands of living with a chronic illness.

32.4.8 Managing Rhythm Disruptions

In addition to helping the patient set goals for more regular rhythms, the therapist collaborates with the patient to be a “detective” in the hunt for triggers, such as social situations or activities that contribute to mood instability. This process is initiated with the history of the illness timeline when the therapist gathers important information about triggers of prior episodes but continues in the day-to-day work of IPSRT as the therapist collaborates with the patient to identify potential *Zeitstörers*. The search may be initiated when the standardized mood assessment reveals a worsening of symptoms or when the week’s SRMs reveal a pattern of increased dysregulation. The goal is to think about changes that have been made in schedules as well as interpersonal relationships.

As one would expect from the social Zeitgeber hypothesis, individuals with mood disorders are very vulnerable to changes in their chronobiological milieu. And yet, changes in routine are an inevitable part of life. Thus, the IPSRT therapist helps patients to anticipate potential changes in routines and to use a variety of skills to facilitate healthy adaptation to these changes. For instance, if a patient is expecting house guests for a long weekend, the therapist might encourage the patient to explicitly inform the house guests about the importance of maintaining a pre-specified schedule and to make a polite request in advance to eschew late nights or other rhythm-disrupting activities to promote the patient’s health.

32.5 Case Vignette

Jordan is a 25-year-old nonbinary individual (they, them pronouns) who presented for IPSRT treatment following hospitalization for their first manic episode. While in the hospital, they were given a diagnosis of bipolar I disorder and placed on lithium. The therapist began by asking Jordan about their understanding of their illness, providing empathic listening as Jordan revealed feeling surprised—and somewhat skeptical—about their diagnosis. The therapist explored cultural aspects of care. In

Jordan's case, they indicated that they were very sensitive to misapplied labels, given their nonbinary gender identity and prior experiences of being misgendered. The therapist listened attentively to their concerns, building rapport by employing nonjudgmental listening and attending to the patient's affect around labels and diagnoses. Avoiding applying specific labels to Jordan, the first sessions focused on gently and collaboratively exploring what it would mean to Jordan to have bipolar disorder, providing space for Jordan to be "undecided" about whether this information pertained to them. Despite rejecting the diagnostic label, Jordan was eager to understand what led to their hospitalization and, hopefully, prevent it from recurring in the future. This provided the therapist with an opening to begin the illness timeline, explaining to Jordan that they could be "detectives" together and review their history to try to figure out what may have triggered the hospitalization.

In the context of the illness timeline, Jordan revealed that they had been working long hours prior to their hospitalization. Jordan was enrolled in a graduate program focused on fine arts with the goal of becoming a graphic designer. To support themselves during schooling, Jordan was also freelancing as a web designer, creating websites for several local businesses. In the weeks leading up to their hospitalization, Jordan slept very little due to the competing demands of schoolwork and their web design business, sometimes only sleeping 3–4 h a day. Initially, they were exhausted by this schedule but soon started feeling "unusually speedy," noticing elevated mood, decreased need for sleep, rapid thoughts, and increased productivity. Eventually, Jordan started becoming suspicious of their web design clients, believing that they were using their websites to spy on Jordan because they suspected they were a pedophile (there was no evidence that Jordan was a pedophile). A client became so concerned about Jordan's increasingly paranoid emails that he reached out to Jordan's roommate who was also becoming concerned about Jordan's erratic behavior, eventually leading to the hospitalization.

The IPSRT therapist pointed out that the changes to Jordan's routines, including longer workdays and decreased sleep, likely contributed to the onset of symptoms. They discussed using an assessment tool, the social rhythm metric, to track Jordan's routines, thereby potentially identifying routine-related risk factors for future illness. Jordan thought this was a good idea and initiated self-monitoring with the SRM.

When reviewing the first week of Jordan's SRMs, both the therapist and Jordan noted tremendous variability in Jordan's daily routines, partially related to Jordan having taken a leave of absence from school and not having many obligations. Their mood was predominantly low, as was their energy level. Providing psychoeducation about circadian rhythms, the therapist explained to Jordan that not having regular routines was probably both a manifestation of their underlying illness and a risk factor for future episodes. Although Jordan initially argued that "it will all be fine when I go back to school," they felt depressed and were therefore willing to start making small, gradual changes to their routines with the hope that it would help with their mood. Over time, they were surprised to find that more regular routines seemed to be associated with more level moods. Although they were initially reluctant to get up at the same time every day, they begrudgingly agreed that having a

consistent wake-up time set the tone for the rest of the day and helped them stay on track with their other routines. They noted that they felt better when they began eating regular meals and exercising most days. The therapist pointed out that they were helping to stabilize their circadian rhythms by stabilizing their routines, which, in turn, likely helped their mood.

In addition to helping Jordan work on their social rhythms, the therapist used the interpersonal inventory to understand more about Jordan's interpersonal life. Jordan had moved to a new city to attend their graduate program, and they knew very few people locally. They lived with a roommate they had met through social media. Jordan did not mind living with their roommate, but they were not close friends. Jordan had an extensive online social network, engaging with other nonbinary individuals in safe spaces such as dating apps that cater to gender-fluid individuals. Jordan met their romantic partner on one of these apps. They interacted almost daily by video chat with their partner but had never met in person. Before moving to this new city, Jordan had been active in their local LGBTQA+ community center, but they hadn't found time to get involved in a comparable group in the new city because of school and work demands. Their parents tried to be supportive of Jordan but frequently misgendered them and did not seem to understand their values and priorities. The therapist and Jordan agreed that they should focus their IPT work on the role transition associated with moving to a new city and starting graduate school, with a goal of building more social support in the context of the new role. It seemed premature to focus on "grief for the lost healthy self" since Jordan was not convinced they had bipolar disorder, but the therapist and Jordan agreed to spend time thinking about the impact of the hospitalization on their life and learning more about Jordan's beliefs around bipolar disorder.

Over time, Jordan developed more regular routines which helped to stabilize their mood. They discussed the importance of maintaining regular routines in the future, when they returned to their graduate program, to maintain mood stability. With encouragement from the therapist, Jordan decided to ask their parents for some additional financial support during this transition back to school so that they didn't need to take on multiple web design clients while restarting classes. They were pleasantly surprised that their parents agreed to their request, indicating an interest in becoming more involved in their child's life. Although Jordan was feeling better after 20 sessions of IPSRT, the therapist and Jordan agreed to continue meeting monthly to monitor SRMs and ensure that social rhythms and mood remained stable.

32.6 Further Learning

Because IPSRT is considered an adaptation of IPT, IPSRT training is housed under the auspices of the International Society of Interpersonal Psychotherapy (ISIPT). ISIPT also runs an IPSRT Special Interest Group for members who wish to discuss IPSRT research or clinical questions. Individuals interested in learning more about IPSRT are encouraged to contact ISIPT at <https://interpersonalpsychotherapy.org/>.

Bradley Stein and colleagues at the University of Pittsburgh developed and tested a self-guided online intervention to train community clinicians in IPSRT. Five community mental health centers were randomly allocated to either in-person IPSRT training with local supervision or online training supported by IPSRT experts. Therapist uptake of IPSRT when participating in the online training was comparable to face-to-face training [51]. The online training program endures and can be accessed for free at <https://www.ipsrt.org/>.

The IPSRT manual [1] and SRT workbook [37] can be purchased from local or online booksellers or their respective publishers.

32.7 Future Directions

IPSRT is an empirically supported treatment for bipolar disorder. Large randomized controlled trials demonstrate its efficacy as an adjunctive (in combination with medication) treatment for bipolar I and II disorder. IPSRT shows promise as a treatment for adolescents with bipolar disorder, as monotherapy for bipolar II disorder, and as a group intervention in routine practice settings but larger follow-up studies are needed. Future research should include definitive efficacy trials for new populations with bipolar disorder (e.g., older adults, co-morbid substance use disorders, women in the perinatal period), dismantling studies to understand the relative contributions of the SRT and IPT components of IPSRT, and implementation studies to evaluate IPSRT's effectiveness and scalability in real-world settings.

32.8 Clinical Considerations and Key Points

- Baseline irregularities in circadian rhythms, including circadian misalignment, are common among individuals with bipolar disorder and are likely both etiologic and caused by the disease itself.
- During a mood episode, bipolar pathology disrupts important circadian phenomena, including the sleep-wake cycle, energy fluctuations, and appetite.
- Circadian rhythms may be shifted purposefully or accidentally by exogenous or endogenous sources.
- Interpersonal and social rhythm therapy (IPSRT) is an evidence-based psychological treatment for bipolar disorder that combines psychoeducation with two distinct, evidence-based psychosocial interventions, interpersonal psychotherapy (IPT) and social rhythm therapy (SRT).
- Social rhythms are those daily activities that are thought to exert an effect on underlying biological rhythms implicated in bipolar mood instability, such as time out of bed. These rhythms can be tracked using the social rhythm metric (SRM).

- IPSRT rests on the belief that stable social rhythms promote stable biological rhythms through a process of entrainment. In turn, stable rhythms lead to stable moods as well as short- and long-term recovery.
- In IPSRT, using psychoeducational, interpersonal, and behavioral strategies, therapists help patients understand and monitor their illness, learn strategies to improve their interpersonal functioning and establish and maintain regular social rhythms.

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Chapter 33

Family-Focused Therapy



David J. Miklowitz

33.1 Introduction

Treatment guidelines for bipolar disorder (BD) involve combinations of pharmacological and psychosocial interventions at different stages of the illness [1]. Psychosocial treatments are designed to reduce the impact of psychosocial stressors through increasing stress management skills, the protective effects of family and other social supports, and enhancing quality of life. Guiding this approach is a biopsychosocial model [2] that incorporates psychoeducation, illness management strategies, and skills training into standard medication management. This chapter reviews research on one biopsychosocial approach that incorporates these three elements: family-focused therapy (FFT). I will explore its history, core clinical techniques, empirical database from randomized trials, and application in pediatric-onset populations. I offer two clinical cases that illustrate the FFT methods (one young person, one elderly) and offer future perspectives.

33.1.1 A Brief History of Family-Focused Approaches

Studies of the family and psychiatric disorders have a long and complicated history. Early theories blamed mothers for causing their offspring's mental illness through "double-bind messages" or "schizophrenogenic" parenting. Separate theories attempted to explain bipolar disorder as an illness provoked by family dynamics (e.g., [3]). These theories came out of observations of patients with

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already-diagnosed schizophrenia or bipolar disorder and their families, often during periods of hospitalization. Their cross-sectional designs did not address whether family communication disturbances had diagnostic specificity, whether they antedated the disorder's onset, or whether these disturbances reflected the considerable disease burden of mental illness on caregivers (e.g., [4]).

Modern approaches to family intervention emphasize the role of genetic and neurophysiological variables in the onset and course of BD. Consistent with family system notions, modern approaches assume that illness in one family member affects the psychological health and relationships of other members, and in turn, that the reactions of these members affect the functioning of the person with the illness. For example, some families stick rigidly to established patterns of interaction that maintain harmony and equilibrium but inadvertently reinforce dysfunctional behavior; others become highly dysfunctional in their interaction patterns, creating high levels of distress in the person with the disorder and the family. Depending on how they understand the person's symptoms and functioning, the family's reactions can protect against or contribute to that individual's risk of recurrences. The family therapist's presentation of this biopsychosocial view makes it easier for family members to accept the illness and its treatments, and draw on effective coping strategies to manage it [5].

An advance in this area came in the mid to late 1970s, when evidence emerged that expressed emotion (EE) in caregivers (parents or spouses) of concurrently ill patients (i.e., levels of criticism, hostility, or emotional overinvolvement) and negative face-to-face interactional behaviors between caregivers and patients were associated with more recurrent courses of schizophrenia and bipolar disorder [6–9]. High levels of EE have many causes among caregivers, but one appears to be their understanding of the illness: parents and spouses who are rated high in EE tend to attribute negative behaviors by the patient as caused by internal and controllable factors (e.g., willfulness, personal choice), whereas parents and spouses rated low in EE are more likely to attribute these same behaviors to less controllable factors, such as the presence of an illness [10, 11].

33.1.2 Family-Focused Therapy

The family-focused therapy (FFT) model for BD has its roots in the schizophrenia literature, where behavioral family therapy has been shown to be an effective adjunct to antipsychotic medications in reducing rates of psychotic relapse (for review, see [12]). FFT addresses family risk factors such as EE and negative interactional (caregiver/patient) behaviors as these occur within the families of persons with BD. The objectives are to reduce family stress by [1] increasing family members' understanding of the illness, including how to recognize early warning signs of new episodes and how to intervene to help prevent recurrences (psychoeducation); [2] enhancing constructive caregiver/patient communication through rehearsing skills such as active listening, making requests for changes in another person's behavior,

and balancing positive and negative feedback; and [3] improving family problem-solving skills to enhance family and social functioning. All three FFT modules provide opportunities for patients to learn behavioral strategies to modulate affective intensity and duration when provoked by others.

FFT is begun during the stabilization period following an acute manic or depressive episode during which the focus is on assisting patients in returning to their pre-illness level of functioning. Typically, therapists meet with individual families (patient, parents or spouse, siblings) in weekly 1-h sessions, followed by biweekly or monthly sessions extending over 6 or 9 months. Longer protocols (i.e., 21 sessions over 9 months) are usually reserved for patients who have fully syndromal manic and depressive episodes, whereas shorter protocols (i.e., 8 weekly and 4 biweekly sessions over 4 months) are recommended for children or adolescents in high-risk states (i.e., those with major depression or subthreshold forms of BD who have a family history of BD I or II).

33.1.3 Clinical Procedures of FFT

Psychoeducation. The first sessions acquaint the patient and family with early signs and symptoms of mood disorder. The patient is framed as the “expert” in the disorder—the one person who can educate other members of the family as to how depression or mania is experienced. The vulnerability/stress model of illness onset is explained, and participants identify stressors affecting the patient (e.g., family conflicts, social or work problems). Patients learn to monitor their daily moods and sleep/wake rhythms with a mood chart.

The capstone event in psychoeducation is the development of a mood management plan (what triggers your mood swings? How do you know you’re becoming manic/depressed? and What coping strategies (by the patient or family members) help improve your mood?). The plan typically involves reducing stress at home through using collaborative communication, implementing mood regulation strategies (e.g., mindfulness meditation exercises, distraction, and self-talk), stabilizing sleep/wake rhythms, and, as appropriate, requesting changes to medication regimens. Families are now in a better position to recognize when the patient is developing prodromal symptoms of new episodes and to follow prevention plans to arrest symptoms.

Communication enhancement training teaches: expressing positive feelings, active listening, making positive requests for change in others’ behaviors, communication clarity, and expressing negative feelings. During role-play/skills training exercises, participants learn to downregulate impulsive expressions of negative emotions by pausing and putting difficult feelings into words, communicate in a manner that does not trigger emotional dysregulation in others, and shift attention from destructive emotions to more conciliatory states. Significant emphasis is placed on between-session practice and implementing these skills in day-to-day family life.

In *problem-solving*, participants learn to manage practical or interpersonal problems using a structured format. First, patients and caregivers learn to break down large problems (e.g., “we don’t get along”) into smaller ones (“we need to use lower tones of voice”), generate a list of possible solutions, evaluate the pros/cons of each solution, and choose one solution or a set of solutions to implement (e.g., alert each other to aggressive tones). Not all family problems can be reduced to small solvable units, but often the problem-solving process helps the family hone in on larger emotional conflicts that have never been resolved.

33.1.4 Empirical Evidence for FFT in Randomized Clinical Trials

There have been five randomized clinical trials (RCTs) of FFT in adults with BD I or II, two in adolescents with BD I or II, and two in high-risk children or adolescents (for a recent review, see [13]). In the various RCTs, FFT was combined with pharmacotherapy and compared to brief psychoeducation, individual supportive therapy, or another evidence-based psychosocial treatment combined with pharmacotherapy. Patients were recruited during or following hospitalization or once referred from outpatient providers immediately following an acute episode. Across studies, FFT plus pharmacotherapy was associated with lower recurrence rates, reductions in depression and mania severity scores, and better psychosocial functioning over periods of 1–2 years compared to brief psychoeducation plus pharmacotherapy.

In two trials, FFT was evaluated against comparably intensive individual therapy (i.e., 21 sessions over 9 months). In the first, which examined an individual case management approach, FFT was associated with a lower rate of recurrence over 1–2 years following the active treatment period [14]. In the second trial—the systematic treatment enhancement program for bipolar disorder (STEP-BD)—three intensive therapies (FFT, interpersonal and social rhythm therapy, and cognitive-behavioral therapy, each given in up to 30 sessions over 9 months) were compared with three weekly sessions of individual psychoeducation guided by a self-care manual (collaborative care). Patients were 293 acutely depressed outpatients with BD I or BD II who were treated with standardized pharmacotherapy. One-year rates of recovery for the three intensive therapies, which did not statistically differ, were 77% for FFT, 65% for interpersonal therapy, and 60% for CBT. Patients receiving the intensive therapies were more likely to remain well in any given month of the 12-month study than patients in collaborative care and had better overall psychosocial functioning, relationship functioning, and life satisfaction [15, 16].

Several RCTs have examined the mechanisms by which FFT is associated with enhanced outcomes of BD. Trials that have examined family communication as a mediating mechanism have concluded that FFT is associated with increases in positive/constructive communication and decreases in criticisms and family conflict by caregivers and patients during face-to-face interactions [17–19].

FFT may be particularly effective in stabilizing depressive symptoms and preventing depressive recurrences in patients, with some of the trials finding stronger effects in patients from high-EE families than in patients from low-EE families (e.g., [20–22]). Overall, RCTs support the use of FFT plus pharmacotherapy in the outpatient treatment of adults with BD [1, 23].

33.1.4.1 Case Example

Zoe, an 18-year-old Latinx female in her senior year of high school, was recruited for a study of FFT for youth at high risk for developing BD. She reported a several-month period of depression, with low mood, social withdrawal, fatigue, passive suicidal thoughts, and feelings of worthlessness. Her biological mother, with whom she was not in contact, had BD I. During a “Kiddie” schedule for affective disorders and schizophrenia diagnostic interview for DSM-5 [24], she reported a history of brief (2- to 3-day) and recurrent hypomanic episodes alternating with lengthier phases of depression. She met DSM-5 criteria for other specified bipolar disorder.

Zoe’s main complaint about her family was that “no one listens to anyone else—everyone just goes about doing their thing.” The family did not eat together and seldom talked about anything other than daily routines; according to Zoe, she had been gradually withdrawing from the family. Her parents had told her she was “moody” and “down and cranky” much of the time, but no one had asked her what was wrong.

The FFT clinician initiated a series of 12 telehealth FFT sessions with Zoe, her biological father, her stepmother, and two older siblings (a brother, aged 27, and a sister, aged 30). The clinician began by encouraging all participants to share their observations about Zoe’s symptoms. All family members had noticed her moodiness and said she seemed down, but each had a different explanation: her older sister believed it was due to an unnamed trauma, her stepmother thought she had inherited it, and her brother simply shrugged, saying “hormones, probably.” Zoe and her family members were surprised to learn of the diagnosis of other specified BD and had many questions about the line between full BD and BD spectrum disorders. No one in the family had considered that Zoe’s short periods of increased energy, impulsive behavior, hypersexuality, and irritability were part of the same disorder as her depressive episodes.

Family members did not agree with each other on Zoe’s need for medications. Zoe, although appreciative of the diagnostic evaluation and family sessions, expressed fear that “there’s something wrong with my brain” and that taking a pill would ruin her chances of getting into a good college. Her father saw no reason for medications but was not adamantly opposed either. Her mother wanted her to try Lexapro (escitalopram), to which her older stepsister had responded. During psychoeducation, the clinician explained that monotherapy with antidepressants would not be the first recommendation for a person with or at risk for bipolar spectrum disorder.

The clinician made use of the fact that more than one member of the family had been previously treated for depression and asked those members to tell Zoe what their symptoms had been like. This intervention made Zoe feel much less stigmatized within the family, a key issue in her willingness to access treatment, and led to her being more open about her subjective experiences of symptoms. This discussion was especially enlightening for Zoe's father, who had been assuming that she was being lazy and really didn't want to go to college. Zoe eventually agreed to a pharmacological evaluation with a child psychiatrist and began a trial of lamotrigine to good effect.

The majority of FFT focused on the family's difficulties with open communication: being able to listen to each other's expressions of emotional pain or confusion while also being able to request changes in each others' behavior and balance positive with negative feedback. These exchanges involved role-playing of new communication strategies between Zoe and her siblings or her stepmother. Two sessions were reserved only for Zoe and her father, where the nature of her biological mother's illness was discussed in more detail. At the end of the 4-month treatment, Zoe's depression had stabilized, and the family reported considerable improvement in their communication and understanding of her mood states.

33.2 Special Populations

33.2.1 *Early-Onset and High-Risk Youth*

Childhood onset is a reliable predictor of a more pernicious course of BD in adulthood (e.g., [25, 26]). There have been two RCTs of FFT compared to brief psychoeducation in adolescents with BD I or II. The first showed an impact of FFT on the trajectory of depressive and mania/hypomania symptoms over 1 year, compared to brief psychoeducation [27]. The second, a larger trial involving 145 adolescents with BD I or II, did not detect differences between FFT and brief psychoeducation on time to recovery or time to recurrence. Secondary analyses indicated that adolescents in FFT had less severe manic symptoms and higher quality of life scores over 2 years than patients in brief psychoeducation [28, 29].

There has been increasing interest in the role of early psychosocial interventions for youth who are genetically at risk for BD and show early signs of mood disturbance. The long-term goal of such studies is to determine whether early intervention can prevent, delay, or minimize the severity of the onset of the full bipolar syndrome. In a 1-year RCT, 40 youth (ages 9–17) who were symptomatic with major depressive disorder or other specified BD, all of whom had a first-degree relative with BD I or II, were randomly allocated into one of two treatment groups: 12 sessions of FFT-high risk (HR) version over 4 months, or 1–2 sessions of brief psychoeducational treatment. Both groups were assigned a study psychiatrist to monitor medications. Compared to those in brief psychoeducation, youth in FFT-HR experienced more rapid recovery from their baseline mood symptoms, more weeks in

remission at follow-up, and greater improvement in hypomanic symptoms over 12 months [30].

In a second trial involving three sites and 127 high-risk youth—those with major depression or other specified BD and a familial history of BD—the 4-month family intervention was associated with a longer time to prospectively observed mood episodes than 4 months of standard psychoeducation and individual support. FFT-HR was not associated with a lower rate of conversion to bipolar I or II, although the mean duration of follow-up (2 years) was not long enough to observe many conversions [31]. There were no differences between the groups in medication regimens.

33.2.2 Adolescents and Young Adults at Risk for Psychosis

Adolescents and young adults who meet the criteria for a prodromal psychosis syndrome—often referred to generically as clinical high risk (CHR)—suffer from attenuated (subthreshold) positive symptoms (e.g., paranoia and suspiciousness), brief and intermittent periods of psychosis, and/or genetic risk for schizophrenia with functional deterioration. These individuals have a 16–30% risk of converting to a full psychotic disorder, most often schizophrenia, within 2 years [32, 33]. There is a limited window of opportunity, typically in mid to late adolescence, when early intervention may play a preventative role.

Between 2010 and 2014, we conducted an RCT of a family-focused intervention in CHR individuals, in collaboration with eight sites of the North American Prodromal Longitudinal Study Network-2. The trial included 129 CHR youth (mean age 17), most of whom lived with their parents. We compared FFT as manualized for CHR youth (FFT-CHR) in 18 sessions over 6 months to three sessions of family education, followed by routine care and symptom monitoring over 6 months (enhanced care; EC). Youth who participated in FFT-CHR had greater decreases in attenuated positive symptoms over 6 months (the primary outcome) than youth in EC [34]. Those who showed the most symptom improvement were those who began the trial with higher levels of attenuated positive symptoms, cognitive impairment, and functional deterioration in the previous year [35].

To measure the extent to which FFT-CHR engaged its mechanistic target of improved family communication, CHR persons and their parents completed a family interaction task in which they discussed problems with each other for 10 min. This laboratory task was done at baseline and again post-treatment at 6 months. CHR youth and their parents in FFT-CHR showed greater increases from baseline to 6 months in the proportion of constructive communication behaviors (e.g., active listening, praise) and greater decreases in the proportion of conflictual and critical communication behaviors (e.g., criticisms, expressions of irritability, off-task comments) from pre- to post-treatment compared to CHR youth and parents in EC [19].

We are currently conducting a larger confirmatory efficacy trial in seven sites in the U.S. and Canada that compares FFT with a more intensive psychoeducational comparator and follows CHR participants over 18 months [36]. This trial should

clarify the degree to which individuals in FFT achieve long-term symptom remission, the changes in family communication that putatively mediate treatment effects, and the subgroups of CHR youth that show the greatest benefits.

33.2.3 *Elderly Couples*

Elderly individuals with severe psychiatric disorders—particularly persons of color—are greatly under-served by the mental health system [37]. We have recently begun treating elderly couples (“elderly” being defined as older than the author) where one member has BD. Frequently, these are patients who have been ill for lengthy periods of time but are still struggling with mood instability. Cognitive impairment is more salient in these individuals. Their well-spouses often have acquired a great deal of information about the disorder from previous doctors or from their own reading, but still say they desire pointers on what signs to look for when their spouse is prodromal, how best to communicate with the patient during active symptomatic periods, and when to encourage greater effort on the patient’s part. In this population, physical health concerns often take center stage in FFT, as well as the distinction between depressive states and early signs of dementia.

33.2.3.1 Case Example

Gabriela, a 70-year-old Latinx woman with bipolar 2 disorder, lived with her husband Alexandro (Alex), age 71. They had been married since they were in their early twenties and had several adult children and grandchildren. The family was spread out, with one son and his family living in Spain, two sons living on the east coast of the US, and one daughter and her family in Mexico. Gabriela had had numerous depressive episodes since her late twenties, although she had run a successful dry cleaning business for years. In the past 5 years, she had been suffering from unremitting, treatment-resistant depression. She was taking lamotrigine, aripiprazole (Abilify), and a low dose of escitalopram (Lexapro). In the earlier stages of her illness, she had responded to lithium but was wary of taking it again due to her compromised kidney functioning. The precipitating event for FFT was a short episode of hypomania during which Gabriela became enraged, broke several drinking glasses, and confronted her husband on how “you’ve always tried to control me. You’ve always told me what to do, you’re always in my face.” She had threatened to leave and dissolve their 40-year marriage.

Because Gabriela presented with depression and withdrawal, the challenge for the FFT clinician was how to encourage her to become more active in her day-to-day life. She spent the majority of her day in bed, rising only to cook dinner, work a jigsaw puzzle, or occasionally speak on the phone. The clinician began by providing didactic information about bipolar depression, emphasizing that Gabriela’s excessive sleeping was an unresolved symptom of depression rather than “laziness”

(her husband's attribution). The first stage of FFT involved educating the couple about the benefits of behavioral activation strategies: having a structure to her day, social engagements that were meaningful to her, regular contact with her children and grandchildren, and a maximum of 9 h/night of sleep (without intermittent naps). The clinician framed depression and hypomania as challenges for the couple, not only for Gabriela.

Gabriela and Max discussed how her depressive and hypomanic episodes had influenced their communication as a couple (Max's responses to these symptom states and Gabriela's reactions to Max's interventions). In communication training, Max practiced active listening to learn how to "back off" (his words) or to pull back from his repeated commands and lectures about how she should take care of herself. He was coached to avoid giving advice. In turn, when Gabriela was the listener, she was instructed to paraphrase his point of view, acknowledge its helpful intent, and express why she disagreed. They also learned the skill of "making a positive request for change" in the partner, such as changing personal criticisms (e.g., "you're depressed because you never do anything") to positively-toned suggestions (e.g., "I'd appreciate your taking a walk with me – it would make me feel less lonely and might brighten your spirits").

Problem-solving was used to address a central problem: Gabriela's difficulty structuring her day. The couple discussed the various dimensions of this problem and split the discussion into separate sub-problems (e.g., her sleeping too late in the morning to follow through on social plans or volunteer work and her feeling of being unprepared for social activities). They generated a list of potential solutions that would be both rewarding for her and keep her engaged with others (for example, calling her grandchildren in the late morning, at the time they would be getting home from school in their time zone). Later, with the clinician's assistance, the couple discussed the pros and cons of various medication strategies that had been recommended by her psychiatrist for treatment-resistant depression (such as restarting lithium or trying a different antidepressant). She eventually restarted lithium at a low dose, with careful monitoring of her kidney functioning, and then started a trial of bupropion (Wellbutrin) to help her with physical energy.

Gabriela's mood gradually improved in small steps. A key event during treatment was Max's decision to retire, allowing them to travel more often so that she could see her grandchildren and extended family. At first, she dreaded this change, thinking more would be expected of her than she was capable of providing. By the end of FFT, however, Gabriela's depression had lifted, and they had taken several international trips to visit family and friends.

33.3 Limitations of FFT

FFT, being a conjoint therapy, has an obvious limitation: engaging entire families or couples can be a challenge, particularly when the patient has been struggling with the disorder for many years and family members have become disengaged.

Clinicians find it challenging to get family members to understand the importance of their role in the success of treatment. There are strategies for encouraging family involvement [38] but there will always be patients for whom family engagement is not feasible.

In the majority of the clinical trials on FFT, the experimental groups received a greater number of sessions than the control (TAU) conditions, raising the question of whether treatment gains can be attributed to the amount rather than the type of therapeutic contact. Although group differences in session frequency have not emerged as explanatory factors in statistical analyses [28], future studies need to compare FFT with frequency and duration-matched individual, group, or other family treatments, with equal attention paid to therapist fidelity and patient buy-in.

33.4 Future Perspectives

33.4.1 Identifying the Active Ingredients of Successful Therapy

Our recent network meta-analysis (NMA; [23]) of randomized clinical trials of psychotherapy for BD examined whether certain modalities were more effective than others in delaying recurrences or stabilizing symptoms in BD. We found 24 trials comparing at least two modalities where the outcome was recurrence over 1 year. The NMA revealed that psychoeducation with guided skill practice and self-monitoring, delivered in a family or group format, is more effective in reducing recurrences than the same two treatment components delivered in an individual format. We were unable to determine how long psychoeducation needs to be in order to be maximally effective.

Family/conjoint therapy, CBT, standard psychoeducation, and brief psychoeducation were each associated with more favorable recurrence rates compared with treatment-as-usual, which in these RCT studies was pharmacotherapy with standard clinical management or supportive counseling. When examining depression stabilization as the 1-year outcome, CBT and, with less certainty, family or conjoint therapy and interpersonal and social rhythm therapy were each associated with improved outcomes compared with TAU. The results were similar when examining the stabilization of mania symptoms, although with greater uncertainty because the majority of the trials did not include patients who were acutely manic at the inception of therapy.

Within the NMA, we explored whether certain therapeutic techniques were more effective than others in BD. This was accomplished by asking independent raters to classify each treatment on whether it included or did not include specific treatment elements (examples: cognitive restructuring, regulation of daily routines). Treatment in a family (vs. individual) format and encouraging patients to monitor their prodromal symptoms were the most potent treatment components associated with lower

recurrence rates. Cognitive restructuring, regulating daily rhythms, and, with less certainty, family communication training were the most potent components in enhancing the stabilization of depression symptoms.

33.4.1.1 “Assembler” Treatments

The results of the NMA suggest that it should be possible to create personalized psychotherapies for individual patients from a “toolkit” of potentially effective therapy strategies. There is no inherent reason why cognitive restructuring or social rhythm stabilization can’t be done in a family format or why communication training or problem-solving must always involve family members. Data on mediators of clinical improvement in different therapeutic modalities should enhance the process of assemblage. For example, improving the emotional tone of family communication appears to be an important mediator of the effects of FFT on symptomatic outcomes, but there may be briefer and more effective ways of modifying communication than the role-playing/rehearsal protocols currently in use. We have begun examining the use of mobile phone applications to remind individuals to practice communication skills in their daily lives, with preliminary results suggesting the utility of digital tools [39, 40].

33.4.2 *Psychosocial Treatment for Whom?*

We know relatively little about whether various forms of psychotherapy are more vs. less effective in subgroups of patients with BD. Involvement of the family in treatment, maintaining regular daily rhythms, or cognitive restructuring may have greater or lesser therapeutic benefits for patients at different phases of the illness. Hypothetically, family involvement is more feasible when patients are younger and on their first few episodes, whereas group psychoeducation may be the preferred option for older patients who lack family support systems. In older individuals with cognitive impairments, group psychoeducation in combination with functional remediation may be most cost-effective (e.g., [41]).

The current literature has yet to identify best-practice psychosocial treatments for those with the most severe forms of BD: treatment-resistant depressed patients with active suicidal behaviors or self-harm, or patients with substance abuse, rapid cycling, and/or comorbidity with personality disorders or other axis I disorders. Clarification of the effective components of treatment for different stages, polarities, or comorbidities may lead to the development of more effective forms of therapy for BD.

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Part V

Special Populations

Chapter 34

Pregnancy and Breastfeeding in Bipolar Disorder: A Clinical Guide



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34.1 Sex Differences and Hormonal Influences on Bipolar Disorder

According to the World Mental Health Survey Initiative, the global lifetime and 12-month prevalence rates for bipolar disorders (BD) are 2.4% and 1.5%, respectively [1]. In the Global Burden of Disease Study of 369 diseases and injuries, BD ranked 12th among adolescents and 28th among people of all ages worldwide in years lived with disability [2].

Women experience higher rates of depression and anxiety compared to men in both clinical and community samples with an approximately 2:1 ratio [3–10].

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Women have an overall higher risk for major depressive episodes (MDE) [3, 4, 7]. Conversely, although some studies have found higher rates of bipolar disorder type II (BD-II) in women compared to men [11–14], research has not demonstrated substantial sex differences in the prevalence of type I BD (BD-I) [6, 15–17]. Regardless of subtype, clinical characteristics of BD vary between sexes. In a sample of 1225 individuals with BD, female sex was strongly correlated with an increased risk of rapid cycling, cycle acceleration (reduction in inter-episode duration over time), and greater severity of mood episodes over time [18]. Women with BD are also more likely than men to have depressive onset [19] and predominant depressive polarity [19, 20], which are both associated with a longer duration of untreated BD and a worse prognosis, including a higher risk of suicide [21]. General misdiagnosis rates for BD reach as high as 90% in primary care [22, 23] and 70% in outpatient settings [24–26], and women are especially likely to be treated with unopposed antidepressants [27], which may trigger hypo/manic episodes [28].

Recent research has linked the recurrence of mood episodes to hormonal fluctuations during specific reproductive transitions [29–31], such as menstruation, peripartum, and peri- and post-menopause [30, 32, 33]. The impact of steroid hormones on affective disturbance among a vulnerable subgroup of individuals has been extensively documented in research [29, 34–37]. Studies have demonstrated clinically symptomatic reactions to experimental manipulations of steroid hormones in individuals with premenstrual dysphoric disorder (PMDD) [34], postpartum depression [38], and depression during perimenopause [39]. Though the underlying cause of this vulnerability remains uncertain, research into the pathophysiology of reproductive mood disorders suggests that these disorders are related to abnormal sensitivity to changes in steroid hormone levels rather than their absolute levels [36, 37, 40]. During pregnancy, there is a notable surge in ovarian hormones such as estrogen, progesterone, and allopregnanolone, which abruptly decline after birth [32]. Sensitivity to this rapid hormonal change has been proposed as a key biological mechanism underlying postpartum depression (PPD) [33, 41].

Clarifying the impact of steroid hormones on the brain and their role in neuropsychopathology requires an understanding of the dynamic interplay between excitatory and inhibitory neurotransmitter systems regulated by steroid hormones [42]. Neurotransmitters, including glutamate, GABA, acetylcholine (ACh), serotonin (5-HT), and dopamine (DA), are pivotal in the modulation of mood and behavior. Research has long supported the presence of a bidirectional relationship between neurotransmitter systems and steroid hormones within the central nervous system (CNS): [43] Activation of neurotransmitter systems modulates the binding of hormones inside the CNS [43], while steroid hormones regulate the process of transcription and protein synthesis, facilitating the integration of neuronal information within the CNS [44]. Progesterone and estrogen have opposing influences on excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmitter systems [42]. Progesterone has been shown to inhibit glutamatergic response [45] while enhancing GABAergic neurotransmission [46]. In contrast, estrogen has been found to facilitate glutamate transmission [47] and inhibit

GABAergic inputs [48], including estrogenic upregulation of N-methyl-D-aspartate (NMDA) [49–51] and AMPA receptors [52, 53]. Estrogen has been shown to promote synaptic and dendritic plasticity, neuronal processes that play vital roles in cognition, learning, memory, and emotional regulation [42, 54]. Moreover, estrogenic modulation of the serotonergic system has been shown to increase tryptophan hydroxylase-2 enzyme activity and reduce 5-HT uptake, thereby facilitating extended synaptic presence of 5-HT and promoting serotonergic function [55], constituting another mechanism through which estrogen can influence neuroplasticity and support cognitive processes. Many neurobiological factors such as hypothalamic-pituitary-adrenal (HPA) axis dysregulation, epigenetic modifications, neuroinflammation, and circadian gene abnormalities have been implicated in the pathogenesis of BD [56, 57], but the bidirectional regulation of steroid hormones and neurotransmitters may optimally explain the mood disturbances observed at reproductive transitions in those individuals who are sensitive to the physiological fluctuations in hormonal levels.

The interactions between BD, biological sex, and hormonal transitions have significant clinical implications. In this chapter, we will provide an overview of the epidemiology and risk factors for BD during the perinatal period and shed light on screening and treatment practices tailored to the management of BD during preconception, pregnancy, and postpartum.

34.2 Epidemiology and Screening

34.2.1 Epidemiology and Risk Factors

Up to half of individuals with BD experience a mood episode in the perinatal period [58]. Although pregnancy itself does not appear to directly increase the risk of bipolar mood episodes, behaviors associated with pregnancy, such as medication changes or discontinuation, increase the risk of episode recurrence [59]. The postpartum period, on the other hand, is a significant independent risk factor for recurrence, with a 37% overall risk of relapse and some studies citing a risk of up to 70% in the absence of treatment [60, 61]. Postpartum depression is a common first manifestation of BD [62], and BD is a major risk factor for the development of postpartum psychosis [63–65], a serious complication and psychiatric emergency. For individuals diagnosed with BD prior to pregnancy, major risk factors for recurrence during pregnancy or postpartum include younger age at disease onset, lack of current pharmacological treatment, longer duration of illness, and a higher number of previous episodes [59]. Previous episodes during the perinatal period, mixed episodes, and a history of rapid cycling are also predictors of recurrence [59]. The prevalence of undiagnosed BD is 2.6–4.5% in pregnant people with no prior psychiatric history [58].

34.2.2 Screening for BD in the Perinatal Period

As in any psychiatric condition, the efficacy of treatment is dependent on the accuracy of the clinicians' assessment and diagnosis. Figure 34.1 depicts a suggested algorithm for screening, diagnosis, and treatment of BD in pregnant individuals, adapted from that of Clark and Wisner [66]. Universal screening for depression during pregnancy and postpartum with the Edinburgh Postnatal Depression Scale (EPDS) without concomitant screening may lead clinicians to mistake depressive episodes of BD for unipolar depression [67]. Conversely, while over 30% of perinatal people may screen positive on the Highs scale for hypomania during early postpartum, few of these cases represent true BD [68]. Racial biases, as well as a lack of understanding of racial differences in BD symptom presentation among clinicians (i.e., lower frequency of prototypical manic symptoms such as elevated mood) [69, 70], make misdiagnosis more likely in Black people compared to White people [71, 72]. Misdiagnosis can beget significant negative outcomes; treatment with unopposed antidepressants may precipitate mania and/or psychosis [73] and has been associated with the risk of infanticide [74]. For this reason, it is recommended that

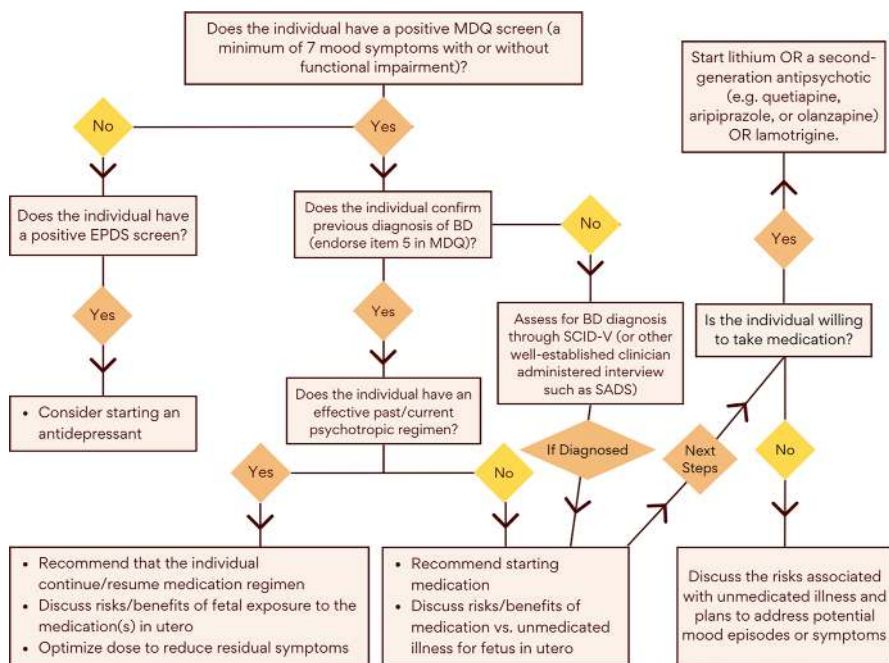


Fig. 34.1 Suggested algorithm for screening, diagnosis, and treatment of BD in pregnant individuals (MDQ: Mood Disorder Questionnaire; EPDS: Edinburgh Postnatal Depression Scale; SCID-V: Structural Clinical Interview for Mental Disorders, DSM-V; SADS: Schedule for Affective Disorders and Schizophrenia). Adapted from Clark & Wisner, *Obstet Gynecol Clin*, 2018 [66]

BD is always screened before initiating pharmacotherapy for anxiety or depression [75]. Routine screening is of particular importance in individuals with risk factors such as a family history of BD, and the CANMAT guidelines recommend universal screening for BD in pregnancy [76].

Pregnant people are routinely screened for depression with the EPDS, which asks about depressive symptoms over the past 7 days. Adding screening with a modified Mood Disorder Questionnaire, which excludes supplemental question 3 (degree of impairment), can identify nearly 70% of obstetrical patients with underlying BD. Reducing the score threshold to 4 rather than the usual 7 and excluding both supplemental questions 2 and 3 (multiple concurrent symptoms and impairment) further increases the sensitivity to 81%; while this reduces specificity to 69%, the most essential trait of a screening tool for perinatal BD is avoiding missed cases as further interviewing is required before a diagnosis is made regardless [77, 78].

34.3 Family Planning

34.3.1 Patient Concerns About Family Planning and Heritability

Family planning is an important consideration in any person with BD who has the potential to become pregnant. Key concerns voiced by individuals with BD include the heritability of BD, the possibility of harm to the fetus from mood-stabilizing medications, the potential for BD relapse due to changing medication to an alternative with a more favorable reproductive risk profile, consequences of untreated illness during pregnancy, and impacts of mood episodes on partners [79–81]. Clinical guidelines and patient feedback suggest that early counseling from physicians is beneficial, ideally at the initiation of pharmacotherapy or at initial consultation. Patients expect counseling to be provided supportively and nonjudgmentally and appreciate having this information provided both verbally and in written form via leaflets and handouts [80]. Healthcare providers' communication can have a significant impact on patients' perceptions of their ability to have a safe pregnancy. In one survey, nearly half of respondents reported being advised not to become pregnant by a healthcare professional, advice that is NOT supported by the authors of this current book chapter [79]. When provided with balanced information on the risks and benefits, personalized to the patient's medical and psychiatric history in a pre-pregnancy consultation with a psychiatrist, patients are empowered to make autonomous decisions on whether to pursue pregnancy [79].

Individuals with BD and their family members may also have concerns about the heritability of this disorder. In one study, 35% of participants were unwilling or less willing to have children due to their strong family history of BD after a genetic model of the disease was endorsed [82]. BD has a strong genetic component, with an estimated heritability of up to 89% [83]. Monozygotic concordance is 40–70%,

indicating that environmental factors also play a significant role [84]. Offspring of people with BD are at 2.7 times higher risk for development of any psychiatric disorder and four times higher risk for developing a mood disorder than children of parents with no psychiatric illness [85], and have an incidence of bipolar spectrum disorders ranging from 14–50% [86].

34.3.2 *Hormonal Contraception*

Hormonal contraception and psychotropics commonly interact. Some anticonvulsants that are also used as mood-stabilizers, such as carbamazepine, induce subtypes of hepatic CYP450 isoenzymes that metabolize hormonal contraceptives, and thus can decrease their duration, intensity of action, and corresponding contraceptive efficacy [87]. Inversely, hormonal contraceptives can also impact the metabolism of mood-stabilizing medications. Ethinyl estradiol-containing combined hormonal contraceptives reduce serum concentrations of lamotrigine by up to 64% [88, 89], while it is unaffected by progesterone-only formulations [90]. Valproate, although not advised for persons with childbearing potential due to high risks for fetal malformation [91], may also be cleared more rapidly when co-administered with oral contraceptives.

In female patients of reproductive potential who wish to avoid pregnancy or find that valproate is the most effective treatment option for BD, intrauterine devices (copper or progesterone-containing) have high efficacy, reduce the burden on the patient for compliance, and lack interaction with mood-stabilizing anticonvulsants.

34.3.3 *Preconception Considerations*

Preconception consultation ideally occurs at the initiation of pharmacotherapy and at least 3–6 months prior to conception to allow for appropriate tapering and adjustment of medications, with time to monitor for symptom recurrence [59, 69, 92]. The risk of symptom worsening or episode recurrence is reduced if the individual is euthymic with a sustained period of mood stability before conception. Medication regimens should be optimized to the fewest medications, with the best safety profiles during pregnancy, at the lowest therapeutic doses while still targeting the most effective control of the patient's symptoms [93]. Adjunctive agents such as benzodiazepines are ideally tapered prior to conception. Some patients may wish to discontinue all psychotropic medication prior to conception. Although medication is the mainstay of treatment for BD, individuals with a history of mild severity of previous episodes and low recurrence risk may be supported in discontinuation of medications with close clinical monitoring [59]. Unfortunately, the time it takes to become pregnant is highly variable, and 15–20% of couples in the general population take over 1 year to conceive [94]. As this can put patients with BD who have

discontinued their mood stabilizers at significant risk of relapse (see Sect. 34.4.2), a compromise of maintaining prophylactic treatment until conception should be discussed with the individual who is trying to conceive.

It is also essential to discuss the individual's social circumstances and interpersonal relationships, including their social supports, when available, both to address where supports may be optimized to aid in care for the future infant and also to augment mood stabilization. Many nonpharmacological lifestyle interventions can reduce the severity of BD and should be encouraged, including discontinuing or minimizing nicotine, caffeine, cannabis, and alcohol intake, practicing good sleep hygiene, optimizing nutrition, exercising regularly, and participating in wellness activities [69]. All of the above counseling should be done with an acknowledgment of systemic inequities and barriers and a focus on harm reduction [69]. Furthermore, persons with childbearing potential who take mood-stabilizing anticonvulsants known to increase neural tube defects (valproate and carbamazepine) should be supplemented with high-dose folic acid (4 mg/day) in case of unplanned pregnancy to minimize this risk [95].

If a person with BD is planning to conceive, it is important to consider the impacts of certain psychotropic drugs on fertility. Through anti-dopaminergic action, antipsychotic-induced hyperprolactinemia may decrease fertility, and, therefore, antipsychotics with a lower risk of increasing hyperprolactinemia are preferable [96]. Valproate, in addition to being contraindicated in individuals who are trying to conceive due to its teratogenicity, is also associated with symptoms of polycystic ovarian syndrome, including risks of infertility, which may persist after treatment is discontinued [97].

34.3.4 Unplanned Pregnancy

Although preconception counseling is ideal, patients with BD have a high rate of unplanned pregnancies, over three times the rate in healthy controls [98]. Adolescent girls with BD have 20 times the risk of pregnancy than those without and 25 times the risk of repeated pregnancy before the age of 20. Unplanned pregnancy in this population has been associated with increased impulsivity, hypersexuality, and risk-taking behaviors associated with mania and hypomania, as well as substance use and less uptake of and adherence to hormonal methods of birth control in favor of “traditional” methods such as cycle-tracking and withdrawal [98, 99]. Preventing unplanned pregnancy is important because individuals who discover that they have become pregnant unexpectedly are more likely to abruptly discontinue their psychotropic medications, significantly increasing their risk of withdrawal symptoms and recurrence [100]. Abrupt discontinuation may be reduced by family planning counseling at the initiation of treatment and intermittently revisiting this topic as appropriate. Interestingly, the adequate dosage of medications used to treat BD greatly reduces the risks of unplanned pregnancy by about 70%, which may be explained by a reduction in high-risk sexual behavior due to the antimanic and

anti-impulsivity effects of mood-stabilizing medications [99]. Overall, healthcare professionals must be equipped to approach patients prior to or post-conception, and Fig. 34.2 depicts a suggested approach to these scenarios adapted from that of Altshuler et al. [101]

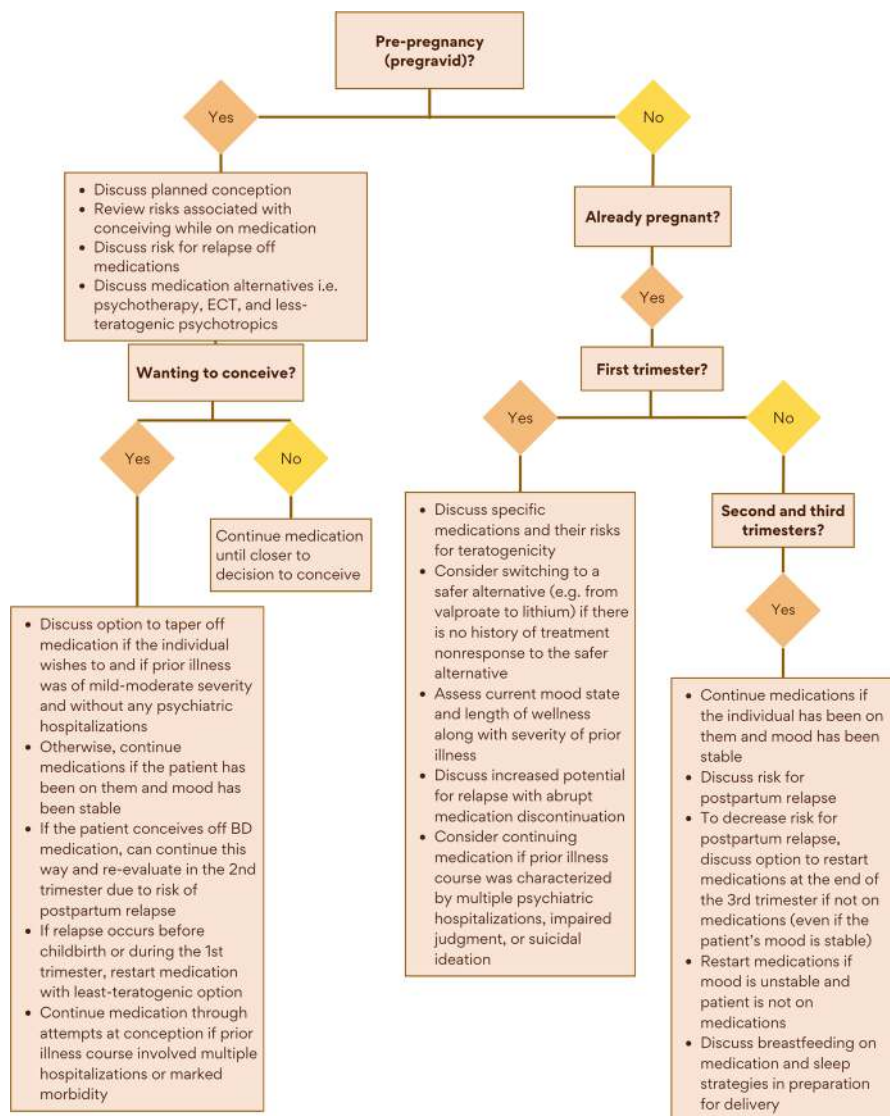


Fig. 34.2 Suggested approach to individuals with BD who are pregnant or considering pregnancy. Adapted from Altshuler et al., *Current Psychiatry*, 2003 [101]

34.4 Management of Perinatal Bipolar Disorder

34.4.1 *Interface of Obstetrics and Psychiatry*

Diagnosis and treatment are optimized when psychiatric and obstetrical services work collaboratively [102]. Currently, most primary care and obstetrics-based perinatal mental health programs are designed for (unipolar) depression only, despite the fact that over 20% of perinatal patients who screen positive for depression in primary care or obstetrical settings may have BD [103, 104]. Obstetricians have reported that they lack formal training on how to assess perinatal individuals for BD and are apt not to screen when they do not have the knowledge or resources to address problems if the screen is positive [58]. Programs that offer physician-to-physician consultation with a psychiatrist lead to increased screening and treatment in obstetrical and primary care settings [58, 103].

34.4.2 *Untreated BD During Pregnancy*

Regardless of treatment status, individuals with BD have higher rates of obstetrical complications, including C-section, induction, gestational hypertension, antepartum hemorrhage, placenta previa, and preterm birth [93, 105]. There are also increased rates of adverse neonatal outcomes in pregnant people with BD compared to healthy controls regardless of pharmacotherapy exposure, including prematurity, low birth weight, intrauterine growth restriction, small for gestational age, fetal distress, and adverse neurodevelopmental outcomes [93, 105, 106]. Appropriate treatment with most psychotropic medications has not been determined to increase the overall risk of adverse pregnancy and birth outcomes in individuals with BD but can mitigate some risks. For example, one study showed that infants of people with untreated BD have significantly smaller head circumferences than those of treated or control patients, which was associated with disadvantaged social demographic factors and protected against by mood-stabilizing medication [107].

Perinatal recurrence of BD is much higher in patients who do not take psychotropic medications. Unmedicated individuals with BD had a 71% recurrence rate during pregnancy, versus only 24% in patients on maintenance therapy (66% relative risk reduction) [108]. Mood episodes during pregnancy confer behavioral risks to the fetus including reduced compliance with prenatal care, inadequate nutrition, and high-risk behaviors including unprotected sexual activity and substance use [109]. Episodes may also involve psychosis which can pose significant risk to both mother and baby [110].

People with BD may discontinue their medication abruptly if they find out they are pregnant, especially when the pregnancy is unexpected [100]. Rapid discontinuation (over fewer than 14 days) is associated with a 50% rate of recurrence within 2 weeks, versus 22 weeks with gradual tapering [100]. Abrupt discontinuation of

psychotropics also may precipitate withdrawal symptoms such as insomnia, which can promote mood instability [93]. Thus, it is essential to proactively counsel any person with BD who has the potential to become pregnant about the importance of not abruptly stopping medications without consulting a physician.

There are certain clinical scenarios where it may be appropriate to try a medication-free period if that is in line with the individual's wishes. They should ideally be clinically stable for at least 6–12 months before attempting to taper maintenance medication [93]. If previous episodes have generally been mild (no psychotic features, hospitalization, or suicide attempts; only mild functional impairment with no social losses; no more than two psychotropic medications needed to attain remission with rapid response to pharmacotherapy), it is reasonable to closely monitor the individual for the first 12 weeks of pregnancy until organogenesis is complete if they remain asymptomatic, and then initiate prophylactic treatment [59]. If the person also has a low risk of recurrence (e.g., single episode, no family history, no early onset, no history of peripartum episodes, no rapid relapse after discontinuation of psychotropic symptoms), then pharmacological treatment may be further delayed until the emergence of symptoms [59].

34.4.3 Non-Pharmacological Interventions

Non-pharmacological strategies to mitigate episodes and severity of BD should be optimized in every person with BD, and pregnant individuals are no exception. Psychoeducation regarding illness management skills is ubiquitously important and can be especially helpful when provided in family or group settings [111]. Psychotherapies such as cognitive-behavioral therapy (CBT), family-focused therapy, interpersonal therapy, and interpersonal and social rhythm therapy have shown efficacy for augmentation in BD therapy [112]. Minimizing substance use, improving sleep hygiene, regular physical activity, and involvement of a partner and other social supports in childcare are also key to maintaining mood stability [59]. Bright light therapy has evidence as an augmentation strategy for residual bipolar depression; if this is to be trialed, the individual should be on an antimanic agent with no evidence of mania, hypomania, or mixed symptoms, as bright light therapy can be a precipitant for mania through similar mechanisms to those of antidepressant treatment [66, 113].

34.4.4 Sleep and Perinatal BD

Sleep is predictably disrupted during the third trimester of pregnancy and postpartum, which plays a causal role in the increased mood episodes occurring during the puerperal time [114, 115]. Sleep habits should be specifically assessed throughout the pregnancy and postpartum, such as by the insomnia symptoms questionnaire [116], as the EPDS asks only about mood-related sleep disturbance. Pregnant

individuals should be encouraged to keep diaries of their daily mood and sleep patterns. Psychoeducation should be provided about sleep hygiene strategies and the relationships between sleep, cognition, and mood [114]. CBT for insomnia (CBTi) has been shown to reduce mood symptoms in pregnant individuals with insomnia [117], and CBTi principles such as stimulus control (i.e., regular sleep and wake times, using the bedroom only for sleep and sex, and leaving the bedroom if unable to fall asleep) have shown efficacy in individuals with BD as well [118]. Sleep-sharing is a helpful practice for reducing sleep disruption in new parents who cohabitate with a partner or other caregiver; this involves alternating which partner wakes up to feed the newborn, allowing each partner two stretches of approximately 4 h of sleep per night. If breastfeeding, the parent with BD can pump breastmilk at the end of their feeds for the helper to use for the subsequent feed [119]. New parents should also be encouraged to nap when the baby is napping, when possible, and allow friends and family to assist with chores [119]. Medications such as trazodone and diphenhydramine may reduce depressive symptoms by improving sleep [120], although patients may refuse medication due to concerns about not waking up for their baby or passage of medication into breastmilk [114]. Medications should only be used if nonpharmacological interventions have failed or insomnia is severe [121].

34.4.5 Fundamentals of Prescribing in Pregnancy

There are a few fundamental principles to prescribing in individuals with BD who are pregnant or considering pregnancy. Medication regimens should be simplified to as few medications as possible in the lowest effective therapeutic doses. In general, it is preferable to use a higher dose of one medication than to use lower doses of two medications, as there is little available data on the combined impacts of medications during pregnancy. Psychotropic medications with the most evidence of exposure risk that fit the individual's clinical needs are preferable, and those lacking risk data should be avoided when possible [93, 110, 122].

Close monitoring is essential throughout pregnancy and postpartum due to high recurrence rates and the potential need for dosage adjustments. Pharmacokinetics of many drugs are altered during pregnancy due to increases in plasma volume, cardiac output, hepatic blood flow, and renal glomerular filtration rate, and reductions in plasma albumin concentration, gastric emptying, and gastrointestinal transit rate, and thus may warrant dose alterations to maintain therapeutic effectiveness in some individuals [123–125]. Some drugs, such as lithium and lamotrigine, decrease in serum concentration during pregnancy due to increased drug clearance. As a result, some patients may have worsening symptoms, and checking the lithium or lamotrigine level to confirm low serum concentration and guide dose augmentation (to target preconception serum levels, if known) helps achieve symptom remission [95, 126]. Post-partum fluid shifts may necessitate dose reduction after delivery if doses have been increased during pregnancy, and it is important to be aware of signs of toxicity in the postpartum period [95]. Further details on drug-level monitoring during pregnancy are included in Table 34.1.

Table 34.1 Perinatal safety and considerations for commonly prescribed mood-stabilizing medications in bipolar disorder

Medication	General Recommendations	Neonatal and obstetrical outcomes	Congenital malformations	Neuro-developmental effects	Metabolism, therapeutic drug monitoring, and dose adjustments	Fetal/neonatal monitoring
Lithium	• Appropriate when patient has high risk of relapse on other treatment options • Close monitoring of maternal serum levels may be required • Hold for 24–48 h prior to delivery, if possible [123]	• Associated with an increased risk of miscarriage, (OR 2.94) [127] • Reports of neonatal adaptation syndrome, floppy infant syndrome, hyperbilirubinemia, cardiac rhythm disturbances, hypothyroidism, and diabetes insipidus [95, 122] • Risks are associated with use in the third trimester, dose-dependent, and mostly occur in cases of maternal toxicity [128] • Neonatal risks may be reduced by holding lithium at onset of labor or 24–28 h prior to scheduled induction or C-section [123]	• Increased risk of cardiac defects (including Ebstein's anomaly) compared to unexposed infants, OR 1.81 (lower than previously reported) • Increased risk of any congenital anomaly, OR 1.86 [129]	• No differences seen in growth, behavior, and general development at ages 3–15 years [95]	Metabolism, therapeutic drug monitoring, and dose adjustments • Narrow therapeutic window (0.6–1.2 mEq/L in serum) • Exclusively eliminated by the kidney [123] • Excretion increases during T1 & T2 and declines during T3 and postpartum. During T3, clearance is approximately doubled compared to preconception [123, 130] • Despite increased clearance, risk of toxicity increases in T3 due to pre-eclampsia requires discontinuation of lithium due to decreased renal function. Lithium is contraindicated in patients with pre-eclampsia without daily serum concentration monitoring with subsequent dose adjustments • Obtain pre-pregnancy serum concentration [95] • Some guidelines recommend monthly lithium serum measurements during pregnancy [95]. In most clinical scenarios, it is acceptable to measure every 3 months and monitor the patient for clinical signs of insufficient dosing (i.e., increased mood instability) or toxicity, and obtain serum levels in the case of symptoms to guide dose adjustments • Increase dose if serum concentration falls below pre-pregnancy baseline by >0.2 mEq/L (or below therapeutic range if baseline unknown), being careful to avoid toxicity [126] • Avoid nephrotoxic drugs (e.g., non-steroidal anti-inflammatory drugs) during pregnancy and postpartum [123] • Check level at presentation for delivery and hold subsequent doses • Restart lithium on first evening after delivery at pre-pregnancy dosage. If pre-pregnancy dose not available, reduce by 30–50% from T3 dose. Check level 24 h later [95] • If patient has symptoms of mood instability or toxicity in the first 2 weeks postpartum (as renal function is normalizing), obtain a serum level [131]	• High-resolution anatomic ultrasound and fetal echo at 16–18 weeks • Monitor neonate carefully during first 48 h [95]

Mood-stabilizing anticonvulsants	Valproate	• Contraindicated in pregnant patients • Stop abruptly in early pregnancy; in later stages, taper over 1–15 days [132] • Patients on valproate who become unexpectedly pregnant should be referred for specialist consultations with psychiatry and maternal-fetal medicine [132] • In patients of child-bearing potential with BD, use should be restricted as a last-line medication with concurrent contraception [95]	• Risk of neonatal adaptation syndrome [122]	• Dose-response relationship exists, but unsafe at any dose [95] • Neural defects are common (adjusted OR for spina bifida = 12.7) [133] • 9-times relative risk of total malformations (rate up to 18%) [134] • Fetal Valproate Syndrome: malformations include neural tube defects, facial clefts, cardiac defects, limb defects, hypospadias, abnormal facial features [122]	• Increased risk of childhood autism (adjusted hazard ratio = 5.2) [135] • Associated with significantly lower IQ scores at 3 years old [136]	• Prescription contraindicated in pregnancy	• Refer to maternal-fetal medicine for fetal assessment [132]

(continued)

Table 34.1 (continued)

Medication	General Recommendations	Neonatal and obstetrical outcomes	Congenital malformations	Neuro-developmental effects	Metabolism, therapeutic drug monitoring, and dose adjustments	Fetal/neonatal monitoring
Carbamazepine	• Not recommended in T1 of pregnancy due to teratogenicity • Supplement all patients of child-bearing potential with folic acid 4 mg/day	• Associated with vitamin K deficiency in neonates; pregnant patients should take 20 mg/day of oral vitamin K during the last month of pregnancy in addition to 1 mg intramuscularly neonate at birth to prevent bleeding diathesis [66]	• May increase overall risk of malformation (OR 1.37) but evidence is inconsistent [93] • Associated with spina bifida [137] • Possible other associated malformations include cleft lip/palate, hypospadias, other neural tube defects, gastrointestinal anomalies, and renal anomalies [123]	• No known associations	• Significant changes in metabolism not expected, monitor symptoms carefully for changes in therapeutic effects [66] • Maintain lowest effective dose established preconception	• Evaluate for neural tube defects with ultrasonography and maternal serum alpha-fetoprotein [110]
Lamotrigine	• A preferred treatment option during pregnancy if appropriate for patient's BD symptomatology (i.e., depressive symptoms) [123]	• Mild neonatal withdrawal is possible [138]	• Once thought to increase risk of oral clefts, but this has been disproven [95, 110] • Overall malformation rate comparable to general population [123]	• No increased risk of neuro-developmental disorders, no significant impact on IQ scores [95] • Maternal rating for sentence skills and autistic traits at 36 months lower than controls [139]	• ↑ Estrogen during pregnancy → ↑ glucuronidation in liver → ↑ renal clearance of lamotrigine [95] • Obtain preconception serum level, when possible • Monitor during pregnancy based on clinical response. If levels were obtained, target preconception therapeutic dose [95] • Changes in clearance are highly variable based on genetic enzymatic variants, with 23% of patients having little change and other having increase of up to 330% by 32 weeks [123] • Many patients will require a 250% dose increase • Clearance rapidly decreases postpartum; if dose was increased during pregnancy, taper by 25% immediately post-partum and back to preconception dose over 2 weeks to prevent toxicity [123]	• Routine prenatal care • Monitor neonate for signs of withdrawal

Antipsychotics	• Older antipsychotics may be preferred by clinicians due to more clinical experience and data • Most antipsychotics appear to have a relatively good safety profile in pregnancy, but evidence is mixed • Preferred antipsychotics in pregnancy are • quetiapine, olanzapine, and aripiprazole • Quetiapine has a significantly lower rate of placental transfer (23.8%) compared to olanzapine (72.1%) and risperidone (49.2%) in T2 & T3 [95] • If using a typical antipsychotic, high potency is preferred (e.g., haloperidol) [110]	• Available data is mixed and inconclusive with respect to causality [95] • Possible increased risk of low birth weight and prematurity • SGAs may increase the risk of gestational diabetes and C-section compared to FGAs [140] • No differences in rates of pregnancy loss or prematurity • T3 exposure associated with neonatal EPS, tremors, muscle tone abnormalities, breathing/feeding difficulties, sedation, and agitation. Concomitant use with mood stabilizers increases likelihood of requiring specialized neonatal care [95]	• Possible increased risk of malformations for second-generation antipsychotics, but evidence is variable and insufficient to draw conclusions • Possible small increase in risk for risperidone specifically [123] • Historical evidence that lower-potency typical antipsychotics may increase risk of malformations [141]	• Possibly associated with transient delays in infant development [95, 123]	• Changes in metabolism are variable based on genetic variants of cytochrome P450 hepatic enzymes [123] • Monitor symptoms closely, adjust doses based on clinical changes [123] • If doses were increased during pregnancy, decrease gradually after delivery	• Routine prenatal care • Monitor neonate closely after delivery

T1 first trimester, T2 second trimester, T3 third trimester, OR Odds ratio, EPS Extrapyramidal symptoms, SGA Second-generation antipsychotics, FGA First-generation antipsychotics

34.4.6 Pharmacological Treatment for Perinatal BD

When considering the safety of various pharmacological agents in pregnancy, it is important to consider teratogenicity and rates of congenital malformations, risk of poor neonatal adaptation syndrome, and risk of long-term neurobehavioral sequelae [122]. While the first trimester is the risk period for medication-induced congenital anomalies as it is the period of organogenesis [142], medication use near delivery increases the risk of poor neonatal adaptation syndrome. Research studies must be interpreted in the context of the baseline rate of congenital malformations in the general population, which is 2–5% [143–145]. Other factors associated with BD, such as substance use, obesity, high-risk behaviors, difficulty accessing and following prenatal care, and medical comorbidities, further confound the outcome data of pharmacological safety studies [122]. For ethical reasons, placebo-controlled trials have not been completed, limiting the ability to account for these confounders [59]. There are increased rates of obstetrical/neonatal complications in pregnant persons with BD regardless of pharmacotherapy [93, 105, 106].

In terms of specific medications, lamotrigine is an antiepileptic with antidepressant properties that has been well-studied in pregnant patients and has a lower risk of weight gain and gestational diabetes than atypical antipsychotics, though it is most effective in individuals with predominantly depressive symptoms or BD-II [123]. Among antipsychotic medications, quetiapine [146, 147] and aripiprazole [148, 149] have demonstrated low reproductive risks [150], and a recent prospective pharmacovigilance study has supported the safety of olanzapine during the first trimester of pregnancy [151]. It is crucial to conduct more prospective observational studies with large sample sizes on individuals taking antipsychotics throughout pregnancy to clarify the relative risks compared to other newer antipsychotics such as paliperidone and lurasidone [129, 147]. Regarding lithium, the risks of exposure are highest during the first trimester and with high-dosage exposures [128], but if clinically indicated for the pregnant person, it is considered low-risk during pregnancy if used at the lowest therapeutic dose with appropriate monitoring of serum levels. Carbamazepine is not recommended in the first trimester, while valproate is contraindicated throughout pregnancy due to elevated risks of malformations and neurodevelopmental problems in the exposed offspring [152]. Benzodiazepines should also be avoided during pregnancy as much as possible, especially during later gestational ages due to the potential for neonatal toxicity, withdrawal, and floppy infant syndrome [122]. Particular considerations regarding common medications for BD in pregnancy are summarized in Table 34.1.

34.4.7 Neuromodulation (ECT and rTMS)

Electroconvulsive therapy (ECT) should be considered in individuals who have failed to respond to three medication trials or in cases of severe dehydration, malnutrition, severe psychosis, or imminent risk of harm [66]. Pregnancy-specific concerns surrounding ECT include the diversion of blood away from the uteroplacental

unit, decreased venous return due to aortocaval compression, increased aspiration risk, and difficulty of intubation [153]. Case reports have demonstrated risks to the fetus [154]; however, this is confounded by significant reporting bias [95] and it does not appear that rates of placental abruption, prolonged fetal heart rate abnormalities, preterm delivery, or stillbirth are significantly increased in individuals who undergo ECT. Furthermore, the ECT protocol can be modified to improve safety during pregnancy. For example, left lateral decubitus positioning with wedge, pre-oxygenation, and prehydration support placental blood flow, and continuous fetal monitoring can be performed after 23 weeks [153]. Propofol can be used to shorten the duration of seizure and related effects on fetal heart rate without decreasing the efficacy of the treatment, and administration of acid-suppressing medications reduces aspiration risk in the pregnant person. Routine intubation should be avoided [153]. Regardless of the number of sessions they have received, it is recommended that individuals receiving ECT during pregnancy follow-up with an ECT session 10–14 days after delivery to prevent recurrence during the vulnerable postpartum period [153]. Repetitive transcranial magnetic stimulation (rTMS) has shown preliminary efficacy in two case studies, but more evidence is required in the perinatal population with BD [155, 156].

34.5 Postpartum and Breastfeeding

34.5.1 Postpartum Mood Episodes

The postpartum period is a high-risk time for development of mood episodes, and maternal suicide during such episodes is a leading cause of maternal mortality [157]. Up to 70% of untreated individuals with BD have a relapse in the postpartum period [61], which is six times higher than the risk of relapse during pregnancy itself. The risk of postpartum depression is higher in individuals with BD-I and BD-II than those with MDD and tends to be more severe [158]. Postpartum is also a common scenario of first mood episodes in previously-well patients; up to 50% of patients who experience their first depressive episode postpartum eventually develop BD [62].

Given the high risk of relapse in the postpartum period, individuals who were medication-free during pregnancy may benefit from starting prophylactic mood stabilization treatment immediately after delivery [60]. Quetiapine and olanzapine have shown efficacy for preventing postpartum mood episodes in BD-I and BD-II. There is not yet any data on the use of brexanolone, the only FDA-approved drug specifically for the treatment of postpartum depression, in individuals with BD. Regardless of the presence of postpartum relapse, new parents with BD report more issues bonding with their infants, so bonding interventions may be beneficial for all individuals with BD after delivery [159].

34.5.2 *Postpartum Psychosis*

The most severe postpartum episode is postpartum psychosis, which is estimated to affect 1–2 per 1000 deliveries [160] and is more common in individuals with BD than those with any other psychiatric diagnosis [63, 65, 96]. Risk factors for developing postpartum include a history of BD (particularly BD-I), previous postpartum psychosis, family history of BD or postpartum psychosis, primiparity, and sleep disruption [161–164]. Fifty percent of individuals with postpartum psychosis present with symptoms as early as day 3 after child delivery, including labile mood, irritability, agitation, anxiety, pressured speech, confusion and disorientation, abnormal thought content, and/or insomnia [65, 93]. It more commonly has a depressive, anxious, or irritable/mixed presentation, while elevated mood occurs less frequently [165]. Families may not recognize these presentations as signs of serious illness [65], emphasizing the importance of providing psychoeducation about these clinical signs prior to delivery. As it may be accompanied by thoughts of harming themselves or their newborn, any postpartum psychosis is considered a psychiatric emergency and should be assessed within 24 h of symptom onset due to increased risks of maternal suicide or infanticide [121]. Individuals with symptoms of postpartum psychosis often need to be hospitalized with a low index of suspicion and may be treated with a combination of mood stabilizers, antipsychotics, benzodiazepines, and/or ECT [166]. A protocol that combines lorazepam, haloperidol, and lithium has shown efficacy, with 63/64 (98.4%) participants achieving full clinical remission and 51/64 (79.7%) participants displaying sustained remission at 9 months postpartum [167].

34.5.3 *Breastfeeding*

The decision to breastfeed on mood stabilizing medications should always involve a risk-benefit discussion with the parent and consider the health and circumstances of both mother and baby. In most cases, if the parent wishes to breastfeed, the clinical benefits of breastfeeding when taking mood-stabilizing medication outweigh the risks [168]. Any infant being breastfed by an individual on mood-stabilizing medication should be monitored closely for signs of poor feeding, sedation, or other adverse effects. Extra caution should be taken if the neonate was born prematurely as the immature hepatic and renal systems are less able to clear medication, which may lead to a higher relative infant dose (RID) [69]. Breastfeeding is often times contraindicated in individuals experiencing postpartum psychosis [93]. Considerations for breastfeeding on various commonly prescribed medications in bipolar disorder are described in Table 34.2.

Table 34.2 Breastfeeding considerations for commonly prescribed mood stabilizing medications in bipolar disorder

Medication	Considerations for breastfeeding
Lithium	• Decision to breastfeed on lithium should be personalized to the mother-infant dyad • Variable transfer to infant; RID up to 30%, M/P ratio 0.2–0.7 (mean 0.58), infant serum concentration 5–67% of maternal level [169] • Limited evidence base, primarily case reports (significant reporting bias) • Reports of elevated TSH, BUN, and creatinine (all transient or resolved with cessation of breastfeeding) [95] • Infant should be followed by a pediatrician and monitored for any changes in behavior, restlessness, sedation, or difficulty feeding • Infant should be evaluated and receive appropriate fluid supplementation if dehydrated or showing signs of infection [169] • If changes in clinical status observed, obtain maternal & infant lithium levels, and infant TSH & renal function tests [66] • Higher risk of adverse effects in premature infants due to immature renal function [66]
Mood-stabilizing anticonvulsants	Valproate
	Carbamazepine
	Lamotrigine
Antipsychotics	

M/P ratio Milk/Plasma ratio (estimated concentration of drug in milk compared to maternal serum), *RID* relevant infant dose (weight-adjusted percentage of maternal dose received by infant), *TSH* Thyroid-stimulating hormone, *BUN* Blood urea nitrogen, *FGA* First-generation antipsychotic

34.6 Clinical Considerations

- Pregnancy and postpartum are periods of elevated risk for bipolar mood episodes and new BD emergence, with significantly increased risks of recurrence for patients not on pharmacological treatment.
- Screening with the EPDS should be accompanied by screening with a modified mood disorder questionnaire (excluding supplemental questions 2 and 3 and decreasing the score threshold to 4).
- Family planning should ideally be initiated early with all BD patients who have the potential to become pregnant.
- When possible, preconception counseling should occur at least 3–6 months before trying to conceive to allow for medication adjustments and monitoring.
- Medication regimens during pregnancy should be guided by the following tenants: as few medications as possible, with the lowest known reproductive risks, at the lowest doses that successfully maintain symptom control.
- Pharmacokinetics of many drugs are altered during pregnancy and reversed after delivery, which necessitates monitoring for mood instability or signs of toxicity and may require dose adjustments.
- Lamotrigine, antipsychotics (quetiapine, olanzapine, aripiprazole), and lithium are appropriate treatment options during pregnancy with minimal reproductive risks.
- Valproate is contraindicated in pregnancy due to teratogenicity, and carbamazepine is teratogenic in the first trimester.
- Nonpharmacological management strategies should be employed in every patient, including psychoeducation, quitting/minimizing substances, proper sleep hygiene, optimizing nutrition, regular exercise, psychotherapy, and stress management.
- Most mood stabilizing medications are supported in breastfeeding with appropriate monitoring of the infant.

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Chapter 35

Pediatric Bipolar Disorder: Phenomenology, Differential Diagnosis, and Course



The Child and Adolescent Bipolar Spectrum Disorders Services (CABS)

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Tina Goldstein, and Dara Sakolsky**

35.1 Introduction

Considering the developmental stage of the child or adolescent, and with some exceptions (see below), the criteria to diagnose bipolar spectrum disorders (BD) in this age group are like the criteria utilized to diagnose BD in adults and described in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision (DSM-5-TR) [1] and the International Classification of Mental and Behavioral Disorders (ICD-11) [2].

Promptly and accurately diagnosing BD early in life is critical to improve the prognosis of this illness and minimize its deleterious effects on psychosocial development, including risk for substance abuse, behavioral and legal problems, and suicidality [3–5]. Unfortunately, on average it can take 5–10 years for a person with BD to receive an accurate diagnosis, delaying initiation of treatment and worsening the prognosis [5, 6].

The goals of this chapter are: (1) to provide information regarding the clinical picture and the challenges of diagnosing BD in youth and (2) to present the current knowledge regarding the course, complications, and etiology of BD in youth.

Throughout the chapter, the word “youth” refers to children and adolescents, unless otherwise indicated.

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DSM-5-TR uses the diagnoses of other specified bipolar and related disorders, instead of the BD-Not-Otherwise Specified (BD-NOS). However, given that all existing studies were done using the term BD-NOS, this chapter will address this subtype of BD as BD-NOS.

35.2 Prevalence

BD usually onsets during adolescence, but it may also occur in prepubertal children [3–5]. In fact, a large study showed that 30% of adults with BD reported the onset of significant mood symptomatology before age 13 [7].

A comprehensive meta-analysis of the lifetime prevalence of bipolar spectrum disorders (BD-I, BD-II, cyclothymic disorder, or BD-NOS) in community samples ($n = 56,000$, ages 5–20 years old) in various countries reported a prevalence of 3.9% and for BD-I 0.6% [8]. As expected, the prevalence was higher in youth older than 12 and in studies that evaluated lifetime prevalence. However, the results were very heterogeneous, possibly due to methodological differences among the studies, such as the use of self-reports vs. clinical interviews, the clinical expertise of the assessors, the use of different diagnostic criteria, interpretation of the symptoms, and disentangling the symptoms of comorbid disorders. The rates of BD-I/II in the United States were similar to those in other countries, but BD-NOS was more often diagnosed in the United States [4, 8, 9]. Similar differences have been reported for adults with BD [6].

A prior study based on chart reviews and billable services reported a 40-fold increase in the diagnosis of BD in the United States [4, 5, 10]. However, it is important to note that improvements in diagnostic techniques and increased awareness can lead to more frequent diagnoses. This may be especially apparent in disorders that initially had low rates of diagnosis. For example, if ten youths per year were diagnosed with BD, and due to better diagnostic techniques and awareness, the following year, 20 youths are diagnosed with BD, the rate of diagnosis would have increased by 100% [5]. Due to the complex clinical picture and course of BD, this illness may not only be overdiagnosed but also misdiagnosed or underdiagnosed. These issues will be discussed in the next section.

35.3 Clinical Picture

As per the DSM-5-TR, a diagnosis of BD-I in children and adolescents requires elevated mood or irritability along with increased energy/activity. Other symptoms, but not necessarily all of them, are needed including grandiosity, decreased need for sleep (e.g., sleeping 3–4 h per night and not feeling tired the next day), increased distractibility, talkativeness, flight of ideas, agitation, increased goal-directed activity (e.g., rearranging and cleaning her/his bedroom or the house at inappropriate

hours), and inappropriate sexual thoughts/behaviors. Sometimes hallucinations and delusions are observed.

A meta-analysis of 20 studies ($n = 2226$) of youth with bipolar spectrum disorders showed that most common symptoms across bipolar subtypes included increased energy (79%), irritability (77%), mood lability (76%), distractibility (74%), goal-directed activity (72%), euphoric/elated mood (64%), pressured speech (63%), hyperactivity (62%), racing thoughts (61%), poor judgment (61%), grandiosity (57%), inappropriate laughter (57%), decreased need for sleep (56%), and flight of ideas (54%) [11]. Perhaps due to methodological problems (e.g., criteria to diagnose BD, analyses of the effects of comorbid disorders, instruments used, interpretation of the clinical assessment, and training and supervision of the interviewers), symptom rates were very heterogeneous.

A diagnosis of BD-I requires that the manic symptoms occur most of the day for at least 7 days (or less if the youth is hospitalized because of mania), and importantly, the symptoms should occur in clusters. Although the DSM only requires one episode of mania, the presence of recurrent manic episodes increases the certainty about the diagnosis. Also, the symptoms should exceed what would normally be expected for the developmental stage of the child (e.g., it is expected for children to be silly or have age-appropriate grandiose thoughts) and are *not better* explained by other psychiatric (e.g., use of substances and ADHD) or medical conditions, or environmental factors (e.g., abuse), and significantly affect the psychosocial functioning of the youth. Although not necessary to diagnose BD-I, recurrent episodes of major depression are very common and often are the first manifestation of BD [4, 5, 12–15].

BD-II is usually more prevalent in adolescents than children, and the manifestations are like those in adults with recurrent symptoms of hypomania occurring for at least four consecutive days and are present most of the day [1]. Compared to mania, the symptoms of hypomania are less intense and have a lesser effect on the functioning of the youth, but a change in mood and functioning observable by others is required for diagnosis [3–5]. Moreover, some youth experience enhanced functioning during hypomania. Again, the mood symptoms should exceed what is normally expected for the developmental stage of the youth and not be better accounted for by other psychiatric disorders or medical/neurological conditions.

Cyclothymia is manifested in youth by recurrent periods of depressive symptoms and hypomanic symptoms that do not fulfill the criteria for either major depressive disorder (MDD) or hypomania and affect the psychosocial functioning of the youth. The prevalence of cyclothymia is difficult to estimate because it is usually combined with BD-NOS in the literature [16, 17]. Youth with cyclothymia convert to BD-I or II less frequently than those with BD-NOS, but they have impairment in psychosocial functioning on par with BD-NOS [16, 17]. Also, they have more irritability, mood reactivity, and rejection sensitivity—symptoms that in adolescents may be confused with borderline personality disorder.

Often in youth, the symptoms of mania or hypomania described above last only 2–3 days instead of the DSM required minimum episode length, and consequently, these youth are diagnosed with other specified BD or what it used to be called

BD-NOS. These youth are at risk of developing BD-I/II, and their functioning, risk for suicidality and substance abuse, prevalence of comorbid disorders, family history of BD, and polygenic risk for BD are similar to those in youth with BD I/II [3–5, 18–28].

It is also important to define two more mood states, mixed presentations and rapid cycling, because they occur more often in youth than adults with BD [4, 13]. While in a mixed episode, as defined in DSM IV, youth present simultaneously with symptoms of mania/hypomania and major depression for at least a week. The youth may present as very agitated, anxious, or irritable and can exhibit an increased risk for suicidality. In DSM-5-TR, mixed episodes are replaced with “mixed features” to describe three or more symptoms of depression during a manic episode or three or more manic symptoms during a depressive episode. Similarly, these subsyndromal mixed manic symptoms were significantly more common in depressed youth with BD than those youth with unipolar depression ($p < 0.0001$) [15], and mixed features were more prevalent in depressed offspring of parents with vs. without BD (OR: 4.2, 95% CI: 1.2–14.7) [29]. Rapid cycling is diagnosed when there are episodes of mania/hypomania and/or depression that occur separately but recur, according to the DSM-5, at least four times over 12 months. Some studies of BD youth have reported “ultradian cycles” [30, 31] defined as rapid and frequent changes in mood over the course of a day. However, this concept is not currently accepted by most investigators because these rapid changes are expected fluctuations in mood that occur during the same episode and should not be considered separate mood episodes.

The DSM-5-TR uses other specifiers for all subtypes of BD. These specifiers are also used in diagnosing youth and include anxious distress, melancholic features, atypical features (although many adolescents may have atypical symptoms calling into question the label “atypical”) [15], mood-congruent or incongruent psychotic features, catatonia, peripartum, and seasonal pattern [3–5, 12, 32]. For this last specifier, in youth, it is difficult to differentiate whether the symptoms of depression are associated with fall-winter or the depression is more related to the academic and social stress usually associated with school.

35.4 Differential Diagnosis

Diagnosing BD in youth, particularly in children, is often challenging for several reasons. First, the youth’s cognitive, emotional, and social developmental stage may influence the intensity and quality of the mood symptoms. Thus, there may be some differences in the clinical presentations of children and adolescents, with adolescents showing symptoms more like adults [14]. Second, the BD symptoms overlap with the symptoms of other disorders. For example, both BD and ADHD are manifested by impulsivity, poor concentration, high energy, hyperactivity, labile mood, and behavior problems [4, 5, 23, 33]. Third, BD is usually comorbid with these disorders [4, 5, 12, 28].

Some characteristics may help to differentiate BD from other disorders. For example, except for MDD, and in contrast with other disorders, the symptoms of BD are episodic. ADHD and ODD are constant or fluctuate slightly depending on the circumstances, but they do not “come and go” like the symptoms of BD. Thus, it is important to closely follow youth longitudinally to determine the periodicity of the symptoms. Of note, periods of euthymia may also be difficult to ascertain because underlying comorbid disorders or even side effects of medications may disguise the presence of euthymia. Also, euthymia can be confused with hypomania, especially when there is relief from a persistent depressive episode, given that both may be associated with improved functioning and symptoms of hypomania can be difficult to distinguish from normal adolescent behaviors (e.g., increased energy, impulsivity).

For the differential diagnosis, it is important to consider that BD has symptoms that do not often occur in other disorders:

- Due to excessive energy during periods of mania/hypomania, the youth may not sleep at all or may sleep for only a few hours for several nights and the next day, contrary to what is expected, they are not tired and continue to be energetic, talkative, etc. At night while awake, youth with BD may continue to be excessively energetic with increased goal-directed activity and impulsivity. For example, cleaning and rearranging their bedroom or the house, starting new projects, calling or texting friends at 1 or 2 am, making noises or singing aloud, leaving the home, excessive social media activity, etc.

In contrast, youth with ADHD may have initial insomnia because it may be difficult for them to settle down, but they do eventually fall asleep and will feel tired the next day. Youth with depression, anxiety, or other disorders may also have insomnia, but they do not have other manic/hypomanic symptoms and they complain that they are tired at night, although unable to sleep, and feel worse the next day.

- During mania, youths may show inappropriate and exaggerated sexual behaviors or thoughts that are beyond the developmental stage of the child and are not *exclusively* accounted for by exposure to virtual or actual sexual material. The hypersexual behaviors of youth with BD are episodic and cluster with other symptoms such as increased energy, decreased need for sleep, etc.
- Grandiosity may be difficult to differentiate from developmentally appropriate grandiose ideas such as being the best soccer player, musician, etc. Also, normal children or those with other disorders (e.g., ADHD and ODD) may brag about their abilities. However, grandiosity as a symptom of mania is exaggerated, and even when challenged by family or peers the youth may act upon these ideas (e.g., telling the principal of the school how to direct the school). These behaviors affect the youth’s psychosocial functioning, usually are noticed by others, and again, are episodic and cluster with other manic/hypomanic symptoms.
- Elation is also difficult to ascertain because being temporarily euphoric or silly is appropriate in youths, particularly in children. However, if this is exaggerated, out of proportion to the circumstances, episodic, and clusters with other manic/

hypomanic symptoms, it should be considered a symptom of mania/hypomania. In the past, some studies suggested that in youth, and in particular children, BD is mainly manifested by irritability instead of elation [34]. However, a large prospective study showed that most manic/hypomanic presentations are manifested by elation together with irritability and a small proportion only irritability [34]. As per DSM-5-TR, one more manic symptom is needed (irritability + 4 symptoms) for BD diagnosis if the presentation is irritability only without elation.

- Overspending money was not often seen in youth with BD, as expected, but has become more common with access to buying things online. Youth with other disorders may also impulsively spend money, but usually, it is less extreme and does not cluster with other symptoms of mania/hypomania.

The presence of a family history of BD is the major risk factor for developing BD, but as described in more detail below, family history alone is not enough to determine that symptoms are attributable to BD.

It is important to emphasize that like in adults, the initial presentation of BD is often an episode of depression [4–6, 12–14, 35]. Although some studies suggest that the symptoms of bipolar depression are more severe and include melancholic symptoms, clinically it is very difficult to predict which individual will eventually develop manic/hypomanic episodes [15]. However, when major depression manifests at a young age and is accompanied by psychosis, subsyndromal symptoms of mania, family history of BD, and/or pharmacologically-induced mania, the risk of developing mania/hypomania is increased [3–5, 15, 36, 37].

The presence of unequivocal psychotic symptoms should also raise the possibility that the youth has a mood disorder (unipolar depression or bipolar disorder) because schizophrenia is rare, and longitudinal studies of youth with psychosis show that a substantial proportion develop mood disorders, in particular, BD [32].

DSM-5 added a diagnosis of disruptive mood dysregulation disorder (DMDD) (APA 2013). This new disorder is controversial, and it appears that youth diagnosed with DMDD have severe oppositional defiant disorder suggesting that the symptoms of DMDD are more a phenotype than a disorder per se [4, 38]. DMDD was in part derived from the study of youth with severe mood dysregulation; these youth differ from youth with BD because they do not have the symptoms required to be diagnosed with BD and the symptoms are not episodic [39].

Finally, pharmacologically induced mania may be confused with “disinhibition” or agitation which appears in 5%–10% of youth treated with antidepressants [40]. These symptoms usually subside when the antidepressants are discontinued. For these cases, DSM-5 introduced a “induced bipolar and related disorder” diagnosis to consider the presence of mania secondary to a medication or substance use during active use, intoxication, or withdrawal.

35.5 Course

The course of BD can be assessed using different methods including a description of the rates of recovery and recurrence of mood episodes and continuity into adulthood, survival analyses, and the percentage of time spent in each mood state over time. Since the course of BD is heterogeneous, analyzing whether there are subgroups with different trajectories is warranted.

Most studies show that 2–3 years after a mood episode, approximately 60%–90% will experience recovery [4, 5, 13, 19, 30, 41, 42]. However, after recovery, in approximately 2–5 years, most youth with BD will experience one or more mood recurrences, particularly subsyndromal and mixed. A recent study extended the follow-up of the COBY study to a median of 12.5 years (mean age at last assessment: 24.5 years old). Again, after the initial recovery, the median time to the first recurrence was 1.5 years (2 months–12 years) [41]. About 80% had at least one recurrence and 60% had two or more recurrences, with about 70% of the recurrences being depressions. During the follow-up, there was an average of two recovery periods lasting a median of 2.1 years (2 months–15 years).

Childhood and adolescent BD, particularly BD-I/II, continues into adulthood [30, 43]. Family history of mania predicted adult BD-I/II and over half of those youth with BD who did not have mania/hypomania in adulthood continued to have subthreshold manic symptomatology [43].

Studies that have analyzed the percentage of time in different mood states during follow-up show that youth with BD spend 40% of their time asymptomatic and 60% of the time symptomatic (20% syndromal and 40% subsyndromal [13]). While symptomatic, most of the episodes were manifested by subsyndromal mood symptomatology and mixed presentations. Compared with adults with BD-I, youth with BD-I had significantly less time euthymic and more time with mixed episodes and rapid changes in mood; the percentage of time in other mood states (e.g., depression and manic episodes) was similar between the two groups.

The studies noted above reported outcomes for the group as a whole but the course of BD is very heterogeneous. A latent growth analysis in a large sample of youth followed over an average of 9 years found four distinct trajectories: “predominantly euthymic” (24.0%), “moderately euthymic” (34.6%), “ill with improving course” (19.1%), and “predominantly ill” (22.3%). Within each class, youths were euthymic on average 84.4%, 47.3%, 42.8%, and 11.5% of the follow-up time, respectively. The better course was associated with older age at the onset of mood symptoms, less lifetime family history of BD and substance abuse, higher socioeconomic status (SES), and less history at baseline of severe depression, manic symptoms, suicidality, subsyndromal mood episodes, and sexual abuse [44]. For the fourth group, improvement was associated with improvement in parental SES and substance abuse, both of which predated the improvement of the youth [45]. Of note was the presence of a subgroup with persistently good prognosis; these youth had mood symptoms that disappeared over time, suggesting the presence of a

developmental subtype of BD, analogous to what is sometimes seen in early onset seizure disorders, juvenile arthritis, and Tourette's syndrome.

In general, all analyses of the course of BD in youth show that worse prognosis is associated with early-onset, more severe illness (more recurrent and longer-lasting episodes, suicidality), presence of comorbid disorders, poor adherence to treatment, history of physical or sexual abuse, low SES, more service utilization, family history of mania or substance abuse, and living in families with high "expressed emotion" (high emotional over-involvement, critical comments, and hostility) [3, 4, 13, 44, 46–48]. Prognosis is also significantly influenced by the fact that a substantial proportion of youth with BD does not adhere to the treatment [49, 50].

The above studies describe the course for the entire sample and subgroups, but they do not describe the course of a particular individual. Using variables found in the literature to be associated with the course of BD, a risk calculator (RC) to predict the recurrence of depression or mania/hypomania was developed [41]. The 6-month and 1-, 2-, 3-, and 5-year RC showed an accuracy between 72% and 82% for predicting any mood recurrences, and up to 80% for depression and 89% for hypo/mania (sensitivity/specificity both 0.74). The most influential risk factors were shorter recovery lengths, younger age at assessment, earlier mood onset, and more severe history of depression. Although important, other factors associated with recurrence risk, such as inter-episodic subsyndromal mood symptoms and comorbidities, did not influence the RC score beyond the factors noted above. This recurrence RC was externally validated in a large sample of adults with BD [51]. The recurrence RC is available at www.pediatricbipolar.pitt.edu under resources.

Overall, for all analyses, no significant differences were found among BD subtypes (BD-I, II, and NOS). However, it is important to emphasize that up to about 50% of youth with BD-NOS convert to BD-I/II, especially if they have a family history of BD [3–5, 18, 19, 22–28]. An RC to predict the risk of converting from BD-NOS into BD-I/II was also developed with an accuracy of 71% [52].

35.6 Complications

BD, particularly if not treated appropriately, affects the normal psychosocial development of the youth, and increases the risk for legal, academic, familial, work, and social difficulties, hospitalization, use of polypharmacy, being physically or sexually abused, inappropriate or excessive sexual behaviors, psychosis, substance abuse, suicidal behaviors, obesity, and medical illnesses [3–5, 13, 24, 44, 46, 47, 53–59]. In fact, among psychiatric disorders, BD increases the risk of suicide more than any other disorder. As described in the course section, more complications are associated with BD when other factors such as low SES, early illness-onset, history of abuse, presence of comorbid disorders, poor adherence, and family psychopathology are present.

One large prospective study of adolescents with BD who have not yet developed substance use disorder (SUD) showed that 32% of subjects, after a mean of 2.7 ± 2.0 years from intake, developed new-onset SUD (mainly marijuana and/or alcohol) [23]. Factors associated with the onset of SUD included alcohol experimentation, oppositional defiant disorder, panic disorder, more severe mood symptoms, family history of SUD, low family cohesiveness, and absence of antidepressant treatment. Lithium exposure in the preceding 12 weeks predicted a lower likelihood of SUD. There were no differences among the BD subtypes. At study intake, 18% already had SUD; thus, in this study, about 50% of the participants had SUD, highlighting the urgent need to prevent and treat this comorbid disorder.

The prevalence of lifetime suicide attempts in youth with BD is between 20% and 47%. Among youth and among all psychiatric diagnoses, BD is associated with the greatest risk of death by suicide [24, 60, 61]. A large study showed that at intake about 33% of youth with BD (average at intake 12 years) had a history of at least one suicidal attempt [60]. Follow-up of youth who participated in the above study and who never had a history of suicidality showed that 18% had at least one new suicide attempt within 5 years of study intake and of these, 8% made multiple attempts [24]. Thus, for this study, a total of 51% of youths with BD had at least one attempt, emphasizing again the need for successful treatment of BD and suicide prevention efforts. There were no differences among the BD subtypes. Factors that increased the risk for suicidality included being female, more severe depression, mixed features/episodes, psychosis, hospitalization, nonsuicidal self-injurious behavior, panic disorder, substance use disorder, and family history of depression. Moreover, persistent depression, mixed presentations, and active substance use disorder signaled imminent risk for suicidal behavior.

The above findings applied to the group as a whole, but recently RC was developed to predict the individual's risk for suicide attempt within 1 year, with an accuracy of 82% [61]. This RC was recently validated in a large sample of adults with BD-I/II [62].

35.7 Etiology

BD is a highly heritable disorder, with twin and adoptive studies showing a heritability of up to 80% [4, 5]. The most unique factor associated with an increased risk of developing BD is a family history of BD, particularly if the parent developed BD early in life (i.e., <25 years old) [3–5]. The risk of developing BD in offspring is between 15% and 30% for BD and 10–15% for BD-I depending on the methodology of the study [35, 36, 48, 63–69]. In contrast, the risk of developing BD in the offspring of parents with non-BD psychopathology or healthy parents is about 1–3% [35, 36, 63, 65].

A meta-analysis of mainly retrospective studies showed that the prodromal symptoms preceding an initial mood episode lasted 27.1 ± 23.1 months (range, 4.6–130 months) [11]. The symptoms are heterogeneous and nonspecific and

include increased energy (68%), diminished ability to think (63%), indecisiveness (62%), pressured speech (60%), talkativeness (60%), elated mood (58%), academic or work difficulties (56%), insomnia (54%), depressed mood (53%), and increased productivity/goal-directed activity (50%).

Prospective studies by various groups of investigators found sleep difficulties, anxiety, depressive and subsyndromal manic symptoms, mood lability, or irritability to be associated with an increased risk of developing BD [36, 64, 68–70]. A large prospective study of offspring of parents with BD and offspring of control parents with and without non-BD psychopathology also found the presence of ongoing depressive, anxious, and mood lability symptoms, and particularly the presence of subsyndromal manic symptoms, can increase the offspring's risk to develop BD to about 50%, especially if parents have early onset BD [36].

The above findings, although informative, report average risks for the group and not a specific individual. To do this, an RC was created to determine the risk for a specific youth to develop BD [71]. This RC predicted the risk of developing BD with an accuracy of 76%. For the reader's information, the RC is also available at www.pediatricbipolar.pitt.edu under Resources. However, before it is recommended for widespread clinical use, it must be externally validated.

Using the results of genome-wide association (GWAS) analyses of a sample of 40,000 adults with BD [72], polygenic risk scores (PRS) were derived for BD, unipolar MDD, schizophrenia, and ADHD in parents with BD [20, 21]. These results were compared with the same PRS for healthy or parents with non-BD psychopathology. After adjusting for between-group differences, only the BD-PRS significantly separated parents and the offspring from their respective controls. Path analyses showed that the BD-PRS was transmitted from parents to offspring and the higher the BD-PRS in the offspring, the greater the risk to develop BD. However, there was also a significant direct pathway that went from the parents with BD to the offspring with BD without passing through BD-PRS. Possible explanations include the fact that the current BD-PRS GWAS included relatively small samples of patients with BD, and therefore many genes associated with BD were not included, the current BD-PRS did not include rare mutations, and importantly, psychosocial factors that are known to increase the risk for BD were not considered.

It is beyond the scope of this chapter to discuss the neurobiology of BD. It suffices to say that the genes responsible for BD may produce abnormal prefrontal and subcortical brain neurocircuits which in interaction with environmental factors may precipitate the symptoms of BD [4].

35.8 Summary

BD usually onsets during adolescence but can also be present in children. The symptoms of BD in youth are similar to those in adults, but some symptoms rarely appear (e.g., overspending). BD is often difficult to diagnose in youth due to their

cognitive and social immaturity as well as other factors (e.g., comorbid disorders, mixed and rapid cycling presentations).

BD is a highly heritable polygenic illness whose manifestations in the brain are being studied, but still unknown. In fact, the main unique factor that increases the risk of developing BD is a family history of BD with up to 25% of offspring of BD parents developing BD. This prevalence increases to about 50% if the offspring has ongoing depression/anxiety, subsyndromal symptoms of mania, and if parents' BD onsets early. These prevalence rates are for the group as a whole, but a recent RC showed good accuracy in predicting the risk of developing BD for a particular individual. The accuracy of the RC was enhanced when the BD-PRS was added.

Early-onset BD is associated with a worse prognosis and high risk for suicidality, substance abuse, poor academic and work performance, poor family functioning, physical/sexual abuse, and legal problems. Most initial presentations are depressions, and up to 80% recover after the initial episode. However, of those who recover, in a period of 2 months–12 years, about 80% will have at least one recurrence and 60% will have two or more recurrences. Recurrences are mainly depressions followed by mixed presentations/episodes. Some factors, such as the presence of comorbid disorders, history of abuse, less time in remission, and parental psychopathology increase the risk of recurrences. However, a subgroup may have a benign course, and may no longer experience mood symptoms in adulthood. The course of BD in youth is heterogeneous, but an RC to predict risk for recurrences was developed and externally validated with very good accuracy. Moreover, an RC was also developed and externally validated to predict the individual risk for suicide attempts.

A substantial group of youth has BD-NOS mainly because they do not have the DSM required duration of symptoms to be diagnosed with BD-I/II. This group of youth has as much psychopathology, risk for suicidality and substance abuse, family history of BD, and similar genetic profile as BD-I/II and up to 50% eventually will convert into BD-I/II.

The early identification and appropriate treatment of BD in youth is crucial given the deleterious effects of this illness on the psychosocial development of the child and the increased risk for suicidality. Some of these factors that are associated with the onset and increased risk for recurrence are amenable to change and support the importance of delivering evidence-based treatments for youth with BD and their families.

Hopefully, in the future, reliable and valid biological and behavioral markers will be identified to help diagnose BD, predict the prognosis, and individualize treatment.

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Chapter 36

Bipolar Disorder in Older Adults



Bernardo de Mattos Viana, Breno Satler Diniz, and Erico Castro Costa

36.1 Introduction

Population aging is a global phenomenon. The number of elderly individuals with severe mental disorders will experience a significant and concerning surge in the coming decades. Among severe mental disorders, bipolar disorder (BD) is related to the presence of clinical and psychiatric comorbidities, leading to a greater impact on quality of life throughout the lifespan. There is much variability within the diagnostic category of bipolar disorder, also in older adults.

Older age bipolar disorder (OABD) refers to patients with bipolar disorder (BD) aged 50 and over [1]. OABD is a special, more complex subgroup of BD, with a distinct clinical phenotype and higher prevalence of cognitive deficits [2, 3], increased risk of dementia [4], frequent physical comorbidities [5], and premature death [6]. These features of OABD usually limit and complicate treatment and recovery. In addition, decreasing social network size, loss of support from friends and family members, lifestyle choices, and reduced mobility negatively influence

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outcomes in this population. Within the OABD “umbrella,” there are individuals who have the onset of illness in young adulthood (the most common age of onset) as well as those who have illness onset later in life (e.g., 50 years and older).

36.2 Epidemiology of OABD

In general, the prevalence of bipolar disorder decreases with age, a phenomenon probably secondary to the increased mortality of patients with BD compared to the general population [7]. Epidemiologic studies indicate that bipolar disorder affects 0.5–1.0% of older adults, which is lower than the prevalence of 1.4% reported in individuals aged 18–44 years [8]. However, these figures could increase dramatically as the number of older adults continues to rise, our awareness and detection of bipolar disorder improves, and significant improvements in treatment improve the long-term prognosis of younger adults with BD [1]. Nevertheless, older adults living in long-term care facilities are generally not included in these studies, and an older study showed a prevalence that ranges between 3 and 10% in institutionalized older adults [9].

36.3 Diagnosis and Specifiers of OABD

In clinical practice, it is challenging to estimate the disease’s severity and parse out the heterogeneity in the manifestation of OABD. It is essential for subtyping OABD patients to reduce this heterogeneity and to improve personalized treatment. Several markers of illness severity have previously been suggested for bipolar disorder patients of all ages, such as bipolar disorder type I or II [10], presence of psychotic symptoms or suicidal behaviors [11], childhood maltreatment [12], predominant polarity, episode density [13], and neuroinflammation [14].

Two common ways of profiling are to differentiate between bipolar disorder types I and II and to distinguish the bipolar age of onset (early or late-onset). In the past, subtyping by the age of onset of BD was clinically relevant, as late-onset bipolar disorder (LOBD) was often viewed as an expression of preclinical dementia with a poor response to mood stabilizers. In contrast, early-onset bipolar disorder (EOBD) was viewed as a more classic BD manifestation with a positive family history of mood disorders [15]. However, results of the global aging & geriatric experiments in bipolar disorder (GAGE-BD) project [16] found that LOBD might represent a similar clinical phenotype as classic EOBD concerning the core of bipolar disorder symptomatology, functional performance, and comorbid physical conditions, suggesting that the distinction between the age of onset may not clinically relevant in OABD.

Regarding bipolar disorder subtypes, the GAGE-BD reported that BD-I and BD-II older-aged patients are similar in general functioning, cognitive performance, and somatic burden, suggesting that the distinction between both types is not clinically relevant in OABD or can identify individuals that are at particularly higher risk of negative adverse outcomes [17].

36.4 Clinical Course

The clinical progression of OABD is highly heterogeneous. A longer illness duration can lead to treatment resistance, a shorter time between mood episodes, and decreased cognitive functioning [18]. In a Dutch naturalistic cohort study, 37.5% of OABD patients had at least one recurrent episode within a 3-year follow-up, mainly depression. Life events, somatic illness, and use of lithium were not connected with recurrence during a 3-year follow-up [19].

In contrast to the previous literature, recent results from GAGE-BD [20] suggest that both manic and depressive symptoms severity appear to reduce in intensity in older age. Also, a negative age relationship was particularly pronounced among those with lower education, such that depression symptoms in late-life BD were less severe among less educated participants. A previous study with a smaller sample ($n = 220$) [21] also found an inverse association between the duration of diagnosis and depressive symptoms severity in OABD. The authors raised the hypothesis that older adults with BD are more familiar with their diagnosis and symptoms and have devised effective coping strategies, reducing the severity of symptomatic presentation. Another possibility is that the clinical rating scales for mania and depression may not be designed to recognize the way these symptoms manifest in later life [22, 23].

Findings in the adult BD population indicate that social, psychological, and cognitive factors significantly contribute to the clinical course, such as shorter time of relapse, higher frequency of recurrence, and longer time to recovery of BD [24–26].

In OABD patients, recurrence was associated with younger age, female sex, and less family support [27]. Another study did not find a significant association between mood episode recurrence and physical illness, age at onset, onset polarity, and predominant polarity [19].

The COVID-19 pandemic offered the opportunity to study negative life events as predictors for recurrence in OABD [27]. Not having children, greater feelings of loneliness, a passive coping style, and higher neuroticism were found to be associated with more severe psychiatric symptoms during COVID-19. A higher comprehensive knowledge, skill, or accomplishment of COVID-19 was protective initially, but over 6 months, it was associated with a significant increase in mood symptoms. However, participants with a higher comprehensive knowledge, skill, or accomplishment of COVID-19 still reported fewer psychiatric symptoms than those with a lower comprehensive knowledge, skill, or accomplishment of COVID-19 [28].

36.5 Psychosocial Functions

OABD has been associated with lower psychosocial functioning [29]. Earlier OABD studies confirmed that psychosocial functioning was low in several areas, such as autonomy, independence, economic management, occupational performance, and interpersonal relationships [30]. Specific and sensitive assessment methods for daily functioning in OABD are scarce, as many commonly used scales are not specifically designed for OABD.

Recent findings suggested that greater severity of depressive symptoms in bipolar disorder was associated with worse functioning in OABD [31]. On the other hand, a higher somatic burden was not associated with reduced functioning [20]. Finally, a small-sample study showed that nonaffective cognitive impairment was associated with worse social functioning, but this was not the case for affective cognition [32].

36.6 Cognition

Cognitive dysfunction is common in OABD. It is projected that 40–50% of OABD present with cognitive impairment during euthymia. It is one of the most persistent deficits in OABD [33], with a highly variable course. OABD is associated with a significantly higher risk of dementia when compared to nonpsychiatric and other psychiatric populations [4, 34].

In middle-aged bipolar disorder patients, numerous studies have recognized three different groups based on their cognitive profile, fluctuating from severely impaired cognitive functioning to preserved cognitive performance [35, 36]. Concerning the older population, some studies proposed a more severe decline of cognitive functioning in OABD compared with healthy older adults. In contrast, others do not support a progressive course of cognitive impairment in OABD [37, 38].

Distinct hypotheses have been suggested on cognitive impairment in bipolar disorder. The cognitive reserve hypothesis states that patients with a high IQ, education level, or occupation are less likely to develop dementia. In bipolar disorder patients, this reserve is reduced due to vascular burden. Thus, the risk that a bipolar disorder patient develops dementia is believed to increase over time [38]. Conversely, the neuroprogression hypothesis sustains that every single mood episode, particularly with manic and psychotic symptoms, is toxic to the brain [39, 40], and cognitive deficits and structural changes are thought to be the effect of accelerated aging in OABD [41].

A recent meta-analysis demonstrated that multiple cognitive domains are frequently impaired in OABD, even during euthymic conditions [42]. However, dysfunction was typically more intense in episodic memory and executive dysfunction, and there were no significant relationships between clinical illness, demographic

variables, and cognitive impairment [42]. Also, a recent cross-sectional study demonstrated that being older was associated with a selective cognitive decline in bipolar disorder in attention when compared with age-matched healthy participants [42]. Lastly, OABD patients show a more severely impaired cognitive profile when compared with older patients with unipolar depression or healthy participants [43].

It is worth noting that cognitive impairment in OABD is probably multifactorial, being associated with cardiovascular risk factors, medication use (e.g., benzodiazepine use, anticonvulsant use as mood stabilizers), number of mood episodes, later age of onset, and multiple psychiatric admissions [44].

36.7 Physical Comorbidities

OABD is commonly associated with a high medical comorbidity burden, in particular cardiovascular disease, metabolic disorders, and some types of cancer [5]. A Dutch naturalistic study detected one or more physical comorbidities in 62% of OABD individuals, with an average of 1.2 out of eight common chronic medical conditions [44]. Interestingly, the prevalence was marginally inferior in the OABD group compared with the older general population (1.2 vs. 1.6 conditions) at baseline. This lower prevalence may be due to a “survivor effect” in OABD, where individuals with bipolar disorder and higher medical comorbidity burden die younger and those individuals that reach older ages are healthier than the average BD individual. Nevertheless, the OABD groups showed a faster accumulation of chronic medical conditions during the 3-year follow-up [44]. Another large study reported a higher medical comorbidity burden in OABD (mean of 2.4 diseases) in a sample of older individuals from multiple cohorts [20]. The high physical burden has been related to a more severe illness course, decreased general and cognitive functioning, and probably a poorer treatment response and rapid cycling [45].

The mortality risk of people with bipolar disorder is two to three times greater than in the general population [46, 47]. Also, individuals with bipolar disorder have a significant reduction in life expectancy, usually by 9–20 years less than the general population [48]. The mortality risk and lower life expectancy are probably due to the higher medical comorbidity burden observed in this population, especially cardiovascular diseases (CVDs) [49]. Also, OABD is associated with elevated suicide behaviors and completed suicide. However, other factors play a significant role, including the higher prevalence of unhealthy lifestyles and behaviors (smoking, alcohol use, nutrition, physical exercise, stress, sleep), diminished access to higher quality medical care, adverse effects of pharmacotherapy, severity of bipolar disorder, and genetic factors [46, 50].

Comorbidities and Differential Diagnosis

According to the International Classification of Diseases (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR), BD type I diagnosis can be made based on evidence of a single manic episode. Similarly, BD

Table 36.1 Recommended laboratory tests and neuroimaging work-up in patients with late-life bipolar disorder

Blood count
Urea and creatinine
Fasting blood glucose and/or glycated Hb
TSH
Liver enzymes
B12 vitamin
Calcium, sodium, potassium, and chlorine
VDRL
Anti-HIV
MRI or CT scan
(additional PET-CT or NeuroSPECT in highly suspected neurocognitive disorders)

type II is diagnosed when occurring at least one hypomanic episode and at least one depressive episode. The mood episodes should not be better explained by another mental disorder and not attributable to substance use or other general medical conditions.

It is important to notice that older adults may manifest a manic episode related to several physiological stressors, including infections and adverse drug reactions. Moreover, neurocognitive disorders may manifest with maniac symptoms in the early stages, even when there are still no neuroimaging abnormalities. Therefore, a thorough laboratory and neuroimaging assessment is imperative (Table 36.1).

Maniac syndrome has also been associated with stroke, although such association is less strong than with major depression [51]. Secondary mania is more likely to occur in patients with lesions in the subcortical areas of the right hemisphere. Studies on stroke-related maniac syndrome indicate that the clinical manifestation is similar to a manic episode of BD [52, 53]. With secondary mania, Huntington's disease, normal pressure hydrocephalus, and prion diseases are associated with maniform symptoms, although there is no conclusive evidence that they are not mistakenly attributed to a primary manic episode [54, 55].

36.8 Treatment

Once prescribing medication to older adults, it is essential to evaluate for the presence of physical comorbidities and cognitive impairment. Similarly, due to changes in pharmacokinetics and pharmacodynamics, older patients are more susceptible to side effects and drug interactions. In bipolar disorder populations, antipsychotics have been related to an increased risk for many physical diseases, including respiratory disease, cardiovascular disease, thyroid disease, gastrointestinal, musculoskeletal, and renal diseases [56]. Many drugs can be the cause of severe weight gain, e.g. olanzapine, quetiapine, and clozapine [57]. Benzodiazepines and antipsychotics have been associated with cognitive impairment and higher fall risk [44].

Research on pharmacological treatment of OABD is scarce, as older patients or patients with physical comorbidities are often excluded from drug research. However, open-label trials, naturalistic studies, and post-hoc analyses of mixed-aged RCTs propose that medications efficacious in younger adults will also be effective in older adults [58].

The fundamental principle underlying the prescription of psychotropic medication for older adults is: “Start low, go slow, but go!”. Older adults generally need to initiate medication with low doses since they are more prone to side effects. Additionally, dose titration must increase slowly [59]. However, it is imperative to achieve therapeutic levels. Considering these principles, the treatment of geriatric acute mania can be challenging. Choosing medications with a safer side effect profile and effectiveness is imperative while aiming for a rapid response. Another major challenge in the acute management of OABD is that older adults usually have a longer recovery time, although they achieve treatment response at similar rates as young adults [7, 60].

A very important aspect of the management of OABD is improving adherence to the treatment regimen by promoting psychoeducation for both the patients and their families. Psychoeducation is an intervention strategy based on providing patients and relatives with information about the disorder. It has been shown to improve treatment adherence by enhancing their understanding of BD and enabling early identification of warning signs and mood changes [61]. For adjunctive psychological maintenance treatment in adults, psychoeducation is considered a first-line intervention with level 2 of evidence in adults [58, 61]. It has been proposed as an important intervention for older adults and their families [62]. It has also been suggested to add psychotherapy for older adults with BD [63, 64]. Concerning specific psychotherapies, data from adults suggest cognitive-behavioral therapy (CBT) and family-focused therapy (FFT) are preferred options [58].

Sajatovic et al. suggest that lithium, valproate, olanzapine, or quetiapine are first-line treatments for mania in older adults [62]. On the other hand, lurasidone and quetiapine should be considered first-line treatment for depressive episodes in geriatric BD (Grade 2B) [64]. It is important to notice that different acute treatment strategies may be chosen in treatment-resistant episodes, such as monotherapy or adjunctive therapy with different classes of medications.

Once remission has been achieved, maintenance treatment aims to sustain the medication regimen that initially resulted in remission. Nevertheless, Sajatovic et al. suggest switching to lithium rather than other medications for those who cannot tolerate the side effects of the former. Lithium treatment should be 25–50% of the adult daily dose, with serum levels between 0.4 and 0.7 mEq/L. In cases where lithium is not effective and subsequent trials with lamotrigine lead to negative outcomes, it is advised to explore other medications. These alternatives may include aripiprazole, carbamazepine, olanzapine, quetiapine, risperidone, valproate, or ziprasidone [62, 64].

Maintenance treatment should include clinical and laboratory follow-up assessments (Table 36.3). Lithium, valproate, and antipsychotics may cause tremor and movement disorders. Older adults are more prone to develop movement disorders or

Table 36.2 Follow-up assessment during pharmacological management of late-life bipolar disorder

Every 3–6 months	Annually
• Lithium level • Serum creatinine • Estimated glomerular filtration rate • Blood urea nitrogen • Tremor and movement disorders • Gait and falls	• Thyroid function • Fasting glucose • Fasting cholesterol • Triglycerides • Calcium • Complete blood count • Weight and waist circumference • Cognitive screen

Adapted from: Sajatovic and Chen [62, 64]

worsening of Parkinson’s disease signs and symptoms. Second-generation antipsychotics are also generally related to weight gain and the development of metabolic syndrome. The impact on other comorbidities, such as diabetes or dyslipidemia, should not be overlooked (Table 36.2).

It is not yet clear the full impact of medications for BD on cognition. There are several lists of inappropriate drugs for geriatric use. In these lists, benzodiazepines, first-generation antipsychotics, and tricyclic antidepressants are pointed out as the foremost medications that lead to secondary cognitive deficits [65–67].

Acute lithium treatment has been associated with negative effects on cognitive performance, especially short- and long-term memory, slower reaction time, and decreased associative fluency [68–71]. Such effects usually improve after discontinuation of the drug [70]. On the other hand, some studies have pointed out the potential neuroprotective effects of lithium, particularly in reducing the risk of Alzheimer’s disease development in individuals with BD [72–74]. For example, Nunes et al. pointed out that the prevalence of Alzheimer’s disease in bipolar patients without continuous use of lithium was 33%, while those who used it were 5% [74].

Valproate and carbamazepine were initially associated with attention deficits, memory, and information processing, although this association remains inconclusive based on a review of the literature [75]. Valproate can lead to a slight attention deficit, slight short- and long-term memory impairment, decision-making capacity, reduced motor speed and cognitive flexibility [68]. Carbamazepine, on the other hand, pointed to mild deficits in short- and long-term memory but without significant adverse effects on motor speed [68]. Among the mood stabilizers of the anti-convulsant class, only lamotrigine showed no significant adverse effects on cognition. A retrospective study on the efficacy of lamotrigine in BD reported improvement in cognitive performance [76] (Tables 36.3, 36.4, and 36.5).

Regarding the use of antipsychotics, uncontrolled studies have reported worse executive function in BD patients who use antipsychotics compared to those who do not use them. When comparing first-generation antipsychotics with second-generation antipsychotics, the latter are associated with a better cognitive pattern. Studies point to an improvement in cognitive function in patients with schizophrenia using second-generation antipsychotics. However, the improvements are modest

Table 36.3 Treatment of bipolar disorder in older adults

Level of evidence by phase of treatment (Monotherapy)						
	Acute depression		Acute mania		Maintenance (Any mood episode)	
	Older adults****	ISBD 2018 (Adults)****	Older adults****	ISBD 2018 (Adults)****	Older adults****	ISBD 2018 (Adults)****
Quetiapine	First-line*	First-line—level 1	First-line* Second-line***	First-line—level 1	First-line*	First-line—level 1
Lithium	Second-line* First-line***	First-line—level 2	First-line*/positive evidence** First-line***	First-line—level 1	First-line****/ positive evidence**	First-line—level 1
Divalproate	Second-line* Third-line***	Second-line—level 2	First-line*/positive evidence**	First-line—level 1	First-line****	First-line—level 1
Lamotrigine	Second-line*/positive evidence** First-line***	First-line—level 2	Negative evidence	Negative evidence	First-line****/ positive evidence**	First-line—level 1
Lurasidone	First-line* First-line****	First-line—level 2		n.d.		First-line—level 4
Cariprazine		Second-line—level 1		First-line—level 1	n.d.	n.d.
Asenapine		n.d.	Second-line* Third-line***	First-line—level 1		First-line—level 2
Aripiprazole	Third-line**** or refractory*	Negative evidence	Second-line* Third-line***	First-line—level 1		First-line—level 2
Risperidone			Second-line* Third-line***	First-line—level 1		First-line—level 4
Paliperidone 6 mg	n.d.	n.d.		First-line—level 1		Second-line—level 2
Olanzapine			First-line*	Second-line—level 1		Second-line—level 1

(continued)

Table 36.3 (continued)

Level of evidence by phase of treatment (Monotherapy)					
	Acute depression		Acute mania		Maintenance (Any mood episode)
	Older adults****	ISBD 2018 (Adults)****	Older adults*****	ISBD 2018 (Adults)****	ISBD 2018 (Adults)****
Aripiprazole OM		n.d.		n.d.	First-line—level 2
Risperidone LAI		n.d.		n.d.	Second line—level
Ziprasidone		Negative evidence	Second-line*	Second-line comb. T.—level 1	Second-line comb. T.—level 4
Carbamazepine	Third-line***		Third-line***	Second-line comb. T.—level 1	Second-line—level 2
Haloperidol		n.d.		Second-line comb. T.—level 1	n.d.

*Sajatovic and Chen [62, 64]; **Ljubic et al. [63]; ***Keramatian et al. [77]; ****Yatham et al. [58]

First-line: Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch; Second-line: Level 3 evidence or higher for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch; Third-line: Level 4 evidence or higher for efficacy plus clinical support for safety/tolerability

Level of evidence—1: Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison ($n \geq 30$ in each active treatment arm); 2: Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison condition ($n \geq 30$ in each active treatment arm); 3: At least one DB RCT with placebo or active control comparison condition ($n = 10-29$ in each active treatment arm) or health system administrative data; 4: Uncontrolled trial, anecdotal reports, or expert opinion; Not recommended: Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

Table 36.4 Treatment of bipolar disorder in older adults—(Combined treatment)

	Acute depression		Acute mania		Maintenance (Any mood episode)	
	Older adults****	ISBD 2018 (Adults)****	Older adults****	ISBD 2018 (Adults)****	Older adults****	ISBD 2018 (Adults)****
Quetiapine + Li/DVP		First-line comb. T.—level 4	Second-line*	First-line—level 1	Second-line*	First-line comb. T.—level 1
Lamotrigine (adj)		First-line—level 2		Negative evidence—Level 4	Second-line*	First-line—level 4
Risperidone (adj)		n.d.		n.d.		Second line—level 2
Lurasidone + Li/DVP		First-line—level 1		n.d.		Second-line—level 3
Asenapine+Li/DVP		First-line comb. T.—level 4		First-line—level 2		First-line comb. T.—level 4
Aripiprazole+Li/DVP		First-line comb. T.—level 4		First-line—level 2		First-line comb. T.—level 2
Risperidone+Li/DVP		First-line comb. T.—level 4	Second-line*	First-line—level 1		First-line comb. T.—level 4
Olanzapine+Li/DVP		n.d.	Second-line*	Second-line comb. T.—level 1		Second-line comb. T.—level 4
Li + DVP	Second-line*	n.d.		Second-line comb. T.—level 3	Second-line*	Second-line comb. T.—level 3
SSRIs/bupropion (adj)	Third-line***	Second-line—level 1				
Ziprasidone + Li/DVP						
Olanzapine+fluoxetine	Second-line*	Second-line—Level 2		n.d.		Second line—level 2

*Sajatovic and Chen [62, 64]; **Ljubic et al. [63]; ***Keramatian et al. [77]; ****Yatham et al. [58]
First-line: Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch; Second-line: Level 3 evidence or higher for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch; Third-line: Level 4 evidence or higher for efficacy plus clinical support for safety/tolerability
Level of evidence—1: Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison ($n \geq 30$ in each active treatment arm); 2: Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison condition ($n \geq 30$ in each active treatment arm); 3: At least one DB RCT with placebo or active control comparison condition ($n = 10-29$ in each active treatment arm) or health system administrative data; 4: Uncontrolled trial, anecdotal reports, or expert opinion; Not recommended: Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

Table 36.5 Treatment of bipolar disorder in older adults—(Refractory and other treatment modalities)

	Acute depression		Acute mania		Maintenance (Any mood episode)	
	Older Adults****	ISBD 2018 (Adults)*****	Older Adults*****	ISBD 2018 (Adults)*****	Older Adults*****	ISBD 2018 (Adults)*****
Psychotherapy/ Psychosocial treatment	Positive evidence**				Positive evidence**	
ECT	Third-line or refractory****/positive evidence**	Second-line comb. T.—level 4	Third-line or refractory*****	Second-line comb. T.—level 3		Second-line comb. T.—level 4
Haloperidol		n.d.	Third-line or refractory*	Second-line comb. T.—level 1		n.d.
Carbamazepine		Second-line comb. T.—level 3	Third-line or refractory*	Second-line—level 1		Second-line—level 2
Clozapine			Third-line or refractory*			
Levetiracetam			Third-line or refractory*			
Gabapentin			Third-line or refractory*			

*Sajatovic and Chen [62, 64]; **Ljubic et al. [63]; ***Keramatian et al. [77]; ****Yatham et al. [58]

First-line: Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch; Second-line: Level 3 evidence or higher for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch; Third-line: Level 4 evidence or higher for efficacy plus clinical support for safety/tolerability
 Level of evidence—I: Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison ($n \geq 30$ in each active treatment arm); 2: Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison condition ($n \geq 30$ in each active treatment arm); 3: At least one DB RCT with placebo or active control comparison condition ($n = 10–29$ in each active treatment arm) or health system administrative data; 4: Uncontrolled trial, anecdotal reports, or expert opinion; Not recommended: Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

and may reflect only one consequence of symptomatic control [68]. Verbal fluency, psychomotor speed, and verbal memory have been associated with clozapine treatment, and quetiapine and olanzapine have also been shown to have some neuroprotective effects in this population [75].

36.9 Conclusion

Bipolar disorder is a chronic mental disorder that impacts patients and family members. The first mood episode tends to occur during adolescence to early adulthood and may lead to life-long psychosocial and cognitive impairments. However, improvements in treatment and patient and family support have led to an increase in the quality of life and life expectancy of these patients.

As individuals with BD grow older, they face new challenges, such as cognitive decline and functional impairment related to multiple clinical and psychiatric comorbidities. However, pharmacological treatments have shown a favorable balance between side effects and effectiveness in older adults. Additionally, psychosocial interventions are generally needed to promote adherence and provide psychoeducation and family support, especially in increased caregiver burden scenarios.

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Chapter 37

Kidney and Liver Impairment



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37.1 Introduction

Bipolar disorder (BD) has been linked to a variety of physical comorbidities: from an increased risk of cardiovascular, metabolic, and infectious diseases to an increased risk of unintentional physical injuries [1, 2], even during adolescence and young adulthood [3]. Associated with the disorder itself, those comorbidities contribute to the twofold increase in mortality [4] and the 11–20 years lower life expectancy that BD patients have [5]. Notably, an increased number of physical comorbidities also predict worse outcomes when it comes to BD symptoms [4]. A variety of etiologies have been proposed to explain this phenomenon, chronic inflammation being widely accepted as one of the leading causes [6], followed by increased substance usage, obesity, other psychiatric comorbidities, and the treatment used for BD itself [7]. Nonpsychiatric illnesses seem to be neglected in these

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patients, partly due to them not being the main priority for the patients themselves when compared to their psychiatric comorbidities [4].

Not unlike other comorbidities, liver and kidney diseases are constantly reported to be increased in BD patients. In a Chinese study with 766,427 participants, BD patients were found to have a prevalence of chronic liver disease 2.68 times higher than the general population [4]. A North American study with 5319 veterans with diagnosed BD showed a prevalence 7.58 times higher for liver disease when compared to control veterans [8]. Another North American study, with 3557 participants with BD, showed an odds ratio of 3.97 for liver diseases in BD patients when compared to healthy controls; that same study showed that BD patients are two times more likely to have renal failure than the general population [9]. A Taiwanese study with 11,884 patients found an increased incidence of chronic kidney disease in BD patients up to four times higher than healthy controls in a 5-year follow-up [3]. A British study with 1216 BD patients showed an odds ratio of 1.86 for kidney diseases in BD patients; that same study observed a higher prevalence of kidney disease in bipolar type I patients compared to bipolar type II patients [10]. Besides the proposed etiologies for other physical comorbidities in BD patients, many psychotropic drugs used in the treatment of BD directly cause liver and kidney damage [4, 10–12], with some studies proposing a genetic link between inherited liver diseases and BD [13, 14] and between inherited kidney diseases and BD [15–17].

Patients with comorbid BD and hepatic and/or renal diseases have higher morbidity and mortality when compared to patients with BD and no comorbidities. A Portuguese study analyzed over 20,000 hospitalizations directly related to BD—physical comorbidities did not only increase the average duration of the hospitalization but also were more prevalent in the few recorded deaths: of the 0.3% patients that died in this study, 2.4% had chronic kidney disease and 1.3% had chronic liver disease [1]. Higher rates of anxiety, depression, sleep disturbances, and many other psychiatric conditions have been reported both in patients with liver [18–20] and kidney diseases [21].

In this chapter, we analyzed all first- and second-line treatment options for BD according to the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder [22], focusing on how to use these drugs in patients affected by hepatic and renal diseases and how these drugs can cause damage to the kidney and the liver.

37.2 Kidney Disease

Many psychotropic drugs and their metabolites are primarily eliminated by the kidney, and a reduced ratio of renal clearance, as happens in chronic kidney disease, can lead to drug accumulation and an increase in adverse effects [21]. Reduced albumin levels can happen in patients undergoing dialysis due to end-stage kidney disease, reducing the protein binding abilities of psychotropic drugs, and increasing their effective blood levels [21]. Furthermore, some studies point toward a reduced

activity in cytochrome isoforms during end-stage kidney disease, particularly CYP2C9, CYP2D6, and CYP3A4 [23].

37.2.1 *Mood Stabilizers*

37.2.1.1 **Lithium**

Lithium has long been associated with several negative kidney outcomes, the most prevalent being an impaired urinary concentrating capacity resulting in polyuria, present in almost half of the patients after days to weeks of exposure to lithium [21, 24–26]. Among these, 15–40% develop nephrogenic diabetes insipidus (NDI), a clear risk factor for the progression to chronic kidney disease (CKD) [25, 27]. Lithium-induced NDI can lead to reduced quality of life [27], hypovolemia, hypernatremia, and hyperchloremic metabolic acidosis [25, 28]. The diuretics acetazolamide, amiloride, furosemide, and hydrochlorothiazide paradoxically reduce urine output in severe lithium-induced NDI, and as a last-resort option, COX inhibitors can be used [27], although many of those medications have been linked to a decreased lithium excretion and increased chance of toxicity [29]. Other management strategies involve a reduction in doses to maintain a serum level of 0.4–0.8 mEq/L, the use of a single daily dose, and drug discontinuation [26]. In patients with severe polyuria, lithium levels should be monitored every 4–8 weeks, and creatinine clearance, urine osmolality, and 24-h urinary output should be monitored every 6 months [26]. In Box 37.1, a summary of recommendations for minimizing the chances of lithium-induced chronic kidney disease can be found.

Box 37.1 Recommendations for minimizing the chances of lithium-induced chronic kidney disease

- Keep serum lithium levels below 0.8 mEq/L
- Avoid using lithium in patients taking it continuously for over 10 years
- Avoid using lithium in patients with high baseline serum creatinine levels
- Monitor glomerular filtration every 12 months and discontinue lithium therapy if a steep decline in glomerular filtration is observed
- In patients with lithium-induced renal microcysts discontinue lithium therapy if a steep increase in size or number of microcysts is observed

A large-scale epidemiologic Swedish study including 3369 lithium users showed a prevalence of end-stage kidney disease of 1.2%, six times higher than the prevalence in the general population [25, 30]. Risk factors for progression to lithium-induced CKD include usage for more than 10 years, a steep decline over time in glomerular filtration [31], higher initial serum creatinine [32], and high serum levels

of lithium [25], particularly with lithium levels exceeding 0.8 mEq/L [26]. Previous episodes of lithium intoxication were not associated with an increased risk for CKD [31]. Glomerular function is less affected by lithium, with tubulointerstitial damage being its primary form of kidney damage [24]. Progression to CKD is slow, taking over a decade of lithium usage [32], and can lead to focal segmental glomerulosclerosis [25] and even the formation of renal microcysts [32].

CKD is not an absolute contraindication for lithium usage; it demands, though, close monitoring of serum lithium levels, with a target serum level between 0.6 and 0.8 mEq/L for this population [24]. Lithium can even be used in patients on hemodialysis, administered as a single post-dialysis dose of 300–600 mg [24] and monitoring lithium levels before and 2–3 h after the hemodialysis session [24]. Even though some experimental studies with animal models using lithium have shown a protective effect during episodes of acute renal failure [25], that condition remains as a formal contraindication for the continuation of lithium therapy in humans [24]. Renal function in lithium users should be assessed every 12 months to monitor the eventual progression to CKD [26]. A potential new screening method is the noninvasive monitorization of renal microcysts, indicating a progression to CKD when the number and size of the microcysts progressively increase over long periods of time [32].

Up to 40% of patients receiving lithium can develop mild proteinuria, although this occurrence has little clinical significance [33]. A full-blown nephrotic syndrome is rare and is easily reversible after lithium cessation [33].

37.2.1.2 Valproate

Renal adverse effects due to valproate exposure are uncommon [34]. Some experimental studies point toward an increase in oxidative stress, inflammation, and fibrosis in renal tissue exposed to valproate, with evidence of subclinical glomerular and proximal tubular damage in valproate users [35]. In more severe and rare cases, the proximal tubular damage can cause valproate-induced Fanconi syndrome [34]. Most of the affected patients are asymptomatic and the syndrome is suspected due to incidental findings such as hypophosphatemia, hypouricemia, and hyperaminoaciduria [34]. Rarely do patients develop clinical symptoms of Fanconi syndrome, including bone fractures, fever, tachypnea, and edema [34]. The treatment involves discontinuation of valproate, supportive treatment with sodium bicarbonate, vitamin D and carnitine supplementation; proximal tubular function, however, can take months to recover after discontinuation [34].

CKD reduces the protein-bound fraction of valproate, potentially altering its drug monitoring parameters and its clinical profile [36]. Accumulation, however, is unlikely, as valproate clearance is diminished by only up to 27% in patients with renal failure [36, 37]. Valproate's package insert does not recommend dose adjustment in renal failure [37, 38], but caution is advised because of the potentially increased chance of proximal tubular injury [21]. In therapeutic doses, valproate is minimally removed by hemodialysis, as it is mostly protein bound [39], but at

increased doses and in case of intoxication the free-fraction of the drug increases [29], and this excess can be removed by hemodialysis [37, 39].

37.2.1.3 Carbamazepine

Carbamazepine is a relatively safe medication in patients with CKD. The risk of accumulation is low, and dose adjustments are typically not necessary even in cases of severe renal failure [36]. Even though hemodialysis can help in removing excess carbamazepine in overdoses, at therapeutic levels carbamazepine is not removed by hemodialysis and supplementary doses are not necessary [36].

Severe renal side effects are rare, with some cases of acute kidney injury due to presumably allergic tubulointerstitial nephritis being reported [40, 41]. Hyponatremia can happen in carbamazepine users, being more prevalent in elderly patients and patients with low pretreatment sodium levels [42]. Carbamazepine should not be given to patients with baseline sodium levels below 130 millimoles, and periodic monitoring of serum sodium levels during treatment is recommended [42]. Mild and moderate cases of carbamazepine-induced hyponatremia can be managed by fluid restriction and dosage reduction; severe cases may require the use of hypertonic solutions in emergency settings [42].

37.2.1.4 Oxcarbazepine

Oxcarbazepine is a prodrug and is quickly converted to its active metabolite, 10-monohydroxy derivative (MHD) [21, 36], which is primarily eliminated through the kidney [43]. In patients with creatinine clearance below 10 ml/min MHD's half-life increases from 8 h up to 19 h, predisposing accumulation, and thus usage is not recommended in this group [21, 36, 44]. In patients with creatinine clearance over 30 ml/min, no dose adjustment is required; patients with creatinine clearance between 10 and 30 ml/min should have their oxcarbazepine doses reduced by 50% [21, 36, 44].

Although oxcarbazepine use is less associated than carbamazepine with immune-mediated renal injury [29], it has a way higher chance of inducing hyponatremia [29, 42, 45], with incidence estimates ranging from 2.7% [46] up to 10%, being even higher in elderly populations [47]. The recommendations are similar to those mentioned in the carbamazepine section: oxcarbazepine should not be administered in patients with baseline sodium levels below 130 mM, in mild cases of hyponatremia fluid restriction and dosage reduction are valid strategies, and in severe cases, drug discontinuation and the administration of hypertonic solution in emergency settings should be considered [42]. Baseline serum sodium should be obtained before starting therapy with oxcarbazepine, and monitorization of serum sodium levels should be done in intervals of 6 months; if the patient has a previous history of hyponatremia the monitorization should be more frequent [46].

37.2.1.5 Lamotrigine

Lamotrigine pharmacokinetics are minimally affected in patients with renal failure [48], as it is mostly metabolized through the liver [49], so no accumulation of the parent drug is expected [48, 50]. Lamotrigine is metabolized into lamotrigine glucuronide, an inactive and nontoxic metabolite that can have its clearance reduced to as low as 11% of normal values in renal failure, causing accumulation; the accumulation, however, has little to no clinical significance, and no changes in lamotrigine dosage need to be done in patients with renal failure [48]. Lamotrigine is minimally removed through hemodialysis and no supplemental doses are needed [50].

Several cases of acute renal failure secondary to lamotrigine use have been described, most of them developing acute interstitial nephritis, although other histological patterns were also found; this adverse reaction is rare and appears to be linked to other signs of lamotrigine hypersensitivity [51–54].

37.2.2 Antipsychotics

37.2.2.1 Quetiapine

The impact of renal disease on the pharmacokinetics of quetiapine was found to be either statistically insignificant [55, 56] or low enough to not warrant any dosage adjustments [57]. Quetiapine, however, has been associated with some reports of acute kidney injury with a histological pattern of interstitial nephritis, pointing toward a probably allergic, rare, and idiosyncratic cause [58–60].

37.2.2.2 Asenapine

No clinically significant differences in the concentration, clearance, and protein binding of asenapine were found between healthy controls and patients with varying degrees of renal impairment [57, 61]. Therefore, no dose adjustment is needed in patients with renal disease [57, 61].

37.2.2.3 Aripiprazole

Aripiprazole and its metabolites can have their maximum concentrations increased [57, 62] and their capability to bind to proteins reduced in patients with severe renal impairment [63, 64]. Nevertheless, renal excretion of aripiprazole is responsible for less than 1% of the total clearance of the drug, and therefore no dose adjustments are required in patients with CKD [57].

37.2.2.4 Paliperidone

Renal clearance plays a huge part in paliperidone elimination, with mild renal impairment reducing paliperidone clearance by 32%, while severe renal impairment can reduce paliperidone clearance by up to 71% [57]. Dose adjustment should be individualized depending on the patient's renal clearance: Patients with mild renal impairment should receive 3 mg daily as an initial dose, with a maximum dose of 6 mg daily; both should be halved to 1.5 mg initial dose and 3 mg maximum dose in case of moderate and severe renal impairment [57, 65]. Paliperidone has not been studied in patients with estimated creatinine clearance below 10 ml/min and thus no dose adjustment can be recommended in this group [57, 65].

37.2.2.5 Risperidone

Most patients taking risperidone have a five to ten times higher concentration of paliperidone in their blood when compared to risperidone [66], thus both drugs require similar caution when used in renally impaired patients. The total clearance of risperidone is decreased by 50–60% [57, 67] and its half-life is increased [67] in patients with severe renal disease. Dose reduction is advised in these patients [57, 67], and even though the package insert does not recommend a value [68] a literature review published in 2004 recommends a dose reduction of 50%–60% in patients with severe renal disease [24].

37.2.2.6 Cariprazine

No dose adjustment is required for patients with creatinine clearance above 30 ml/min taking cariprazine [69]. No studies with cariprazine have been conducted in patients with creatinine clearance below 30 ml/min, therefore its usage is not recommended in those patients [69, 70].

37.2.2.7 Olanzapine

The pharmacokinetics of olanzapine are minimally altered in patients with varying degrees of renal disease [57, 71, 72], thus no dosage adjustment is required [72]. Olanzapine is not affected by hemodialysis [57]. Of note, olanzapine might increase the risk for interstitial nephritis [73] and, because of its muscarinic effects, it might also increase the chances for urinary retention, especially in the elderly [74].

37.2.2.8 Ziprasidone

The pharmacokinetics of ziprasidone were shown to be minimally affected by mild and moderate renal impairment [57, 75]. Even though these studies broadly recommend that no dose adjustment is required in renally impaired patients [57, 75], no data is available concerning severe renal impairment and ziprasidone usage. Because of its high rate of protein binding, ziprasidone is not removed by hemodialysis [57].

37.2.2.9 Haloperidol

No studies concerning the influence of renal impairment on the pharmacokinetics of haloperidol have been conducted [76], with no recommendation of usage in that population by the American package insert [77]. Package inserts from New Zealand recommend caution when using haloperidol in renally impaired patients, but otherwise recommend that no dose adjustment is required for that population [76].

37.2.2.10 Clozapine

Clozapine has been associated with rare occurrences of acute renal failure and acute interstitial nephritis [78–80]; even though most cases present with eosinophilia and proteinuria, other signs of hypersensitivity like skin rash and arthralgia are curiously absent [78–80]. Onset happens within 3 weeks of initiation in most cases but can take upwards of 90 days of clozapine use to manifest [80]. Most cases resolve quickly after drug discontinuation [79].

An Egyptian study published in 2020 compared the pharmacokinetics of clozapine in renally impaired patients and in healthy controls, showing an increased maximum concentration of up to twofold in renally impaired patients and an increase of 50%–70% in the area under the time-concentration curve in renally impaired patients, indicating a modest reduction in elimination [81]. Package inserts have not yet recognized this study, informing that no pharmacokinetic studies were conducted on renally and hepatically impaired patients and recommending caution and possibly dose reductions when using clozapine in those groups [82]. Considering the vast interindividual differences in clozapine serum levels with the same oral dose [83], slow titration and dose adjustments based on therapeutic drug monitoring seem to be good strategies to treat renally impaired patients with clozapine.

37.2.2.11 Lurasidone

Patients with renal impairment have an increased maximum concentration and reduced excretion of lurasidone, by up to twofold in both parameters in severe renal impairment [84]. Patients with mild renal impairment do not need dose adjustment,

while those with moderate and severe renal impairment should receive an initial dose of 20 mg daily, with a maximum dosage of 80 mg daily [57, 84].

37.2.3 Antidepressants

37.2.3.1 Bupropion

Even though hepatic clearance is responsible for the majority of bupropion elimination, several studies have shown that bupropion clearance is reduced in renally impaired patients [23, 85, 86], with accumulation of hydroxybupropion, an active metabolite, being reported [85]. Most of these studies do not separate groups depending on the severity of renal impairment; nonetheless, the degree by which elimination is impaired seems to be between two and threefold in renally impaired patients [23, 85, 86]. Package inserts recommend caution when using bupropion in renally impaired patients [86, 87], while the manufacturer and the authors of a 2012 systematic literature review recommend a maximum dose of 150 mg daily [85, 88]. Since bupropion is not properly removed by hemodialysis, even a dose of 150 mg daily could cause accumulation in dialytic patients; therefore, a dose of 150 mg every 3 days can be a safer approach [85].

37.2.3.2 Sertraline

The pharmacokinetics of sertraline are unaffected by renal impairment, and thus no dose adjustments are required [89, 90]. As sertraline is highly protein bound, it is not extensively removed by hemodialysis and no post-dialysis supplementation is required [89].

37.2.3.3 Venlafaxine

Venlafaxine and its metabolites are primarily excreted by the kidneys, with venlafaxine's clearance being reduced by over 50% in patients with severe renal impairment [91, 92]. Mild-to-moderate renal impairment requires a reduction of 25% in venlafaxine total daily dosage [93–95]. Patients with severe renal impairment should have their daily venlafaxine doses reduced by 50% or more depending on individualization [91–95].

37.2.3.4 Fluoxetine

No changes in the pharmacokinetics of fluoxetine were found between healthy controls and patients with varying degrees of renal impairment [96–99]. Therefore, no dose adjustments are required in renally impaired patients [98–100].

37.3 Liver Disease

Hepatic insufficiency directly affects many aspects of pharmacokinetics, increasing blood levels and prolonging drug effects due to reduced first-pass metabolism. Reduced albumin levels can affect blood levels of protein-bound drugs, and ascites increase the volume of drug distribution, potentially reducing serum levels of water-soluble drugs [18, 24, 101]. First-pass metabolism does not influence all drugs equally—some drugs might have a boosted effect due to the reduced degradation in first-pass metabolism, while others might have a reduced effect due to the reduced conversion in active metabolites. Some drugs are mainly metabolized by glucuronidation, which is less impaired in mild-to-moderate hepatic insufficiency than first-pass metabolism, thus their blood levels are only intensely affected in severe hepatic insufficiency [18].

Among the various causes of liver disease in BD patients, Hepatitis C Virus (HCV) infection is of particular concern: One in seven patients with HCV has BD and BD patients have a 4–9 times higher risk of contracting HCV [102]. HCV infection has been associated with anxiety, psychosis, and mood episodes [103], thus worsening the prognosis of those patients by itself. Interferon- α , previously used in HCV treatment, was associated with many psychiatric symptoms and increased chances of mood episodes in BD patients, as well as worsening clozapine-induced neutropenia, olanzapine-induced metabolic side effects and promoting bone marrow suppression in patients using carbamazepine or oxcarbazepine [102], although its usage is not recommended in more recent HCV treatment guidelines [104].

The prevalence of nonalcoholic fatty liver disease (NAFLD) is two times higher in BD patients when compared to the general population, being even higher in groups taking atypical antipsychotics, in men and in patients over 50 years old [105]. Patients with NAFLD have more anxiety and depressive symptoms when compared to controls [19], and some studies show that BD patients might have underexpressed genes related to mitochondrial metabolism, glycogenation, and diabetes protection, impairing onto them an increased risk of developing diabetes and more advanced forms of liver injury [14].

Another comorbidity intimately related to liver diseases in BD patients is Alcohol Use Disorder (AUD), present in 33%–62.3% of BD patients at least at one point in their lives [106, 107]. AUD in BD patients has been associated with a higher number of hospitalizations, an increase in the number of appointments with nonpsychiatric doctors [108], an earlier age of onset of BD [109], a higher risk for suicide attempts [110], rapid cycling, mood episodes with mixed features, and poorer adherence to

treatment [107]. Naltrexone and valproate have shown some evidence of contributing to the reduction of alcohol consumption [111, 112], but otherwise lack evidence for a more effective mood stabilization in these patients.

As many of the discussed drugs in this chapter can lead to increases in liver enzymes, following FDA guidelines for drug discontinuation might prove useful; discontinue the suspected drug if any of these happen [113]:

1. Elevations in aminotransferases above eight times the upper limit of normal (ULN).
2. Elevations in aminotransferases above five times the ULN for 2 weeks.
3. Elevations in aminotransferases above three times the ULN with bilirubin levels above two times the ULN and/or INR above 1.5.
4. Elevations in aminotransferases above three times the ULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [113].

37.3.1 Mood Stabilizers

37.3.1.1 Lithium

Lithium is minimally metabolized in the liver and is not protein bound; thus, lithium is generally safe to use in patients with hepatic impairments [18]. In severe hepatic insufficiency dose adjustments might be necessary due to the volume imbalance that ascites generate [24]. Long-term lithium therapy has been associated with changes in liver function tests, especially during episodes of lithium toxicity, although those are uncommon, generally reversible with time, and do not require discontinuation of lithium [18].

37.3.1.2 Valproate

Asymptomatic, dose-related elevations in liver enzymes have been described in as low as 5–10% [114] up to as high as 44% of valproate users [115, 116]. The most affected enzyme is alanine aminotransferase (ALT), with virtually no impact on gamma-glutamyl transpeptidase (GGT) [114]. Up to 61% of patients treated with valproate develop hepatic steatosis, with 25% developing NAFLD; the mechanism behind these findings is still up for debate [103, 117, 118]. Valproate has also been associated with chronic asymptomatic dose-related hyperammonemia, presumably by depleting hepatic carnitine reserves [119, 120]; carnitine deficiency has been reported in up to 80% of adults receiving valproate [116].

Severe valproate-induced hepatotoxicity occurs with a frequency of approximately 1 in 37,000–49,000 patients exposed [24, 118, 121] and can present as three distinct syndromes: hyperammonemia with minimal or no evidence of hepatic

injury, acute hepatocellular injury with jaundice and a Reye-like syndrome that combines hepatic injury with symptoms suggestive of a viral infection, the latter occurring almost exclusively in children [114]. Chronic, indolent hepatotoxicity mediated by valproate has also been linked to an increased risk of cirrhosis [114]. Valproate-induced hepatotoxicity generally occurs within the first 90 days of exposure [115], but can happen after as long as 2 years [120]. Risk factors for valproate-induced hepatotoxicity include alcohol usage, polypharmacy, high baseline lactate dehydrogenase (LDH) [122], urea cycle defects, and mitochondrial dysfunctions, the latter two being contraindications for the use of valproate [37, 103, 123]. In cases of valproate-induced hepatotoxicity, especially due to hyperammonemia, intravenous and oral carnitine supplementation has been recommended [114, 116, 119, 122].

In patients with mild-to-moderate hepatic impairment, classified as Child–Pugh class A or B, the dose of valproate should be decreased by 50%. In severe hepatic impairment, classified as Child–Pugh class C, the dose of valproate should be decreased by 75% [38]. Liver function tests should be applied to all patients receiving valproate before initiating treatment and frequently during the first 6 months of therapy [37, 120].

37.3.1.3 Carbamazepine

Transient elevations of liver enzymes happen in 5%–15% of patients using carbamazepine, but fulminant hepatitis and hepatic failure are rare [124]. Hepatic adverse effects generally appear within the first 3–4 weeks of use and are more common in the elderly [115]. Carbamazepine-induced hepatotoxicity often resembles biliary tract infections, with pruritus, fever, jaundice, and upper right quadrant tenderness, and the most common histological pattern is that of hepatocellular necrosis, although granulomas and mild cholangitis were also described [115]. Severe liver adverse effects are generally associated with a carbamazepine-induced syndrome Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), so fever, rash, facial edema, lymphadenopathy, and eosinophilia are commonly associated symptoms [125]. Symptoms are usually reversed shortly after discontinuation, but liver enzymes might remain abnormal for several months [115].

All patients receiving carbamazepine should have their liver enzymes monitored; the indication for routine monitoring varies from guideline to guideline, tending to be more lax with patients using the extended-release formulation of carbamazepine [115, 124]. Patients with altered baseline results and elderly patients should be monitored more often, and carbamazepine should be discontinued if hepatic function tests exceed three times the upper limit of the normal range [124].

As carbamazepine shows a huge inter- and intraindividual pharmacokinetic variability [126] and given the multitude of adverse hepatic effects, it is no surprise that not even package inserts include a clear dose recommendation for patients with liver disease and liver failure [127–129]. Caution and close monitoring of liver enzymes

should be practiced when prescribing carbamazepine to patients with mild liver impairment, and no clear recommendation can be made about the use in severe liver impairment.

37.3.1.4 Oxcarbazepine

Oxcarbazepine is mainly metabolized by glucuronidation [21], and thus its metabolism is minimally impaired in mild-to-moderate liver disease, with no dose adjustments recommended for Child–Pugh A and B patients [36, 47]. Oxcarbazepine therapy does not demand periodical liver test monitoring [130]. Oxcarbazepine has not been extensively studied in severe liver disease, so no recommendations of use can be made for this population [47].

37.3.1.5 Lamotrigine

Lamotrigine is predominantly metabolized through glucuronidation, a function of the liver that is only impaired in severe liver failure [131, 132]. Thus, it is no surprise that the pharmacokinetics of lamotrigine are not altered in mild-to-moderate liver failure; severe liver failure, however, reduces oral clearance by about 40% in patients without ascites and up to 64% in patients with ascites [131]. Elimination half-life is doubled in patients with liver failure without ascites and almost tripled when ascites are present [131]. Initial and maintenance doses should be reduced by 50–75% in Child–Pugh B and C patients and titration should be individualized according to clinical response [131].

Several cases of hepatotoxicity were related to lamotrigine use, with the vast majority occurring in neurological patients, children, patients using polypharmacy, patients with severe comorbidities, and patients in which titration was done faster than what is usually recommended [133–143]. Hypersensitivity appears to be a common cause among these patients, but a direct toxic effect of lamotrigine metabolites cannot be discarded [134].

37.3.2 Antipsychotics

37.3.2.1 Quetiapine

Patients with hepatic insufficiency have higher serum concentrations [55, 57, 144] and a 25%–30% lower clearance of quetiapine [55, 57]. Target doses should be lower in these patients; the initial dose should be 25 mg/day and titration needs to be careful, with increments of only 25–50 mg at a time while observing side effects and potential changes in liver enzymes [55, 57, 145].

Asymptomatic elevations in liver enzymes have been reported as low as 1% [146] and as high as 30% in patients using quetiapine [132, 147]. Quetiapine users can develop a rare and idiosyncratic form of hepatotoxicity that generally presents with a hepatocellular or cholestatic pattern with onset after 1–4 weeks of quetiapine initiation [147–149]. The incidence of hepatotoxicity seems to be lower when using the extended-release formulation, being comparable to placebo in a study with over 200 patients [144].

37.3.2.2 Asenapine

Patients with mild-to-moderate liver impairment have a 34%–39% increased exposure to asenapine compared to healthy controls, a change that is not clinically significant and does not demand dose adjustments [57, 61]. Patients with severe liver disease (Child–Pugh C), however, had their exposure to asenapine increased five-fold, with the unbound fraction concentration being sevenfold higher when compared to healthy controls; the use of asenapine in patients with severe liver disease is, therefore, not recommended [57, 61].

Liver test abnormalities can happen in 1%–2.5% of patients taking asenapine, a rate that is close to the 0.65%–1.3% observed in the placebo groups, and they spontaneously resolve without the need for dose adjustments in most patients [150]. A single case of moderate cholestatic hepatitis was reported with the use of asenapine, fully resolving after 1 month of discontinuation [150].

37.3.2.3 Aripiprazole

Aripiprazole's clearance is minimally affected by hepatic impairment, with no statistically significant changes in its pharmacokinetics when comparing healthy controls to patients with severe liver impairment [57, 62]. Therefore, no dose adjustment is required in patients with hepatic impairment [57].

The risk for aripiprazole-induced liver injury is relatively low when compared to other atypical antipsychotics [151, 152]. No cases of fatal liver injury or chronic liver injury have been associated with aripiprazole usage, with most reported cases being anicteric and resolving quickly after drug discontinuation [152].

37.3.2.4 Paliperidone

Paliperidone is not extensively metabolized by the liver [66]; its usage increases liver enzymes in less than 1% of users and no cases have been reported of liver toxicity [153]. No pharmacokinetic differences were found between controls and patients with mild-to-moderate liver impairment, and thus no dose adjustment is required in these patients [57, 154]. Paliperidone has not been studied in patients with severe liver impairment, so no recommendations for usage can be made for that group [65].

37.3.2.5 Risperidone

Mild elevations in liver enzymes are relatively common during risperidone usage [155], happening in up to 30% of users [153, 156, 157] and starting during the first 6 weeks of treatment [158], most of them being self-limited and only rarely progressing to liver injury [153]. Many cases of a presumably rare risperidone-induced acute liver injury have been described, the majority of which were cholestatic injuries, rarely including immunoallergic features [155, 156]; most of these cases resolved quickly with drug discontinuation [155, 156, 159, 160]. Patients receiving risperidone should have baseline and periodic monitoring of liver function tests during the initiation and maintenance phases of usage [160].

The pharmacokinetics of risperidone are comparable between healthy individuals and patients with hepatic impairment, with the most prominent change being the increased free-fraction in plasma [57, 67]. Dose reduction is recommended in patients with hepatic impairment [57, 67], although the package insert does not specify by how much [68].

37.3.2.6 Cariprazine

An open label study with 476 schizophrenic patients showed that small, clinically insignificant increases in serum transaminases can happen during the course of cariprazine treatment [161]. No dosage adjustment is required in patients with mild-to-moderate liver impairment [69, 70]. Cariprazine has not been studied in patients with severe hepatic impairment, and thus no recommendations can be made about cariprazine use in that population [69, 70].

37.3.2.7 Olanzapine

Asymptomatic elevations of liver enzymes can happen in 10%–50% of patients using olanzapine [155, 162–164], are more frequent in children and adolescents [165], and have an onset of 1–4 weeks after initiation in most cases [163], but can take up to 3 years to manifest [155]. Drug discontinuation quickly reverts most cases [155], although some might resolve even without discontinuation [163]. Olanzapine is the atypical antipsychotic that has been linked the most with clinically significant liver injury, with an estimated frequency of 1:1200 treated patients [163]. The onset of liver injury generally happens within 1–4 weeks of starting the drug, with a mixed pattern of liver enzyme elevations being the most common, uncommonly accompanying an immunoallergic response [163]. Some fatal cases have been reported, but most resolve quickly following drug discontinuation [163]. An important confounding factor is the presence of NASH since olanzapine is one of the atypical antipsychotics most associated with the development of that disease, with some studies pointing toward an effect in gene expression being one potential cause alongside weight gain [164, 166, 167]. Given all those risks, it is prudent to

perform baseline and routine hepatic enzyme evaluations during treatment with olanzapine [162].

Mild-to-moderate hepatic impairment has been shown to minimally affect olanzapine clearance, even in patients with clinically significant cirrhosis (Child–Pugh A and B) [57, 72], and thus no dose adjustment is required in these patients. No clear data exists for the usage of olanzapine in patients with severe hepatic impairment (Child–Pugh C), and thus caution is recommended when using olanzapine in that group [57].

37.3.2.8 Ziprasidone

Even though hepatic metabolism plays a huge role in the clearance of ziprasidone, studies involving patients with mild and moderate hepatic impairment showed a modest and clinically insignificant reduction in the clearance of ziprasidone [57, 168]. Therefore, no dose adjustment is required in patients with mild and moderate hepatic impairment [57, 168]. No studies have been conducted involving patients with severe hepatic impairment (Child–Pugh C), and thus no recommendation can be made regarding the usage of ziprasidone in that group.

Elevations in liver enzymes during treatment with ziprasidone are similar in frequency to placebo therapy, and the rare cases of liver injury have been mild and associated with larger, systemic hypersensitivity reactions [169].

37.3.2.9 Haloperidol

Up to 20% of patients using haloperidol will develop asymptomatic, mild, and transient liver test abnormalities, reversing even with continuation of the medication given enough time [170]. Clinically relevant liver injury is a rare side effect of using haloperidol, with an estimate of two cases per 1000 patients treated [171]. The pattern of injury is typically cholestatic or mixed, the onset is within 2–6 weeks after initiation, and rarely mild symptoms of hypersensitivity have been reported [170].

Haloperidol is a highly lipophilic compound that is extensively metabolized by the liver, resulting in a large interindividual variability in its pharmacokinetics [172]. Haloperidol has not been extensively studied in patients with hepatic impairment [76], and thus no recommendations for dose adjustments are made by the American package insert [77]. Caution is advised when using haloperidol in these patients, and a reduction in dosage might prove to be prudent [76].

37.3.2.10 Clozapine

Up to two-thirds of patients using clozapine will have asymptomatic elevations in liver enzymes, 10%–20% having elevations above three times the ULN, but up to 60% of these resolve spontaneously after 6–12 weeks even without dose

adjustments [80, 173, 174]. Discontinuation or dose reduction should be considered if liver enzyme elevations accompany nausea, weakness, or abdominal discomfort [173], and drug rechallenge should be considered if psychiatric improvement is clear during clozapine usage [175]. Clinically relevant liver injury has been estimated to happen in 1:2000 patients treated with clozapine, with an onset of days to weeks after initiation and a mixed pattern of enzyme elevations, rarely presenting with signs of hypersensitivity [173]. Most cases resolve after drug discontinuation, with no reported cases of chronic liver disease following clozapine-induced liver injury [173]. Liver enzymes should, therefore, be monitored as a baseline, monthly for the initial 3 months and every 6 months thereafter [176].

Just like in renally impaired patients, package inserts recommend caution when using clozapine in hepatically impaired patients, with no further recommendations since no pharmacokinetic studies were available [82]. A recent Egyptian study published in 2020 compared the pharmacokinetics of clozapine in hepatically impaired patients and healthy controls, showing an increase of up to 150% in the maximum concentration and an area under the time-concentration curve increased by up to threefold, depending on the degree of hepatic impairment [81]. These results are compatible with increased systemic exposure to clozapine, especially in Child–Pugh B and C patients [81]. Considering the vast interindividual differences in clozapine serum levels with the same oral dose [83], slow titration and dose adjustments based on therapeutic drug monitoring seem to be good strategies to treat hepatically impaired patients with clozapine.

37.3.2.11 Lurasidone

Hepatic impairment has little effect on the maximum concentration of lurasidone, but expressively reduces lurasidone's elimination, by up to threefold in patients with severe hepatic impairment [84]. No dose adjustment is required in patients with mild hepatic impairment; patients with moderate and severe hepatic impairment should have initial doses of 20 mg daily, progressing to a maximum of 80 mg daily for moderate impairment and 40 mg daily for severe hepatic impairment [57, 84].

The incidence of liver test abnormalities while using lurasidone is similar to placebo therapy, and there are no published reports of hepatotoxicity related to lurasidone therapy [177].

37.3.3 Antidepressants

37.3.3.1 Bupropion

Less than 1% of patients treated with bupropion will experience modest and asymptomatic liver enzyme elevations, usually not requiring dose adjustments or discontinuation [178]. Clinically relevant hepatotoxicity is rare, usually self-limited, with

an onset within 1–3 months of initiation and sometimes it accompanies hypersensitivity commemoratives [178, 179].

Pharmacokinetic studies with bupropion showed minimal, statistically irrelevant, changes in clearance in patients with mild and moderate liver impairment [86]. Severe liver impairment, on the other hand, substantially impacts bupropion clearance, reducing elimination by up to threefold [86]. Package inserts recommend caution and a reduction in frequency and dosage amount in patients with hepatic impairment [86, 87], limiting the maximum dose to 75 mg daily in patients with Child–Pugh score between 7 and 15 [86].

37.3.3.2 Sertraline

Asymptomatic elevations in liver tests have been reported in up to 1% of patients using sertraline, usually not requiring dose adjustments or discontinuation [180]. Clinically relevant hepatotoxicity is exceedingly rare, occurring within 2–24 weeks of initiation with varied patterns of enzyme elevations [180, 181].

Mild and moderate hepatic impairment can increase sertraline half-life by two to threefold and can increase its maximum concentration by up to 70% [182], with some data pointing to a threefold greater exposure to sertraline in even mild hepatic impairment [90]. Because of the severity of these findings, package inserts do not recommend the use of sertraline in moderate and severe hepatic impairment (Child–Pugh score 7–15) [90]. In patients with mild hepatic impairment sertraline doses should be halved [90]. Increasing the time between dose adjustments to 15 days [183] and/or increasing the dosage interval beyond 24 h [182] are also useful strategies when managing sertraline use in patients with mild hepatic impairment.

37.3.3.3 Venlafaxine

The incidence of liver enzyme abnormalities in patients using venlafaxine is similar to placebo and control groups [184]. Clinically relevant liver injury is estimated to happen in 1 per 5000 patients treated, with an onset of injury within 1–3 months of drug initiation and enzyme elevation patterns varying from hepatocellular to cholestatic [185]. All reported cases were self-limited, resolving after drug discontinuation [184–188].

In hepatically impaired patients, venlafaxine and its metabolites have their half-lives increased and their plasma clearances reduced, by up to 50–60% in both parameters in patients with severe hepatic impairment [91, 93]. Patients with mild-to-moderate liver impairment should have their venlafaxine daily doses halved, and an even greater reduction is recommended in patients with severe hepatic impairment [91, 93, 95].

37.3.3.4 Fluoxetine

About 0.5% of patients taking fluoxetine will develop increases in liver enzymes [189, 190], which are usually modest and do not require dose modification or discontinuation [191]. Clinically relevant hepatotoxicity is rare, presents with a hepatocellular pattern of enzyme elevations, and has an onset within 2–12 weeks of initiation [191].

The pharmacokinetics of fluoxetine are significantly altered in patients with hepatic impairment [96, 192], with accumulation of metabolites happening after a few doses even in patients with compensated cirrhosis [193]. Package inserts advise caution when using fluoxetine in hepatically impaired patients [100], and the authors of one of the pharmacokinetic studies propose a reduction in 50% of the daily doses and a possible reduction in dose frequency as valid strategies in managing fluoxetine usage in these patients [193].

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Part VI
New Approaches to Diagnosis and
Intervention

Chapter 38

Digital Diagnostic and Therapeutic Approaches in Bipolar Disorder



Maria Faurholt-Jepsen and Lars Vedel Kessing

38.1 Introduction

Bipolar disorder is associated with a high risk of relapse and psychiatric hospitalization, and on average, increases the risk of relapse with the number of previous affective episodes [1–4]. Despite the separation of bipolar disorder into type I and II, the clinical presentation and the course of illness in bipolar disorder are complex and heterogeneous both cross-sectionally and longitudinally [5]. Diagnosing and treating bipolar disorder in clinical practice presents significant challenges [6]. In terms of diagnosis, patients with bipolar disorder are frequently misdiagnosed, and the correct diagnosis may be delayed for several years following the onset of the illness [7–9].

Currently, due to the lack of objective tests, the diagnostic process and the clinical assessment and long-term monitoring of the severity of depressive and manic symptoms relies on subjective information, clinical evaluation and rating scales [10]. This subjective evaluation involves a potential risk of patient recall bias, other recall distortions, decreased illness insight (mainly during affective episodes), and individual observer bias [11–15]. Furthermore, when patients present in a remitted or depressive state, it may be difficult for clinicians to determine whether the patients suffer from unipolar disorder or bipolar disorder. Patients may not recall prior (hypo)manic episodes, and clinicians may not be sufficiently observant of the prior course of illness [16]. Consequently, there is a risk of overlooking the bipolar disorder diagnosis. Additionally, the use of rating scales as outcome measures in

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research studies can introduce methodological issues such as non-blinding of raters and patients, variations in rater expertise, missed appointments for outcome assessments, baseline score inflation, and recall bias [17, 18].

Regarding treatment, it is well known from randomized controlled trials (RCTs) that the risk of new affective episodes can be reduced by psychopharmacological treatment with lithium or other mood stabilizers [19]. Furthermore, the prophylactic effect of psychopharmacological treatment may be enhanced by psychological interventions, including psychoeducation [20–23]. However, naturalistic follow-up studies indicate that the progression of bipolar disorder is not always effectively halted by existing treatment options [3, 4, 24, 25]. Several key factors contribute to the limited success of these treatment approaches in clinical practice, including poor adherence to prescribed psychopharmacological regimens [26, 27] and delays in addressing early warning signs of depressive and manic symptoms [28, 29].

Overall, these concerns underscore the need for less biased and more objective markers to aid in the diagnosis and assessment of bipolar disorder and in better treatment options.

38.1.1 Digital Technologies

The stigma surrounding mental health issues and the scarcity of treatment resources leads to long waiting times that may prevent individuals from seeking help or receiving appropriate treatment [30]. On a global scale, it is simply not feasible to propose that practices based entirely on in-person care will ever be able to meet the present treatment demand. Thus, even before the emergence of the COVID-19 pandemic, there was growing interest in the possible role of new technologies to extend care. The rapid international growth in access to and capabilities of digital health technologies presents a feasible route toward augmenting traditional mental health care and bridging the gap between the need for treatment and the capacity to deliver it [31].

E-health reflects the process of providing health services and health-related communication through an electronic medium, such as the Internet or a telephone, and mobile health (mHealth) refers to health services delivered by mobile devices, such as smartphones, mobile monitoring devices, and other wireless electronic devices [32]. The use of sensors embedded within mobile monitoring devices provides enormous opportunities for new areas of research, development, diagnosis, and treatment. A report by the World Health Organization in 2011 stated that “the use of mobile and wireless technologies to support the achievement of health objectives (mHealth) has the potential to transform the face of health service delivery across the globe” [32]. Furthermore, it has been suggested that mHealth interventions have the potential to minimize the traditional barriers of distance, time, costs, and gaps in available clinicians [33, 34]. With electronic devices, detailed data regarding complex psychopathological aspects of bipolar disorder that otherwise would be difficult to collect can be evaluated over prolonged time periods, in naturalistic settings

and in a relatively unobtrusive manner. Moreover, data collected using electronic devices could represent candidate markers of diagnosis and illness activity in bipolar disorder and could allow early intervention for prodromal symptoms outside clinical settings.

38.1.1.1 Smartphones

Ecological momentary assessments (EMA) reflect the methods used to collect assessments of individuals' real-time states repeatedly over time and in naturalistic settings [35–37]. EMA may minimize recall bias, may be sensitive to daily mood fluctuations, can be performed using smartphones, and provides the potential to collect both self-monitored and automatically generated data in an unobtrusive way outside laboratory settings using frequently repeated, fine-grained data collection methods [35, 38, 39]. EMA may be used to reveal dynamic processes, can be integrated with physiological data, can identify context-specific symptoms, and allows for interactive feedback loop options. The use of smartphones extends the use of EMA beyond its classical use for self-reports [39, 40].

Within bipolar disorder, various paper-based daily mood charting instruments, such as the National Institute of Mental Health LifeChart Method (NIMH-LCM) [41], the Systematic Treatment Enhancement Program [42], and the ChronoSheet [43], have been developed. These types of charting instruments enable the collection of detailed longitudinal information regarding daily mood swings and other symptoms relevant to bipolar disorder when patients are outside the clinical setting, and they are often used in the treatment of bipolar disorder. Paper-based mood charting instruments have been used as a facilitating tool to help patients gain illness insight, facilitate patient empowerment, and teach patients to recognize early warning signs of the recurrence of mania, depression, and mixed states. However, several problems regarding paper-based mood charting instruments have been addressed, such as an error-prone entry process, low compliance and potential recall bias when filling in data retrospectively, i.e. when patients complete batches of daily ratings at a single time [44, 45]. Electronic self-monitoring instruments using computers [45–48], personal digital assistants (PDAs) [49–52], text messages [53, 54], and smartphone applications [55–58] have been developed and described in the literature, and a large number of commercial smartphone applications are available in the App Store and Google Play [31, 59, 60].

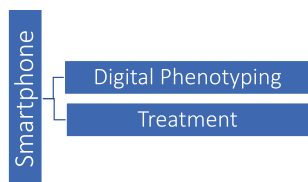
The rapid growth in access to and capabilities of digital health technologies presents a feasible route toward augmenting traditional mental health care and bridging the gap between the need for treatment and the capacity to deliver it. In addition, the rapid evolution and ubiquity of mobile networks have resulted in the increasing development of smartphone-based tools for remote and real-time self-monitoring [31, 61]. Smartphones have quickly become a driving force of digital health, due to special properties defining both the hardware and software of these devices.

Smartphones provide a unique platform for fine-grained symptom monitoring and treatment. They are a convenient means of electronic self-assessment, allowing

patients to record and review their data ubiquitously on-demand daily. The term “digital phenotyping” was introduced to mental health in 2015 [62] and has been defined as the “*moment-by-moment quantification of the individual-level human phenotype in situ using data from personal digital devices*” [63]. From a hardware perspective, smartphones are compact and wireless, with low purchasing and running costs, making them the first devices to provide ubiquitous connectivity/Internet access for a sizable proportion of the global population. The sensors on these devices allow for new data capture and graphical/computing power for delivery of individualized interventions. From a software perspective, the relative ease of building new smartphone apps can in turn be readily proliferated across any number of users, potentially reaching billions of people across the world. Further, smartphones can serve as a digital “hub” for the integration of novel devices such as wearables and other sensors.

Digital phenotyping [both active (self-monitoring) and passive (sensor-based data)] refers to approaches in which personal data gathered from mobile devices and sensors is analyzed to provide health information on physiological functions or behavioral indicators [64, 65]. Digital phenotyping potentially uses smartphones to measure symptoms and behavior. These data can be seen as digital footprints or data traces arising as a by-product of interactions with technology. The rapid evolution and ubiquity of mobile technology have increased the development of tools for remote and real-time self-monitoring and treatment [66].

The number of smartphone mobile network subscribers exceeded 6 billion people in 2022 [67]. Digital treatment strategies, including smartphone-based interventions, have emerged as promising approaches to address challenges in mental health services [31, 61]. Smartphone-based treatment interventions are easy to use by patients in various geographical locations and provide support between outpatient appointments. Furthermore, smartphone-based treatment interventions can be accessed at the patient’s convenience and offer flexibility in engaging with their treatment allowing them to follow their own pace in comfortable settings. Using smartphone-based treatment interventions allows for personalized approaches tailoring and addressing the treatment to the patient’s specific needs and preferences. Also, the personalization and tailoring to specific needs and preferences may enhance user engagement, motivation, empowerment, and illness insight [31]. Combining outpatient treatment and smartphone-based monitoring, including clinical feedback, may lead to better treatment and adherence, and optimize treatment outcomes by providing continuous support, self-monitoring, and psychoeducation between clinical appointments [68]. COVID-19 and the transition of increased digital treatment strategies have shown us the potential for digital innovations to improve access and quality of care in mental health [61].



38.2 Digital Phenotyping

Until recently, our understanding of what triggers the onset, relapse, or fluctuations in mental disorders primarily relied on data from large prospective studies. While valuable, the broader perspectives gained from such data might not capture individual variations or the finer details of how causes and consequences of mental health issues unfold over time. In the realm of healthcare, smartphones have emerged as powerful tools that provide an abundance of data, offering fresh insights into various conditions. This is made possible by their ability to collect increasingly detailed, continuous, and diverse data over time.

To better understand the nature and clinical relevance of this data, it is helpful to distinguish between “active” and “passive” data. While not universally unanimous, some researchers [69] categorize digital phenotyping into two subgroups: “Active data” and “passive data.”

Active data typically refers to smartphone-based surveys—i.e., active patient reports with symptom monitoring or ecological momentary assessments—which can be completed by the user either spontaneously or in response to a prompt, and then stored while crucially timestamped (a digital record of the date and time when an item was completed) onto the collecting app. Active data capture offers a new means to characterize a patient’s clinical course.

Passive data are obtained automatically through sensors, either on the smartphone or via a wearable device, ranging from simple device use metrics to accelerometry, global positioning system (GPS), and voice features. These automatically collected data offer a means to reduce patient burden typically related to active data collection, while also capturing novel digital markers of behavior.

Passive data, in terms of both richness and intricacy, far surpasses the capabilities of current clinical assessments, which often depend on fixed scales prompting patients to recollect symptoms within specific timeframes (e.g., on a weekly basis). Nevertheless, harnessing the depth and diversity of passive data calls for innovative data science approaches, such as artificial intelligence and machine learning, to effectively integrate and leverage this “big data” for advancing mental healthcare [70]. Advances in artificial intelligence and machine learning will likely represent a prominent bridge for translating new data into clinically relevant digital biomarkers [71].

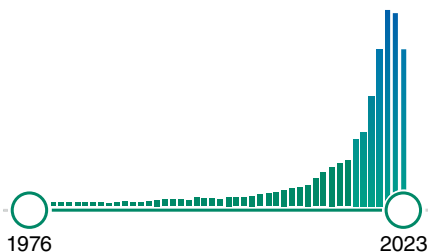
A recent systematic review examined the use of digital phenotyping—both active and passive—for diagnosis, episode identification, and symptom evaluation in bipolar disorder [72]. A total of 27 studies using smartphone-based tools were identified, where the oldest included study dated back to 2011, confirming the novelty of this research topic Fig. 38.1.

Active data: The items of the self-monitoring questionnaires were different between the studies. The majority of studies examining the use of active smartphone-based data employed the Monsenso system [55]. The Monsenso system is a smartphone-based EMA system, which allows for electronic self-monitoring of mood, irritability, sleep, stress, activity level, medicine intake, alcohol consumption, and other objective, passive data. It also includes a bidirectional feedback loop between the healthcare providers and the patients [57, 73–76]. Other studies used mania or depression scales, such as the Altman Self-Rating Mania Scale (ASRM) and the Quick Inventory of Depressive Symptomatology—Self-Report [77]. Overall, a significant association was described between smartphone-based patient-reported data and clinically evaluated symptoms, and significant differences in symptoms between patients with bipolar disorder type I and II were identified [72, 78, 79]. Furthermore, recent studies have suggested that the use of active data may assist in the discrimination/classification between patients with unipolar disorder and bipolar disorder [74, 76, 80–82] as well as bipolar disorder, borderline personality disorder, and healthy individuals [83].

Passive data: Core clinical features of bipolar disorder that have been addressed in the literature include changes in psychomotor activity and behavioral activities [84–89]. Psychomotor activity consists of multiple domains, such as gross motor activity, body movements, speech, and motor response time [89].

Studies have shown that changes in the level of engagement in social and communicative activities [84, 90–92] and in speech activity [93–96] represent central aspects of illness activity in bipolar disorder. Alterations in psychomotor and speech activity are central features in the clinical presentation of bipolar disorder and are included in standardized clinical rating scales measuring the severity of depressive and manic symptoms. The majority of studies included in the systematic review included smartphone-based metadata (e.g., number and duration of calls and text messages), step counts, light exposure, GPS parameters, and voice features [72]. Some of these parameters, which were assumed to reflect physical and social activity and circadian rhythms, were associated with clinically evaluated symptoms and

Fig. 38.1 Increase in published studies concerning “digital phenotyping” according to PubMed



allowed to distinguish between manic, mixed, depressive, and euthymic states [78, 79, 97, 98]. Furthermore, recent studies have suggested that the use of active data may assist in the discrimination/classification between patients with unipolar disorder, bipolar disorder, and healthy individuals [99–101].

Overall, the collection of active data requires both patients' direct involvement and illness/mood insight, which could be unstable over time. Possibly also for these reasons, when possible, acquiring passive, objective data in addition to active patients' mood self-monitoring appears to provide slightly better results for mood state detection. In such cases, data is gathered through smartphone's sensors by an application running in the background.

38.3 Smartphone-Based Treatment

In addition to providing the afferent limb of assessment [through patient reports or sensor-based data from smartphones (see below in the section concerning digital phenotyping)], smartphones have the ability to provide the efferent limb of intervention, which can, in turn, be optimally delivered by just-in-time-intervention (JITAI) titrated through continuous feedback from digital phenotyping [65]. Recent studies have shown that patients with bipolar disorder are generally predisposed toward smartphone-based interventions [102]. Nevertheless, despite the huge number of potential smartphone-based interventions for bipolar disorder already available in the Google Play and iOS stores, very few meet evidence-based medicine quality standards [103, 104].

The potential for more personalized digital health interventions is bright—JITAI. Thus, patient reports and sensor-based data may aid in the development of personalized and real-time intervention strategies [105, 106]. Based on patient reports, the smartphone may be able to infer a lowering in mood in the context of social isolation and offer a relevant intervention, while, in another circumstance, it may infer a lowering in mood in the context of poor sleep and recommend an alternative intervention. Although in its infancy, using JITAIs to offer “closed loop” mental health interventions is a promising area for future research.

A recent systematic review and meta-analysis by the International Society for Bipolar Disorders (ISBD) Big Data Task Force examined the efficacy of smartphone-based interventions in bipolar disorder [107]. A total of six RCTs evaluated the efficacy of different smartphone-based interventions in bipolar disorder comparing differences in depressive and/or manic symptoms assessed with clinician-administered scales between groups [73–76, 108–110]. Surprisingly, none of the RCTs showed overall efficacy in reducing depressive or manic symptoms or improving functioning when compared to active controls but showed an effect when compared to inactive controls (paper-and-pencil monitoring or treatment-as-usual) [109, 110]. The first consideration is that comparisons in the RCTs ranged from inactive controls (normal use of smartphones [73–76]) to controls with highly active interventions (face-to-face intensive psychoeducational sessions plus smartphone

self-monitoring [110]). Notably, some of the RCTs identified an effect of the smartphone-based intervention in subanalyses on reducing patient perceived stress and increased patient-evaluated quality of life [73, 75]. Moreover, the control groups in the included RCTs were highly heterogeneous among studies, thus precluding a uniform comparison. The same issue was identified when trying to identify specific “active” aspects of the smartphone-based interventions, ranging from self-monitoring to feedback from clinicians on a regular basis. The heterogeneity in the design of the studies and the lack of uniform registered variables and definitions impeded the overall analyses. The mechanism of change in smartphone-based interventions is poorly understood, such as whether self-monitoring by itself may affect change or if therapeutic elements that draw from evidence-based interventions such as CBT are impactful beyond self-monitoring. Furthermore, most of the patients included in the RCTs were euthymic or presented with mild affective symptoms. It is known that the magnitude of affective symptom reduction increases with the initial severity of symptoms both depressive [111] and manic symptoms [112]. Therefore, the expected reduction in depressive and manic symptoms scales was non-existent to minimal in the identified RCTs which included patients presenting mainly euthymic or subsyndromal. The meta-analysis supported the need for expert consensus to establish how studies assessing the efficacy and effectiveness of smartphone-based interventions for patients with bipolar disorder should be designed, including valid outcome measures, clear definitions of active versus inactive or partially active controls, clear presentation of the characteristics of the patients included and reporting of cost-effectiveness.

A recent RCT (not included in the meta-analysis) investigating the effect of a smartphone-based intervention during 48 weeks on relapse did not detect a significant improvement in the primary outcome of time to relapse [113].

Overall, there are limitations of smartphone-based interventions for patients with bipolar disorder that should be acknowledged. First, bipolar disorder is a disease with high neurobiological underpinnings requiring interventions capable of modifying these altered mechanisms such as pharmacological treatments in order to control the fluctuating course of the disease [114]. Psychological interventions for patients with bipolar disorder, adjunct to pharmacotherapy, have proven beneficial in reducing affective relapses, particularly depressive [115] as well as in overall illness management [116]. However, in an illness with such a high biological load, psychological interventions alone are unlikely to stabilize the course of the illness.

During the last decade, there has been a gradual shift from focusing on affective episodes to inter-episodic mood instability [5, 54, 117, 118]. A substantial proportion of patients with bipolar disorder experience subsyndromal mood swings on a daily basis more than 50% of the time between episodes [54, 119, 120]. This mood variation (variability in mood registrations) is reflected as mood instability reflecting core psychopathology in bipolar disorder [119–122]. Furthermore, mood instability has been associated with increased perceived stress, decreased quality of life and functioning, and increased risk of relapse and hospitalization [82, 120, 122–124]. In addition, mood instability has been suggested to be associated with biological measures of stress-hormone dynamics [125]. Due to the increased focus

on the impact of mood instability, mood instability has been suggested as an independent treatment target and as a more sensitive outcome measure in randomized controlled trials (RCTs) than, for example, relapse or recurrence of affective episodes [57, 107, 117, 121, 126].

Using mood instability as the primary or a central secondary outcome measure in randomized controlled trials as this imply several advantages: mood instability has internal validity as a real-life measure for patients and high external validity as it reflects patients' illness severity and functioning. Mood instability appears to be a more sensitive measure of outcome in RCTs than more conventional outcomes focusing on relapse or recurrence of affective episodes [57]. This is because, unlike traditional clinician rating scales that are labor intensive and capture brief periods of time, mood instability can be captured daily by self-report for long time periods (intermittently up to years) with high adherence and low cost from a large sample of individuals thus having the potential to increase statistical power and sensitivity to detect effects in RCTs.

38.4 Ethical Concerns

Large-scale clinical studies should build evidence for the benefits of digital monitoring tools and interventions in mental disorders and support establishing new standards of care. Ethical issues regarding privacy, transparency, and confidentiality must be adequately addressed for the patient to be able to trust and engage in a meaningful therapeutic relationship [127].

38.5 Clinical Considerations

- The rapid growth in access to and capabilities of digital health technologies presents a feasible route toward augmenting traditional mental health care and bridging the gap between the need for treatment and the capacity to deliver it.
- Digital phenotyping can be divided into *active* and *passive* data.
- Digital phenotyping—both active and passive—may assist in the monitoring of illness and illness activity in bipolar disorder.
- Surprisingly, RCTs examining the use of smartphone-based treatment interventions in bipolar disorder have not identified overall efficacy in reducing depressive or manic symptoms.
- Issues concerning patients' online security, privacy, data storage, legal and cultural differences between nations, economic evaluations, and potential conflicts of interest need to be clearly addressed and reported for the evaluation and comparison of smartphone-based solutions.

38.6 Future Perspectives

Technological development moves faster than science, and due to rapid development and competitive commercialization, many smartphone-based solutions are not evidence-based, which undermines the quality and safety of these solutions in treatment settings. Commercial applications are frequently not updated, may be suddenly removed from app stores, or malfunction.

Well-designed and well-conducted RCTs set the methodological standard of excellence in medical research [128]. To evaluate the evidence regarding smartphone-based treatment interventions, rigorously designed and preregistered RCTs with critical evaluations of the beneficial and harmful effects of electronic interventions on both depressive and manic symptoms/episodes should be conducted, and positive, negative, and neutral findings should be reported accordingly.

Individual studies of complex electronic treatment interventions using standardized reporting guidelines could provide tools to clearly identify the content and context of the interventions, interpret how the interventions were implemented in the specific trial settings, and facilitate the replication of study findings [129]. The use of unvalidated applications with potentially poor-quality information or maybe even misinformation may lead to harmful effects. It may not in all cases be clearly stated whether or not a monitoring tool is for commercial or medical purposes. One of the main concerns to consider and address continuously when using electronic monitoring in bipolar disorder should be patient safety and personal privacy.

Overall, the long-term aim of smartphone-based technologies is not to substitute human interactions but rather to aid and support medical care, providing more capillary, continuous, personalized, and at the same time objective information on illness and illness activity in patients with bipolar disorder.

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Chapter 39

Neurostimulation and ECT



Helena Bellini and André Russowsky Brunoni

39.1 Introduction

Bipolar disorder (BD) is a severe psychiatric condition marked by intense and recurrent mood fluctuations, including mania, hypomania, depression, mixed states, and euthymia. With a lifetime prevalence estimated at 1–2%, BD results in considerable healthcare utilization and hospitalization. Furthermore, BD is globally recognized as one of the most debilitating noncommunicable diseases, imposing a significant burden on individuals and healthcare systems [1].

In recent years, there has been increasing concern regarding the efficacy of current treatments for BD [2]. The management of BD Depression (BDD) presents particular challenges, as a recent long-term study has shown a significantly reduced likelihood of recovery compared to manic episodes [3]. Notably, approximately 40% of patients do not respond to quetiapine treatment for BDD after 8 weeks [4]. First-line medications, including lithium, lamotrigine, olanzapine, or the olanzapine-fluoxetine combination, yield outcomes that are either similar or less favorable [5].

In addition to encountering significant resistance to pharmacological treatments, the relapse rates in BD are extremely high. One study indicated that up to 60% of cases within the initial 2 years experience relapse, and this number increases to 75% within 5 years [6]. Consequently, the prevalence of polypharmacy has been steadily increasing [7]. Polypharmacy is often associated with a heightened risk of transitioning to hypomania and/or mania and rapid cycling, especially when combined with antidepressant use [8]. Furthermore, it is linked to a greater incidence of side

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effects such as weight gain, metabolic dysfunction, and sedation, all of which contribute to nonadherence or treatment discontinuation [9].

Within this framework, neuromodulation techniques are increasingly being employed in BD treatment, functioning as either adjuncts or alternatives to existing therapies [1]. These techniques can be divided into implantable and non-implantable methods. Implantable methods, which are surgical, encompass vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Non-implantable methods can be further categorized into convulsive and nonconvulsive modalities. Convulsive techniques, such as electroconvulsive therapy (ECT) and magnetic seizure therapy (MST), necessitate assisted ventilation and general anesthesia, which includes a neuromuscular blocker and a hypnotic. Conversely, nonconvulsive methods, like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), do not require general anesthesia [10] (Table 39.1).

Understanding these therapeutic modalities is crucial to optimize their clinical application, improve therapeutic outcomes, and consequently enhance the quality of life for individuals facing the challenges of BD. This chapter aims to discuss the efficacy, potential adverse effects, and clinical application of the main neuromodulation techniques used in the context of BD. It is divided into four main sections: (1) Electroconvulsive therapy, (2) transcranial magnetic stimulation, (3) transcranial direct current stimulation, and (4) new approaches (MST and implantable techniques). Wherever possible, the content is presented separately for the acute (bipolar depression, (hypo)mania, and mixed states) and the maintenance phases of BD. A section with the most relevant points is provided in the concluding part.

Table 39.1 Neuromodulatory interventions (Fonte: Mutz et al. [1])

Neuromodulatory interventions
<i>Electroconvulsive Therapy (ECT):</i> Two electrodes on the patient’s head create an electric potential, producing a high-intensity current that induces generalized convulsions by depolarizing a significant neuronal population.
<i>Transcranial Magnetic Stimulation (TMS):</i> A coil generates a magnetic field that penetrates the scalp, inducing a focal electric current in brain tissue, which can modulate cortical excitability.
<i>Transcranial Direct Current Stimulation (tDCS):</i> TDCS modulates cerebral activity using a mild current (0.5–2 mA) through scalp electrodes. It fine-tunes the neural membrane’s resting potential, influencing brain reactivity. Anodal stimulation increases excitability, while cathodal stimulation decreases it.
<i>Magnetic Seizure Therapy (MST):</i> MST involves the application of high-frequency magnetic pulses to a specific brain target, resulting in the induction of a seizure-like activity. This intervention is characterized by a more precise targeting compared to ECT, focusing on the prefrontal cortex.
<i>Deep Brain Stimulation (DBS):</i> DBS requires surgically implanting electrodes into the brain, connected to a neurostimulator beneath the skin near the chest. This setup delivers electrical stimulation to specific brain regions.
<i>Vagus Nerve Stimulation (VNS):</i> VNS includes electrically stimulating the afferent projections of the vagus nerve to the brain. In surgery, electrodes are wrapped around the left vagus nerve and linked to a pulse generator implanted beneath the skin near the upper chest.

39.2 Electroconvulsive Therapy

ECT is widely recognized as a neuromodulation technique extensively employed in psychiatric treatment [11]. The treatment parameters frequently studied to optimize clinical outcomes include electrode positioning (Fig. 39.1), electrical magnitude (low, moderate, or high), and pulse duration (brief or ultra-brief) [1].

According to the American Psychiatric Association (APA) [12], ECT is most frequently used as a second-line treatment when the patient exhibits refractoriness to previously prescribed treatments, intolerance to drug side effects, clinical deterioration, or an exacerbation of suicide risk and lethargy. The technique can also be considered a first-line treatment when a rapid therapeutic response is necessary, in cases of severe syndromes characterized by psychotic symptoms or catatonia, for populations at high risk related to drug use (such as the elderly or pregnant women), or when a history of a good response to ECT during previous episodes of illness is reported.

39.2.1 Efficacy of ECT in BDD

There is substantial evidence supporting the effectiveness of ECT for treating depression, but there is a scarcity of studies specifically focusing on BDD [2].

Some studies suggest that ECT success rates for treating BDD range from 68% [13] to 80% [14]. However, the impact of bipolar disorder on ECT effectiveness for depression remains unclear. One retrospective study showed more significant

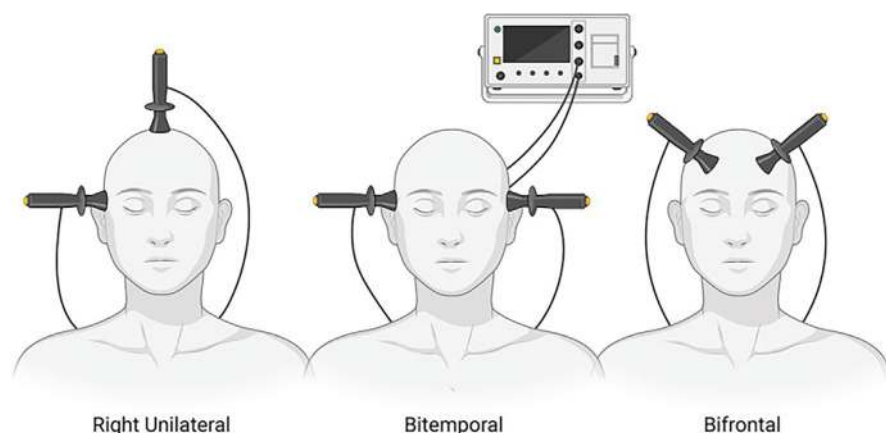


Fig. 39.1 Summary of primary ECT electrode positions. Displaying right unilateral electrode placement on the left, bitemporal electrode placement in the middle, and bifrontal electrode placement on the right (adapted from [1])

improvement in major depressive disorder (MDD) patients compared to BDD [15]. Another study found a higher remission rate in 17 MDD patients compared to 113 BDD patients [16]. On the other hand, a 2012 meta-analysis involving 790 MDD patients demonstrated a remission rate of 50.9%, while the BDD group ($n = 316$) had a remission rate of 53.2%, but this difference was not statistically significant [17]. Similarly, a more recent 2019 meta-analysis reported response and remission rates for unipolar and bipolar depression, with BDD patients showing higher response rates and faster response times but similar remission rates [18]. Overall, current evidence suggests no substantial differences in ECT efficacy for treating unipolar and bipolar depression.

ECT shows efficacy in treatment-resistant bipolar depression (TRBD) as well. Three studies [16, 19, 20] compared remission and response rates between acute TRBD and treatment-resistant depression (TRD) patients undergoing bitemporal ECT for an average of 6–10 weeks. The pooled odds ratio was 0.919 (95% CI = 0.44–1.917), $I^2 = 13.98$, $p = 0.822$, indicating no significant difference in ECT efficacy (measured in terms of response rates) between patients with TRBD versus TRD [5]. In a multicenter randomized clinical trial in Norway, 73 TRBD patients were randomly assigned to receive either ECT or algorithm-based pharmacological treatment. The ECT protocol, involving three sessions per week for up to 6 weeks with right unilateral electrode placement and brief pulse stimulation, demonstrated superior efficacy compared to algorithm-based pharmacological treatment. The response rate was significantly higher in the ECT group compared to the group receiving algorithm-based pharmacological treatment (73.9% vs 35.0%) [21].

In elderly individuals with BD, a retrospective study of 34 patients aged 65 years or older undergoing ECT showed reduced illness severity and improved cognitive function after treatment, with no serious adverse events reported [22]. Additionally, another retrospective study suggested that ECT had superior anti-suicidal effects compared to pharmacotherapy in patients with MDD or BDD [23].

Regarding electrode placement, Abbott et al. [24] conducted a systematic review analyzing prospective longitudinal investigations from 2000 to 2018. They compared clinical outcomes among bipolar patients with different electrode placements (right unilateral, bitemporal, and bifrontal, all at supra-threshold) and found no statistically significant differences among them.

39.2.2 Efficacy of ECT in Mania

The evidence highlights the efficacy of ECT in treating acute mania. In the pre-antipsychotic era (1945–1949), a study showed 100% of ECT patients achieving eventual social recovery compared to 44% in a historical control group (1931–1939) [25]. A sham-controlled trial [26] demonstrated marked superiority of bitemporal ECT (BT ECT) and chlorpromazine over sham ECT and chlorpromazine in improving manic symptoms. Another trial reported similar efficacy to chlorpromazine but a longer hospitalization time [27]. Additionally, another study reported more

substantial improvement with ECT (78%) compared to lithium (62%) or no treatment (32%) [28], with ECT proving vital in treating treatment-resistant mania, achieving a 75% response rate [13].

Mukherjee et al. [29] examined prospective and retrospective reports across the world literature from 1942 until 1992, finding that 80% of 589 manic patients showed substantial clinical improvement or remission following ECT. Similarly, a review [30] of 12 RCTs, that included 863 patients, assessed ECT combined with medication versus medication alone for acute mania. The ECT group experienced a greater reduction in manic symptoms, albeit with a higher level of memory impairment.

Regarding electrode placement, evidence suggests comparable efficacy of right unilateral and bitemporal ECT in mania, with bifrontal ECT showing a faster response and better cognitive profile [31–33].

Concerning concomitant pharmacotherapy benefits, a retrospective chart review reported equivalent efficacy but noted larger treatment numbers, longer hospitalizations, and a higher seizure incidence in patients receiving ECT and concomitant anticonvulsants. However, recent trials did not support these concerns, showing no significant differences in treatments or hospital stays between ECT alone and ECT with anticonvulsants [34].

39.2.3 *Efficacy of ECT in Mixed States*

Mixed states present heightened clinical complexity and are less responsive to standard pharmacological treatments, underscoring the potential role of ECT in this condition [35]. Unfortunately, a systematic review by Mutz et al. [1] found no RCTs comparing ECT to pharmacotherapy or sham ECT for this population.

Nevertheless, evidence from retrospective studies supports the efficacy of ECT in severe mixed states, with response rates of up to 68%, and a significant reduction in the severity of both depressive and manic symptoms [35]. For instance, in a prospective study, Devanand et al. [36] compared the clinical course and response to ECT in depressed, manic, and mixed groups, revealing response rates of 76.3%, 100%, and 80%, respectively. However, mixed patients experienced prolonged hospitalization and required more ECT sessions compared to depressed patients, indicating additional challenges in treating mixed states with ECT.

In cases of treatment-resistant mixed states, early reports from 1988 showed a 70% response rate for unilateral ECT [37]. Similarly, Medda et al. [38] observed response rates of 67.4% and 76% after bilateral ECT in patients with treatment-resistant mixed states and BDD type I, respectively. Nonetheless, the mixed-state group reported higher levels of residual agitation and psychotic features compared to purely depressive patients.

39.2.4 Efficacy of ECT in the Maintenance Phase

ECT is typically discontinued after symptom remission, but post-ECT relapse rates are high, especially within the first 6 months. In unipolar depression, about 51% relapse within 12 months, with 37.7% relapsing within 6 months, even with pharmacotherapy [39]. Without treatment, the relapse rate within 6 months can reach 84%. Rates are lower for patients with psychotic symptoms, older age, or shorter pharmacological resistance history [40].

Limited research has focused on relapse and recurrence rates post-ECT in bipolar affective disorder, yielding conflicting results [41]. In a recent prospective study [42], bipolar disorder patients with severe depression or mixed states unresponsive to pharmacological treatment but responsive to ECT showed promising outcomes. Complete symptom remission was achieved by 80.5% of patients after an average of 6.7 weeks post-ECT treatment, with 47.2% remaining in remission for over 70% of the follow-up period. However, 36.1% experienced depressive relapse during follow-up, with an average duration of 20.4 weeks. The time to relapse correlated with the length of the index episode, with longer episodes leading to shorter relapse periods.

Continuous ECT sessions following remission from acute mood disorder episodes have been documented since the 1940s [43]. Although there are no specific randomized controlled trials for bipolar disorder, some studies on maintenance-ECT (m-ECT) have included bipolar disorder patients. Naturalistic studies suggest that m-ECT may significantly reduce hospital admission rates or days spent in the hospital [41]. Moreover, there may be a reduction in the number of episodes and prolongation of interepisode euthymic intervals, particularly in treatment-resistant bipolar disorder, mainly rapid cycling [34].

In a recent 4-year follow-up of 14 rapid-cycling bipolar disorder patients, m-ECT showed promising results [41]. Eight patients (58%) did not relapse during the 2-year follow-up, and six patients (42%) experienced one relapse each year. The illness duration decreased significantly, and illness-free intervals increased. Factors associated with improvement included male sex, BD type II diagnosis, hyperthymic temperament, and younger age. Despite clinical severity, m-ECT was linked to an increased length of the illness-free interval and a subsequent decrease in episode frequency.

39.2.5 Side Effects, Neurocognitive Effects, and Tolerability of ECT

ECT is generally considered safe, with a mortality rate estimated at 2.1 per 100,000 treatment sessions [44]. Nonetheless, the technique can lead to cognitive and non-cognitive side effects. Common noncognitive side effects include transient symptoms such as mental confusion, headache, myalgia, nausea, and vomiting.

Additionally, cardiovascular issues and rare medical complications may occur, necessitating cardiovascular monitoring and general anesthesia during the procedure.

Primary cognitive impairments associated with ECT include postictal disorientation, anterograde amnesia (inability to retain new information), retrograde amnesia (inability to recall past memories), and non-amnestic cognitive skill impairments such as processing speed and executive functioning. While anterograde amnesia and non-amnestic skill impairment typically improve after the 15th day [45], they may persist for several months [46], whereas retrograde amnesia may extend for years [47].

Several strategies have been explored to mitigate ECT's cognitive side effects, including unilateral electrode placement [45] and ultra-brief pulse (UBP) utilization [48], but these approaches have not fully resolved the limitations. Consequently, cognitive side effects, particularly autobiographical retrograde amnesia, remain a significant concern with ECT treatment.

In treating bipolar depression with ECT, there is concern about the risk of transitioning to mania. The incidence of ECT-induced mania may be as high as 24% [49]. Managing ECT-induced mania lacks consensus, but anecdotal evidence suggests lithium treatment may reduce transition risk and manage emerging manic symptoms during ECT. Additionally, continuing ECT treatment in case of a transition to mania is another approach [2].

39.2.6 Pharmacotherapy During ECT

The pre-procedural assessment in ECT requires a comprehensive examination of patient medications, with particular attention to those posing potential risks such as QT interval prolongation or exacerbation of procedure-related side effects. While medications for cardiac arrhythmias, hypertension, epilepsy, and other conditions are typically continued during ECT, there is a notable deficiency in research assessing their specific impact [12].

Attention is warranted for medications that may hinder proper seizure induction, such as benzodiazepines and anticonvulsants, which could compromise ECT efficacy and should be avoided when feasible [50]. If discontinuation is not possible, reducing or halting administration the night before the procedure may be considered. Nonetheless, stimulus dose titration may partially mitigate the impact of anticonvulsants on seizure induction [34].

The concurrent use of lithium during ECT remains debatable and requires caution. While some studies suggest its safety [51], reports of serious adverse effects, including prolonged seizures and serotonin syndrome, have been noted [52]. Patients undergoing ECT with lithium have a significantly higher risk of delirium, thus lower lithium doses are recommended with vigilant monitoring [53].

Regarding antidepressants, findings regarding their use during ECT are inconclusive. While a randomized prospective study did not identify significant additional adverse effects associated with maintaining antidepressant use [54],

concurrent administration of Venlafaxine is linked to elevated cardiovascular and transient cognitive side effects [55, 56]. Bupropion administration reduces the seizure threshold, potentially increasing the risk of status epilepticus [57].

In schizophrenia treatment, the concurrent use of conventional and atypical antipsychotics does not significantly impact adverse effects occurrence overall [58]. However, low-potency antipsychotics notably prolong seizure duration [58]. Limited well-controlled studies on the simultaneous use of clozapine and ECT suggest good tolerability and increased efficacy, albeit with reported adverse reactions including prolonged seizure, elevated heart rate and blood pressure, postictal confusion, and memory issues [59].

Keypoints: ECT in BD
Advantages
• ECT can be effective in treatment-resistant and complex cases • ECT demonstrates a rapid therapeutic response
Limitations
• ECT can cause cognitive and noncognitive side effects • Stigma surrounding ECT may affect patient acceptance of the treatment
Evidence Base
• ECT is safe and effective for treating mania, depression, and mixed states • Studies suggest its superiority over pharmacotherapy during acute BD episodes • Combining ECT with medication proves more effective than either treatment alone • ECT achieves success in over 80% of challenging cases, such as catatonia • ECT aids in preventing relapses and recurring mood episode.
Clinical Recommendations
• Indicated for treatment-resistant conditions or patients who are intolerant to drug side effects • It can also serve as a first-line option for cases requiring rapid therapeutic response, severe syndromes, high-risk populations, or individuals with a history of positive ECT response
Future Directions
• Studies needed to minimize cognitive effects and develop continuation protocols for ECT • More RCTs are required to assess efficacy and safety of ECT in BD

39.3 Transcranial Magnetic Stimulation

Cortical stimulation through pulsed magnetic fields initially served for brain region mapping but was later found to induce mood alterations in healthy volunteers, leading to the development of TMS as we know it today [60].

TMS employs a coil generating a magnetic field inducing a focal electric current in brain tissue, modulating cortical excitability, either decreasing or increasing it based on stimulation parameters [60]. Repetitive TMS (rTMS) protocols for MDD typically administer 10 Hz stimulation to the left dorsolateral prefrontal cortex (DLPFC) over 4–6 weeks in daily sessions. Coil placement is determined using anthropometric methods or neuronavigation techniques, with treatment dosage personalized based on the motor threshold (MT), defined as the intensity moving the contralateral abductor pollicis brevis 50% of the time [61].

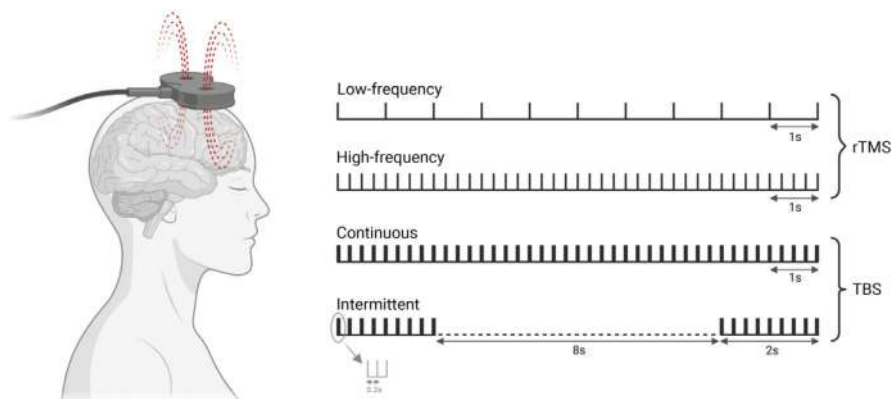


Fig. 39.2 Standard repetitive transcranial magnetic stimulation (rTMS) involves identical stimuli with identical intervals, either low frequency (LF rTMS ≤ 1 Hz) or high frequency (HF rTMS > 5 Hz). Theta burst stimulation (TBS) comprises bursts of HF stimulation, each containing three pulses at 50 Hz, repeated with a 200 ms inter-stimulus interval (5 Hz). In intermittent TBS (iTBS), bursts last 2 s followed by a 10-s interval. In continuous TBS (cTBS), bursts are repeated continuously for 40 s (adapted from Mutz et al. [1])

TMS protocols involve specific parameters such as frequency, duration, and interval, tailored to target different brain regions and conditions (Fig. 39.2). They consist of various techniques, including standard repetitive TMS (rTMS), theta burst stimulation (TBS), and others (Table 39.2). These protocols are essential for optimizing TMS treatment outcomes [60].

39.3.1 Efficacy of TMS in BDD

Meta-analyses consistently demonstrate significant differences favoring active rTMS over placebo (sham) for depression treatment, whether alone or combined with medication [10]. With response rates for left prefrontal high-frequency (HF) rTMS generally ranging from 20% to 30% [62–64], the Canadian Network for Mood and Anxiety Treatments (CANMAT) [65] recommends rTMS as a first-line treatment for patients with depressive episodes who have not responded to at least one antidepressant therapy.

However, the clinical effects of rTMS remain modest compared to ECT [66], which is more effective, especially for psychotic or treatment-resistant depression [67, 68]. ECT also yields faster responses, typically within 2 weeks, compared to 4–6 weeks for rTMS [62, 64, 69]. Consequently, for cases requiring rapid response or treatment-resistant patients, ECT remains the preferred treatment [70]. Nonetheless, rTMS research has expanded in recent decades, aiming to improve bias control and identify predictive biomarkers. Moreover, rTMS is better tolerated than ECT.

Table 39.2 TMS protocols

TMS protocols
<i>Repetitive Transcranial Magnetic Stimulation (rTMS)</i> involves delivering magnetic pulses repeatedly to specific brain regions to modulate neural activity. High-frequency (>5 Hz) stimulation excites neural activity, while low-frequency (≤ 1 Hz) stimulation inhibits it. Common treatment protocols include high-frequency stimulation of the left dorsolateral prefrontal cortex, low-frequency stimulation of the right dorsolateral prefrontal cortex, and bilateral stimulation of the dorsolateral prefrontal cortex
<i>Theta Burst Stimulation (TBS)</i> is a form of rTMS characterized by bursts of high-frequency stimulation. It can be delivered in two main forms: <i>Continuous Theta Burst Stimulation (cTBS)</i> : Bursts of stimulation are continuously administered for a typical period of 40 s without interruption <i>Intermittent Theta Burst Stimulation (iTBS)</i> : Bursts of stimulation are delivered intermittently, with each burst lasting for 2 s followed by an 8-s pause, repeated in cycles
<i>Accelerated Transcranial Magnetic Stimulation (aTMS)</i> involves administering multiple treatment sessions of rTMS daily to shorten the overall treatment duration. Up to four sessions per day are conducted to achieve a rapid clinical response
<i>Priming Transcranial Magnetic Stimulation (pTMS)</i> involves preceding low-frequency rTMS with a brief period of low-intensity high-frequency stimulation to enhance the neural response to rTMS
<i>Deep Transcranial Magnetic Stimulation (dTMS)</i> utilizes a different coil configuration (H-coil) that enables larger volumes and deeper structures of the brain to be stimulated. An intriguing innovation is the H-coil, shaped like a helmet, which permits stimulation up to approximately 5 cm deep into the brain
<i>Synchronized Transcranial Magnetic Stimulation (sTMS)</i> involves positioning rotating spherical neodymium magnets along the midline of the scalp to deliver stimulation synchronized to an individual's α frequency

Studies on rTMS in BDD have yielded mixed results. Some trials found significant improvements with active rTMS, while others reported no significant differences compared to sham treatment. Further investigations have explored refining rTMS protocols, including variations in frequency and location targeting the left DLPFC. Flexible approaches to rTMS protocols have been suggested, with innovative techniques like the H1-coil and TBS showing promise in improving depression scores. Continued research is essential to optimize rTMS protocols and identify biomarkers for treatment response [71].

39.3.2 Efficacy of TMS in Mania

Studies on TMS in bipolar disorder primarily focus on depression, with a limited investigation into its efficacy during the manic phase due to concerns about inducing manic episodes. In the limited studies conducted during the manic phase, traditional TMS protocols targeting the right DLPFC have been predominant [71].

An early trial by Grisaru et al. [72] found significant improvement in mania symptoms with right prefrontal TMS compared to left prefrontal TMS, prompting

further research. Other studies observed improvements in manic symptoms with HF rTMS over the right DLPFC [73, 74]. However, the study by Kaptan et al. [75] found no significant difference between active TMS and sham treatment, suggesting the need for more intensive protocols. Additionally, discrepant findings emerged in studies with adolescents, suggesting metabolic differences between adults and adolescents may influence treatment response. Therefore, further research is needed to confirm efficacy and understand potential differences in treatment response between adults and adolescents [71].

39.3.3 Efficacy of TMS in Mixed States

In a study conducted by Pallanti et al. [76], an open trial investigated the efficacy of 1-Hz right DLPFC rTMS in patients experiencing a mixed state in BD. Initially, 40 participants underwent treatment with valproate for 4 weeks. Following this, rTMS was administered at 110% MT for 420 stimuli per session over 15 treatments spanning 3 weeks. The trial yielded promising results, indicating improvement in both depressive and manic symptoms. However, the open design of this study is an important limitation. Therefore, RCTs are necessary to establish the efficacy of rTMS for mixed states in BD before it can be recommended as a standard treatment protocol.

39.3.4 Efficacy of TMS in Maintenance Phase

A limited number of studies have explored the use of TMS in the maintenance phase of BD. In a small open-label study, weekly maintenance rTMS showed varying efficacy, with three patients completing 1 year without relapse, while four experienced multiple relapses [77]. In parallel, a preliminary study on deep TMS (dTMS) showed that maintenance sessions may protect patients with bipolar disorder or recurrent major depressive disorder from developing depressive or manic relapses over a 12-month follow-up period. This study involved drug-resistant patients with a current depressive episode, where all participants underwent daily dTMS sessions for 4 weeks. The maintenance group received additional weekly or bi-weekly dTMS sessions. After the first dTMS cycle, there was a significant reduction in Hamilton Depression Rating Scale scores in all participants. The results suggest that dTMS maintenance sessions may be helpful in maintaining euthymia over a 12-month follow-up period [78].

Further research with larger samples and controlled designs is necessary to confirm the long-term benefits of TMS in the maintenance phase of bipolar disorder. Nonetheless, these studies offer valuable insights into TMS as a therapeutic approach for stabilizing mood and preventing relapses in these conditions.

39.3.5 *Side Effects and Tolerability of TMS*

TMS is recognized for its high tolerability and minimal side effects. Compared to ECT, TMS is better tolerated, with a higher likelihood of being well tolerated, ranging from 52% to 16% for rTMS compared to 14% for ECT [66]. Common side effects like scalp discomfort and transient headaches are manageable and rarely prompt therapy discontinuation [65].

While convulsive seizures are a rare but severe complication, their occurrence is minimal, estimated at 0.01–0.1%. HF stimulation is contraindicated in patients with a seizure history, though some clinicians caution against TMS in those with epilepsy [79]. Less common adverse effects include gastrointestinal issues, eye problems, and muscle twitching. Rare side effects encompass dizziness, insomnia, muscle pain, fatigue, difficulty concentrating, anxiety/panic episodes, hypomania, tinnitus, skin pain, facial pain, depersonalization, paranoid ideation, crying, subjective deterioration of mental state, and suicidal ideation [80].

Despite contraindications, some experienced centers may consider TMS for select cases. Comfort measures during sessions, such as providing a comfortable position and specialized armchairs, enhance the experience and reduce discomfort. Notably, there is no heightened risk of migraine headaches associated with TMS, and the likelihood of conversion to hypomania/mania during depressive episode treatment is minimal. Overall, TMS remains a safe and well-tolerated option for various neuropsychiatric conditions [79].

39.3.6 *Neurocognitive Effects of TMS*

A systematic review of RCTs found no cognitive differences between real and sham TMS for BDD, but TMS might improve cognition during euthymia [81]. In one trial, rTMS improved verbal learning but not other cognitive aspects [82]. Another trial showed improved cognition in euthymic patients receiving rTMS compared to sham [83]. Holtzheimer III et al. [84] noted significant improvements in neurocognitive battery scores, particularly the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), during a 6-week follow-up. Similarly, Loo et al. [85] reported improved scores in the Trail Making Test A for the sham group compared to a decline in the active group.

Keypoints: TMS in BD

Advantages

- *Noninvasive alternative to surgery or medication*
 - *Minimal, temporary side effects like headaches or discomfort, leading to high patient tolerance*
 - *No need for anesthesia or relaxation during treatment*
 - *Potential improvement in cognition during euthymia*
-

Keypoints: TMS in BD

Limitations

- *Efficacy limitations: TMS effectiveness varies among patients and conditions*
- *Cost: Multiple TMS sessions can be expensive*
- *Treatment time: TMS involves multiple sessions over weeks, potentially inconvenient*

Evidence Base

- *Evidence remains inconclusive due to the absence of RCTs and long-term studies, particularly for hypomania, mania, or mixed states*
- *Clinical Studies: Research on TMS for BDD shows mixed outcomes, with some indicating modest improvement in depressive symptoms*

Clinical Recommendations

- *Individualized Approach: Due to limited evidence, TMS treatment decisions for bipolar disorder should be tailored to each patient, considering potential benefits and risks*
- *Multimodal Treatment: TMS can complement medication and psychotherapy in bipolar disorder management*
- *Clinical Monitoring: Close monitoring of TMS treatment response is essential, with adjustments based on symptom progression and treatment tolerance*
- *Caution: Healthcare providers should be cautious about the risk of inducing mania or hypomania in bipolar patients undergoing TMS, taking necessary precautions for symptom management*

Future Directions

- *Exploring brain circuits and nodes further is necessary to enhance treatment effectiveness*
 - *More research is needed to identify the best treatment parameters and patient characteristics*
 - *Conducting well-powered RCTs is essential to establish the efficacy of rTMS before clinical recommendation*
-

39.4 Transcranial Direct Current Stimulation

In tDCS, two electrodes on the scalp transmit a low-intensity electrical current (typically 0.5–2 mA), with only 10% reaching the brain. This stimulation modulates cortical excitability in superficial brain regions, influencing synaptic transmission without inducing action potentials [86]. Electrodes are strategically placed over target cortical areas, where the anode induces depolarization, increasing neural excitability, and the cathode induces hyperpolarization, decreasing cortical excitability (inhibitory effect) [87, 88]. Various factors, such as current intensity, direction, session duration, pharmacological treatment, and baseline brain activity, can influence excitability changes [89]. tDCS also modulates long-term effects of use-dependent plasticity, resembling a long-term potentiation (LTP)-like process [90].

Studies on tDCS and MDD [91] utilized a bifrontal montage, placing the anode over the left dorsolateral prefrontal cortex (F3) and the cathode over the right dorsolateral prefrontal cortex (F4), right lateral orbitofrontal cortex (F8), or right supra-orbital cortex (Fp2). The rationale stems from functional imaging studies revealing prefrontal asymmetry in unipolar depressed patients, with hypoactivity in the left DLPFC and relative hyperactivity in the right DLPFC [92, 93].

Neuroimaging studies suggest potential correlations between bipolar disorder pathophysiology and brain regions involved in emotion processing, emotion regulation, and cognitive control [94]. However, there is no available evidence guiding electrode montage and stimulation parameters for BD [86].

For depressive episodes, tDCS targets are similar to MDD. Conversely, for manic episodes, the anode is placed over the right dorsolateral prefrontal cortex, reflecting a hypothesized reverse mechanism. The euthymic phase involves prefronto-cerebellar montages, with the anode over F3 and the cathode over the cerebellar cortex. This is based on observations of neurocognitive impairment in the euthymic state, with decreased prefrontal activity and increased cerebellar activation, along with dysfunction in the prefronto–thalamic–cerebellar circuitry correlated with neurocognitive impairment [95]. Figure 39.3 provides a visual representation of the electrode positions described.

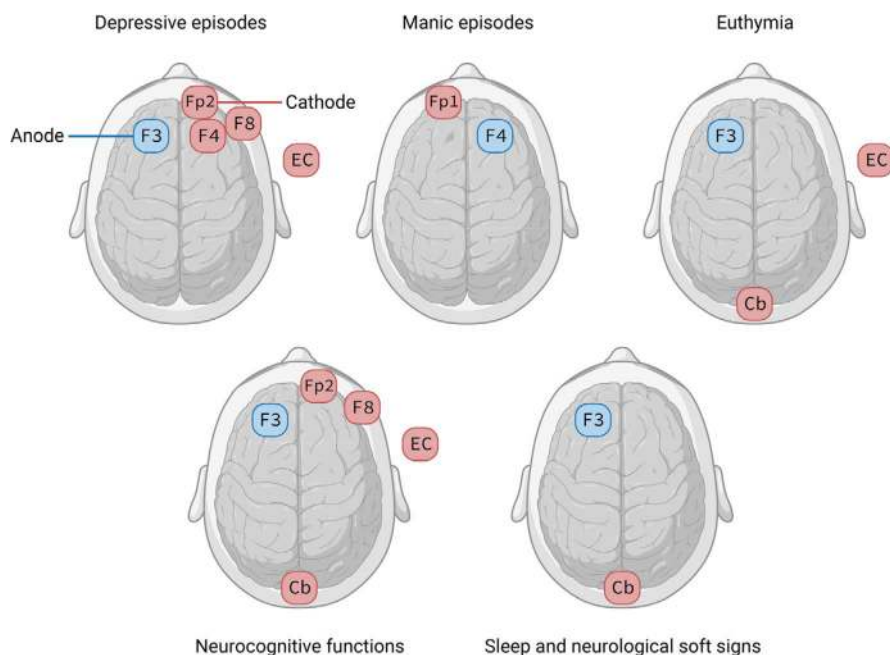


Fig. 39.3 TDCS electrode placements for bipolar disorders: (1) Depressive episodes, (2) manic episodes, (3) euthymia, (4) neurocognitive functions in depressive episodes or euthymia, and (5) sleep and neurological soft signs during euthymia. Blue denotes anode; red denotes cathode. Cb cerebellum, EC extra-cephalic (right upper arm), F3 left dorsolateral prefrontal cortex, F4 right dorsolateral prefrontal cortex, F8 right lateral orbit cortex, Fp1 left superior orbital cortex, Fp2 right superior orbital cortex. Electrode placements from Dondé et al. [95]

39.4.1 *Efficacy of tDCS in BDD*

TDCS shows potential antidepressant efficacy in various studies and meta-analyses [91, 96–98]. However, results are mixed, with some studies reporting success [99, 100], while others find no significant improvements compared to sham [101].

An IPD meta-analysis of nine large RCTs indicated no difference between active and sham tDCS during the short acute treatment phase, suggesting potential increasing stimulation effect sizes in the follow-up period [102]. This may account for the reason why some studies with a limited number of sessions yielded negative outcomes.

The effects of tDCS for patients with BD are contradictory due to the inclusion of both MDD and BDD patients in most studies, making it challenging to discern differences in tDCS effects between the two groups [86]. Preliminary evidence in bipolar disorder type I suggests that combining tDCS with pharmacotherapy leads to greater depressive symptom reduction than pharmacological monotherapy [103]. Similarly, a review covering bipolar disorder states indicates moderate effectiveness of tDCS in treating depressive symptoms [95].

In a pilot study [104], response and remission rates following tDCS in bipolar patients were comparable to those in unipolar patients (40% and 20%, respectively). A recent open-label trial comparing responses to tDCS in unipolar and bipolar depressed patients demonstrated equal improvement not only in depression scores but also in cognitive performance, anxiety, and psychosocial functioning [105]. Conversely, Li and colleagues reported a higher treatment response rate in bipolar patients (40%) compared to unipolar ones (30.8%) [106].

Results from a recent systematic review, including 14 clinical studies with a total of 207 patients, consistently suggest tDCS effectiveness in treating BDD, with post-treatment Hamilton Depression Rating Scale (HDRS) score reductions ranging from 18% to 92% [86]. However, only one study by Sampaio-Junior et al. [107] showed a significant difference favoring real tDCS over sham, emphasizing the importance of its randomized double-blind sham-controlled trial design and being one of the few to specifically study bipolar depression with the largest sample in the literature.

Heterogeneity in outcomes between studies may stem from differential contributions of relevant predictor variables [108]. Factors influencing treatment and the time-course of symptom improvements in BDD, including treatment parameters, concomitant drug use, history of pharmacological resistance, or other clinical factors, remain to be elucidated. In a meta-analysis, bipolar depression has been suggested as a positive predictor of tDCS response, even with a low percentage of bipolar patients in the overall sample (3.8%) [91]. However, a recent open-label trial including patients with MDD and BDD found similar response rates to tDCS in both groups [105], consistent with an individual patient data meta-analysis that found no evidence linking bipolar disorder status to treatment response relative to

MDD (OR = 2.28, 95% CI: 0.72–7.22) [102]. Another potential predictor of a positive response to tDCS is the presence of anxiety disorders, while higher baseline depression severity and treatment resistance are associated with worse response [108].

39.4.2 Efficacy of tDCS in Mania and Mixed States

The availability of data on tDCS in cases of mania is limited. A case report observed that tDCS used as an adjunct to pharmacotherapy was able to improve manic symptoms. However, in this specific case, the 5-day course of tDCS was conducted simultaneously with the introduction of psychotropic medications, including Clozapine [109]. To date, there has been no research examining the efficacy of tDCS in mixed states.

39.4.3 Efficacy of tDCS During Euthymia

In a prospective open-label study with 26 patients diagnosed with MDD or BDD, continuation tDCS was administered after an acute treatment phase. The results indicated that weekly tDCS application for the initial 3 months resulted in the majority of initially responsive patients maintaining euthymia [110]. Similarly, another recent study involving 24 MDD or BDD patients showed promising outcomes following 15 acute tDCS sessions. Participants were monitored for up to 6 months or until relapse, defined as clinical deterioration and/or a Hamilton Depression Rating Scale (HDRS) score exceeding 15. During the follow-up period, tDCS given twice weekly for 24 weeks led to a low relapse rate (26.5%) after 6 months, particularly in nontreatment-resistant individuals [98]. These findings suggest a potential role for tDCS in preventing relapses during the maintenance phase.

Apart from its efficacy in preventing new episodes, recent studies have investigated the impact of tDCS on cognition in euthymic patients with bipolar disorder [111]. Consistent with previously observed brain activity patterns characterized by frontal hypoactivity and cerebellar hyperactivity during euthymic states [112, 113], a prefronto-cerebellar tDCS montage significantly enhanced visuospatial memory and executive function in two studies involving 40 euthymic patients [114]. Additionally, preliminary evidence from a study with 25 euthymic patients suggested that tDCS not only improved neurological function but also enhanced sleep quality [115]. These findings are particularly relevant given that many individuals with bipolar disorder experience sleep disturbances following the resolution of mood symptoms [116]. However, further research is necessary to consolidate these findings and comprehensively understand the potential of tDCS in improving cognitive and neurobiological functions during the maintenance phase of BD.

39.4.4 Side Effects, Tolerability, and Cognitive Effects of tDCS

Studies have explored the safety and tolerability of tDCS [86]. Generally, adverse effects are mild and temporary, including redness, itching, tingling at electrode sites, headaches, nausea, fatigue, and mild-to-moderate visual disturbances. Only Loo et al. [101] reported severe adverse events, such as increased suicidality, headaches, and blurred vision, which were related to underlying health conditions rather than the tDCS procedures, except for potentially heightened suicidal ideation, which may have had some association with tDCS intervention in patients with prior suicidal thoughts and behaviors. Additionally, cases of treatment-emergent affective switches have been reported. However, these cases did not require hospitalization, trial discontinuation, or specific treatment [107].

Regarding cognition, studies have shown improvements in processing speed, selective attention, and executive function after tDCS sessions in patients with BD and MDD. However, conflicting evidence exists, with some studies not finding significant cognitive differences post-treatment across various cognitive domains [1]. A meta-analysis in BDD patients did not find independent cognitive effects of tDCS beyond changes in depressive symptoms, though data limitations were acknowledged [117]. Conversely, a large RCT in BDD patients suggested improvements in certain cognitive functions with tDCS treatment [118].

Keypoints: tDCS in BD

Study Limitations: Most tDCS studies in bipolar disorder face constraints like open study designs and small sample sizes, contributing to limited evidence, particularly in the BD

Need for Further Research: Encouraging initial findings underscore the importance of additional research in tDCS for BDD, emphasizing the urgency for studies on hypomanic, manic, or mixed states due to a lack of data in these populations

Efficacy in BDD: tDCS demonstrates promising efficacy in treating bipolar depression symptoms, with indications that bipolar depressed patients may benefit more than unipolar patients, especially with appropriate continuation protocols

Individualized Treatment Approaches: Recommendation to stratify treatment protocols based on patient characteristics or use machine learning for personalized adjustments, coupled with the understanding that optimization of treatment parameters can enhance tDCS effectiveness

Safety and Low Adverse Effects: tDCS is highly praised for its safety profile with mild and nonspecific adverse effects, coupled with a low risk of causing affective

Portability and Economic Viability: A significant advantage of tDCS lies in its portability, allowing home-based treatment, and is considered economically viable compared to current standards of care

39.5 New Approaches

39.5.1 Magnetic Seizure Therapy

The challenge in inducing more focal seizures with ECT stems from the impedance of the scalp and skull, which disperses most of the electric current throughout the brain via cerebrospinal fluid. In contrast, these structures offer no resistance to a magnetic field, allowing for relatively more focused stimulation [119]. Magnetic stimulation induces an electric field that reaches approximately 2 cm below the scalp, primarily affecting the superficial cortex and sparing subcortical structures involved in mnemonic cognitive processing circuits [120, 121].

The use of brain magnetic stimulation for depressive disorders dates back to the early 1900s [122]. However, deliberate seizure induction through magnetic stimulation gained purpose in 1994, when Sackeim [123] proposed it with devices then known as TMS. Beyond its theoretical potential for more focal stimuli, it was believed that TMS, if delivered at subconvulsive levels, could have antidepressant effects comparable to ECT but potentially more robust if a seizure occurred [124, 125]. This led to the development of the first devices for the procedure, eventually named MST (Fig. 39.4).

Similar to ECT, MST is a form of convulsive therapy, but the electric field is induced directly in the cortex through magnetic stimulation. The procedure involves placing a coil near the patient's head vertex to create a high-intensity alternating magnetic field (0.5–2 Tesla). This magnetic field induces an electric current on the

Fig. 39.4 MST Session with a double coil positioned at the vertex. Institute of Psychiatry, Hospital das Clínicas, Faculty of Medicine, University of São Paulo (IPq HC-FMUSP)



brain's surface and deep structures, causing generalized neuronal depolarization until a seizure is triggered [119]. Typically, the treatment plan consists of an initial series of 8–12 sessions over 3–4 weeks, similar to ECT.

39.5.1.1 Clinical Outcomes of MST in BD

The exploration of MST originated in 1998 through groundbreaking experiments by Lisanby et al. [126]. The early MST devices could deliver only 400 pulses at a peak intensity and frequency of 50 Hz, 100% intensity, and 8 s duration [127]. Demonstrating feasibility, studies on non-human primates and humans revealed good tolerability and effectiveness [128, 129]. Furthermore, post-mortem neuropathological analysis of animals subjected to MST indicated the absence of structural brain damage, affirming the procedure's safety [130].

In a double-blind randomized study comparing the side effects of ECT and MST in major depression patients, MST recipients reported fewer subjective side effects after four sessions. They displayed lower rates of disorientation, inattention, retrograde amnesia, and impaired verbal fluency in the immediate postictal period [131]. White et al. [132] compared 20 severely depressed patients allocated to receive either bitemporal ECT (BL ECT) or MST, with both groups showing a reduction in Hamilton Depression Rating Scale (HAMD) scores. The effect was significantly greater in the ECT group (average reduction of 24 points versus 18 points for MST, $p < 0.05$), and the MST group exhibited a shorter reorientation time after treatment.

Initially administered at 50 Hz, MST has evolved to include high-frequency stimuli (100 Hz) for enhanced efficacy. High-frequency MST was believed to maintain cognitive benefits over ECT [133]. In 2011, Kayser et al. [134] conducted the first controlled randomized double-blind comparative study between right unilateral ECT (RUL ECT) and high-frequency MST in patients with treatment-resistant depression of bipolar disorder (BD) or major depressive disorder (MDD). Comparable antidepressant responses and no cognitive effects were observed in both groups. Response rates ($\geq 50\%$ reduction in MADRS) were 40% for ECT and 60% for MST, with remission rates (MADRS < 10) of 40% for ECT and 30% for MST. However, RUL ECT was administered with a load equivalent to three times the seizure threshold, possibly contributing to reduced side effects and therapeutic effects.

In 2013, Fitzgerald et al. [135] investigated therapeutic effects and cognitive profiles of high-frequency MST in treatment-resistant depression in MDD through an open-label clinical trial. Although the response to MST was inferior to ECT, it demonstrated clinical efficacy. No cognitive impairment was detected, but the study's major limitation was the lack of a sham control.

More recently, Daskalakis et al. [136] compared the effects of high-frequency (100 Hz), medium-frequency (50 or 60 Hz), and low-frequency (25 Hz) MST using 100% stimulator output. High-frequency MST produced the best response and remission rates in adults with MDD. Response rates were 41.7% and 60%, and

remission rates were 33.3% and 53.3% for those who completed the trial adequately (8 sessions or more) and per protocol (achieving complete remission or completing a maximum of 24 sessions), respectively. No significant cognitive effects were observed.

Recent studies reinforce the hypothesis of MST's non-inferiority to ECT in terms of antidepressive effects [137–139]. One nonrandomized study [137] reported response and remission rates of 72.2% vs 81.5% and 61.1% vs 63% for MST and ECT, respectively. Additionally, MST demonstrated a more favorable cognitive profile with better neurocognitive performance, shorter postictal reorientation times [132–135, 137, 140], and increased psychomotor speed [139].

It is noteworthy that many studies showed no impairment in cognitive abilities post-MST [136, 141, 142], and some even suggested a positive relationship between MST and cognitive performance, possibly related to reversing cognitive deficits of depression [129, 131, 134–137, 139, 142].

Chen et al. [143] conducted the first meta-analysis on the antidepressive efficacy and cognitive side effects of MST, including controlled trials from 2001 to 2020. MST showed no significant difference in antidepressive efficacy compared to ECT, with shorter recovery and reorientation times and less impairment in cognitive abilities.

The first major study exclusively involving bipolar depression patients was conducted by Tang et al. [144], presenting results in three publications [144–146]. In an open-label trial, participants with treatment-resistant bipolar depression were treated with MST. Response and remission rates were lower than in unipolar depression, but cognitive measures remained stable. MST was associated with reduced suicidal ideation, and 57.1% of initial responders maintained response or remission during a 6-month continuation treatment phase.

To date, there are no published data on the efficacy of MST in treating other bipolar disorder states.

39.5.2 Vagus Nerve Stimulation

VNS can be achieved through two main methods: invasive (iVNS) and noninvasive transcutaneous VNS (tVNS). iVNS involves surgically implanting a pulse generator subcutaneously in the left thoracic region, with electrodes attached to the left cervical vagus nerve. This FDA-approved method, initially for refractory epilepsy in 1997, delivers intermittent electrical stimulation to the vagus nerve. Conversely, tVNS is a noninvasive alternative that attaches a stimulator to the auricular concha via ear clips, delivering electrical impulses to the afferent auricular branch of the vagus nerve subcutaneously [147].

Initially approved for refractory epilepsy, iVNS gained FDA approval for unipolar treatment-resistant depression (TRD) in 2005 [148, 149]. The mechanism of action in TRD involves the afferent projections of the vagus nerve to key cerebral areas linked to depression's pathophysiology, such as the raphe nuclei,

locus coeruleus, and nucleus tractus solitarius, ultimately impacting the limbic system [150]. VNS shows promise for exploring novel treatment approaches in bipolar disorder.

39.5.2.1 VNS in BD: Clinical Evidence

National treatment guidelines recommend VNS for TRD, but evidence supporting its efficacy is moderate to low [65, 151]. A meta-analysis of six outpatient multi-center clinical trials on iVNS in chronic TRD showed superior efficacy compared to standard care [152], although large-scale controlled trials have produced conflicting results [153], possibly due to the slow onset of VNS action. In an RCT comparing iVNS with sham-iVNS, no significant differences were observed in the 3-month primary outcome, but responders increased at 12 months, exceeding the treatment-as-usual group [154]. Similarly, a prospective observational study with 795 patients over 5 years showed improved clinical outcomes, higher response rates, and significant remission rates in the adjunctive VNS group compared to treatment-as-usual [155].

Transcutaneous vagus nerve stimulation (tVNS) also appears promising in treating depression, with some studies showing reduced depressive symptoms and positive effects on brain networks [147, 156].

Comparative studies between VNS effects in MDD and BDD have shown no significant differences, indicating stabilizing properties and reduced depressive recurrences in the long term [157, 158]. In rapid-cycling BD, a pilot study demonstrated improvements in overall illness, depressive symptoms, and functionality with VNS [159, 160]. Also, recent research suggests that VNS, when added to treatment-as-usual, leads to better responses, faster outcomes, longer periods until relapse, and reduced suicidality in patients with treatment-resistant bipolar depression over 5 years [148].

While the cognitive effects and tolerability of VNS for BD are not extensively studied, overall tolerability is reported as good. Side effects are generally related to surgery or electrical stimulation, with advantages including optimal compliance, no impact on pregnancy, and compatibility with other medications and stimulation techniques. Treatment-emergent manic symptoms are infrequent and manageable through parameter adjustments, medication, or temporary discontinuation of VNS [149].

39.5.3 Deep Brain Stimulation

DBS entails surgically implanting electrodes into the brain, which are linked to a neurostimulator placed near the chest. These electrodes are strategically positioned subcortically or within deep cortical areas to influence specific neural circuits [1]. DBS is regarded as an enhanced substitute for ablative neurosurgical

methods because it is fully reversible and adjustable. It should be reserved for well-defined cohorts of patients with highly severe, treatment-resistant mental disorders [161].

39.5.3.1 Clinical Outcomes of DBS in BD Treatment

DBS was initially developed to address medically intractable movement disorders such as tremors, Parkinson's disease, and dystonia, with established safety and efficacy dating back to 1963 [162]. Its inaugural application in psychiatry emerged in the mid-1990s, specifically targeting otherwise intractable obsessive-compulsive disorder (OCD). Notably, during DBS trials with OCD patients, mood enhancement was observed prior to the reduction of OCD symptoms. Since then, there has been significant interest in its investigational use for highly refractory depression [2].

The etiology of MDD is linked to overactivity in limbic-cortical brain regions. DBS has demonstrated the capacity to inhibit excessive stimulation and normalize activity in these areas, potentially alleviating MDD symptoms [163]. Other targets for DBS in depression treatment include the ventral capsule/ventral striatum (VC/Vs), nucleus accumbens (NAc), subcallosal cingulate gyrus (SCG), and medial forebrain bundle (MFB) [162].

Evidence suggests that DBS yields higher response rates compared to sham treatments in depressive disorders. A recent meta-analysis [164] incorporating data from 190 patients across nine studies indicated significantly higher response rates and reductions in mean depression scores for patients receiving active treatment versus sham.

In bipolar patients, available findings suggest efficacy in bipolar depression, even in treatment-resistant cases. A study by Ramasubbu et al. [165] compared long versus short pulse width subcallosal cingulate stimulation in a sample of 22 individuals, with three out of five treatment-resistant bipolar depression (TRBD) patients responding positively during the 6-month follow-up.

An open-label trial [166] explored the effects of DBS of the subcallosal cingulate (SCC DBS) for treating TRD in 10 MDD and 7 BD patients. After a 4-week sham stimulation cycle followed by active stimulation for 24 weeks, significant decreases in depression and improvements in function were noted. Response and remission rates were observed in varying proportions across different intervals of stimulation. Importantly, chronic DBS was well tolerated, with no spontaneous relapses among patients achieving remission.

Another open-label, long-term follow-up study [167] examined data from 28 patients with TRD (19 with MDD and 8 with bipolar II disorder) undergoing SCC DBS. Response and remission rates were sustained at $\geq 50\%$ and $\geq 30\%$, respectively, during years 2–8 of the follow-up period. Three-quarters of all participants met the treatment-response criteria for more than half of their duration in the study, with 21% of all patients showing continuous response to treatment from the first year onward. The procedure itself was generally safe and well tolerated, with no acute or chronic stimulation side effects.

To date, there are no published data on DBS efficacy in treating other bipolar disorder states, as these patients have largely been excluded from trials [2]. Current clinical indications for DBS use in depression require a confirmed diagnosis of MDD based on DSM-5 criteria, with bipolar disorder serving as an exclusion criterion [162].

No studies have explored the cognitive effects of DBS in bipolar disorder patients. Common adverse effects in MDD patients include incision pain, wound infection, headaches, and agitation [1]. Notably, focal stimulation of the subthalamic nucleus (STN), globus pallidus (GP), or VC/VS can precipitate hypomania or mania [2]. A review of DBS in bipolar disorders identified one patient experiencing two hypomanic episodes during treatment, which were resolved with treatment parameter adjustments [1].

39.5.4 Keypoints: MST, VNS, and DBS in BD

Keypoints: MST, VNS, and DBS in BD
Overall Potential of MST, VNS, and DBS
• MST, VNS, and DBS hold promise as treatment options for severe and treatment-resistant cases of depression • Further research is needed to fully understand their efficacy and long-term effects across diverse patient populations
Lack of Investigational Studies
• There is a deficiency in investigational studies regarding the effectiveness of these techniques, particularly in relation to other states of bipolar disorder such as mania, mixed states, and maintenance phases
MST
• MST offers a more targeted stimulation compared to ECT • Studies comparing ECT and MST in MDD have shown fewer subjective side effects with MST and comparable antidepressant responses • MST practice is currently limited to clinical research settings and follows established technical protocols similar to ECT
VNS
• VNS received FDA approval for TRD in 2005 but is not approved for BD
DBS
• Current clinical guidelines for DBS use require a confirmed diagnosis of MDD based on DSM-5 criteria, with BD as an exclusion criterion • There is a lack of data on DBS efficacy in treating other states of BD
Advantages and Limitations of DBS and VNS
• One advantage of DBS and VNS is optimal treatment adherence • DBS offers immediate effects, while VNS has a delayed onset, which may not be preferable for some patients • DBS and VNS can be combined with other treatments, including medication and ECT, but due to their invasive nature, they are limited to the most challenging-to-treat patients

39.6 Clinical Considerations

- Brain stimulation offers a comprehensive approach to managing all phases of BD, potentially reducing the need for multiple medications. It could address challenges in treating complex bipolar cases, especially in difficult-to-treat patients. During acute phases, brain stimulation can enhance pharmacological treatment, while in maintenance phases, it may help prevent further episodes.
- New brain stimulation protocols may also target cognitive dysfunction, addressing a current treatment gap.
- Larger randomized controlled trials with long-term follow-up are needed to clarify crucial questions regarding treatment efficacy, tolerability, frequency of treatment-emergent affective switches, and cognitive effects.
- Implantable methods like DBS and VNS require surgical procedures, limiting their availability and tolerance. DBS carries risks like electrode migration, malfunction, strokes, or infections, while VNS has a well-established safety profile but requires a longer time for therapeutic effects. Both techniques are best reserved for cases where other options have been exhausted.

39.7 Future Perspectives

- Refining treatment parameters is crucial in managing bipolar disorder. Optimal parameters, including electrode placement and stimulation goals, vary across different stages of the disorder and among patients. Tailoring treatment configurations to target specific brain alterations at each stage is essential for improving therapeutic outcomes.
- Segmentation based on diagnostic subtypes is essential due to limited insights into how individual patient characteristics affect treatment effectiveness and tolerability. Analyzing brain stimulation patterns within and across bipolar disorder subtypes is vital for customizing treatment strategies to meet each patient's unique needs.
- Continuation and maintenance studies are vital in bipolar disorder treatment. Despite evidence of benefits for some patients after mood symptom remission, treatment discontinuation is common. Comprehensive investigations into the benefits of continued treatment are needed to optimize long-term outcomes.
- Research into portable and accelerated treatment protocols is crucial for overcoming barriers to the widespread adoption of brain stimulation interventions. Reducing time requirements for treatment can improve accessibility and effectiveness.
- Standardizing adverse event reporting is important for evidence synthesis and quality assurance in bipolar disorder treatment. Systematically documenting treatment-induced affective changes and cognitive effects enables comprehensive evaluation of treatment modalities, driving advancements in clinical practice.

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Chapter 40

Machine Learning Techniques in Bipolar Disorder



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40.1 Introduction

Bipolar disorder constitutes a substantial public health burden on a global scale. According to the Institute for Health Metrics and Evaluation (IHME), the disorder afflicts approximately 2.4% of the world's population, with an additional 2.3% experiencing subclinical manifestations [1]. The World Health Organization (WHO) recognizes bipolar disorder as a leading cause of disability-adjusted life years (DALYs) specifically among young adults. Furthermore, suicide rates within this

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population group demonstrably surpass those of the general populace, reaching 7.8% for males and 4.9% for females [2].

Current understanding of bipolar disorder is limited by the inherent shortcomings of traditional statistical methods. While randomized controlled trials (RCTs) and meta-analyses, reliant on such methods, have successfully identified effective treatments like lamotrigine and quetiapine, they prioritize group-level averages at the expense of individual heterogeneity. This focus on central tendency and variance offers broad generalizations about patients with bipolar disorder in response to treatments but fails to capture the intricate variations within individual cases [3]. Notably, positive findings in these trials may not translate to real-world benefits for specific patients. Furthermore, the populations studied in RCTs often lack the real-world diversity observed in patients with bipolar disorder. The very characteristics that define many bipolar disorder cases, such as comorbidities, are frequently excluded from clinical trials, creating a disconnect between research and the complexities of managing bipolar subjects in clinical settings.

Achieving optimal management for bipolar disorder remains a complex endeavor. Many individuals endure a prolonged period of trial and error before identifying an effective treatment regimen. Unselected treatment approaches or those solely guided by existing guidelines frequently yield suboptimal outcomes, with approximately 60% of patients experiencing relapse into depression or mania within 2 years of treatment initiation [4, 5]. This highlights the need for more personalized treatment approaches and potentially the development of novel therapeutic strategies to improve the long-term management of bipolar disorder.

Implementing early intervention strategies holds the potential to transform the trajectory of bipolar disorder treatment, protecting patients from irreversible harm. Such harm includes cognitive impairment, particularly in areas such as attention and executive functioning; increased risk of suicidal behavior, damaged social and occupational functioning—often leading to job loss, strained relationships, and decreased social engagement, and even structural brain abnormalities, particularly in areas related to mood regulation, memory, and decision-making [6]. Thus, early identification and treatment are paramount in mitigating the progression of bipolar disorder, avoiding an increase in frequency and severity of mood episodes, while also preventing severe complications.

Therefore, there is a compelling need to refine diagnostic methods for bipolar disorder and ensure greater adherence to evidence-based treatment guidelines. By addressing these critical areas, we can significantly improve the lives of individuals living with bipolar disorder and alleviate the associated burden on individuals, families, and healthcare systems.

40.2 Definitions

40.2.1 *Big Data*

The exponential growth of information in recent years, driven by the emerging trend of pervasive data acquisition, has birthed a new scientific frontier: Big data. Beyond its immense volume, big data encompasses complex and diverse datasets that challenge traditional data processing methods. Big data is characterized by three key pillars: Volume, velocity, and variety [7]. While volume remains a defining feature, the speed at which data is generated (velocity) and the diversity of its formats (variety) are equally important.

Velocity captures the dynamic nature of this data universe. Unlike static archives, big data pulsates with life, reflecting the ever-evolving rhythm of our world. Stock prices fluctuate in real time, social media trends morph hourly, and sensor networks capture environmental shifts continuously. This necessitates specialized tools and techniques for the capture, storage, and analysis of this rapidly flowing data stream.

Variety shatters the boundaries of structured numerical data. Text, images, videos, social media interactions, and sensor readings represent just a fragment of the diverse data types that paint the diversity of big data. This multimodality demands flexible and adaptable analytical approaches to extract meaningful insights from this intricate complex ecosystem of information.

Moreover, *pervasive data acquisition* is gaining traction, involving the continuous and unobtrusive collection of data from various sources, such as wearable devices, social media, online behaviors, environmental sensors, and electronic health records. These methods could enable the collection of comprehensive health data, including sleep patterns, physical activity, medication adherence, social interactions, and online behavior.

Our understanding of big data is constantly expanding, with two crucial aspects receiving increased attention: Veracity and value [8]. *Veracity* acts as a cornerstone, ensuring the data we collect is trustworthy and reliable. This reliable foundation is essential for accurate analysis. *Value* builds upon veracity by highlighting the importance of integrating all the previously identified pillars of big data [9]. By taking this integrated approach, we can generate actionable insights that lead to significant improvements in treatment and monitoring protocols for patients. Ultimately, this focus on veracity and value translates to enhanced patient care, delivering tangible benefits for families, caregivers, and individuals struggling with bipolar disorder.

This broader understanding can empower healthcare professionals to personalize treatment plans and track patient progress. Big data analysis by machine learning techniques provides the means to move beyond group-level statistics into individual subject classification based on accuracy, sensitivity, specificity, and *area under the receiver operating characteristic (ROC) curve (AUROC)*. Notably, a confusion matrix can be used to visualize this classification performance, helping to identify potential biases and areas for improvement in the machine learning model. However,

the vast volume and complexity require specialized infrastructure and advanced computational tools for processing and analysis. Ensuring the *veracity* and *ethical use* of sensitive data demands rigorous quality control and adherence to privacy regulations. Yet, the potential rewards are immense. From personalized treatment plans and predicting disease outbreaks to improving drug development and resource allocation, big data holds the key to unlocking various advancements in healthcare.

40.2.2 Machine Learning

Machine learning, also known as pattern recognition, represents a range of computational techniques used to analyze complex data by identifying patterns of interaction among several variables. The use of these techniques has been increasing in the psychiatric field in the past years and may provide predictive models for clinical practice with the potential to improve diagnosis and treatment. Its algorithms rely on data to make predictions or decisions. Evaluating their effectiveness is crucial, and machine learning metrics serve as essential tools for this purpose. Choosing the right metrics, similar to selecting the appropriate tools for a specific task, is important for ensuring the success of your machine learning project. The study of machine learning can be broadly divided into three main approaches: Supervised, unsupervised, and reinforcement learning [10]. Each approach operates under distinct principles and utilizes unique sets of metrics for performance evaluation.

Supervised learning operates under the guidance of labeled data, where each data point comes with predefined inputs and their corresponding desired outputs. Imagine training a model to distinguish between bipolar disorder and patients with major depressive disorder. The model receives labeled data points featuring patient characteristics, mood measurements, and behavioral observations along with the corresponding diagnosis of either bipolar disorder or major depressive disorder. This labeled data allows the model to learn the underlying patterns and relationships within the data relevant to bipolar disorder and major depression disorder. In this scenario, metrics like accuracy, sensitivity, specificity, *F1-score*, *AUC-ROC curve*, and the *confusion matrix* become instrumental in assessing the model's ability to correctly identify between bipolar disorder and major depressive disorder in new, unseen patients. On the other hand, unsupervised learning delves into the field of unlabeled data, where data points lack predefined labels or categories. The objective here is to uncover hidden patterns or structures within the data itself. Picture analyzing patient self-reported symptoms and medication adherence data to identify groups of patients with similar clinical presentations or treatment responses. In this case, metrics like the silhouette coefficient and the *Calinski–Harabasz* index become crucial for evaluating the quality and effectiveness of the identified clusters, ensuring they are well-separated and clinically meaningful [11–14].

Reinforcement learning (RL), a branch of machine learning, holds promise for personalized mental healthcare. Imagine an RL system for bipolar disorder [15]. It would analyze user data (sleep, activity, and mood) to recommend real-time interventions. For example, the system could detect potential manic episodes and

suggest personalized preventative measures based on user preferences. Beyond early warnings, the system could adapt to the current mood, recommending mood management strategies such as calming activities for low moods or high-energy outlets for manic episodes. It could even promote treatment adherence by reminding users about medication and therapy [16]. This user-centric approach empowers individuals by fostering self-management and paving the way for future personalized healthcare solutions, bringing additional granularity to patient evaluation by providing precise and passive collection of data, yielding a more valid ecological model. Such an approach lays fertile ground for the development of more targeted interventions based on real-world patient experiences.

To facilitate practitioners’ understanding of the new terminology introduced in this field, a concise glossary of terms is provided in Table 40.1. Additionally, Table 40.2 outlines key considerations for conducting machine learning-based studies, while Table 40.3 displays evaluation metrics in machine learning. Figure 40.1 visually depicts the recommended workflow for a machine learning experiment.

Table 40.1 Important terms and their respective definitions

Term	Definition
Double dipping	Circular analysis of the test data set. The researcher uses the test data twice, overestimating the predictive power
Overfitting	Model too adjusted to the training set. This leads to problems of generalization
Underfitting	Model not well adjusted to the data. This usually implies that a more complex model is required
Feature selection	Selecting the most important predictors, either by domain experts or in a data-driven manner
Hyperparameter tuning	Model induction algorithms usually rely on hyperparameters. These are chosen by the user and can be optimized for better results
Kernel	Kernel is a way of computing the dot product of two vectors “x” and “y” in some (possibly very high dimensional) feature space. Kernel methods are a class of algorithms for pattern analysis, whose best-known member is the support vector machine
Internal validity	Validating results from different contexts. This shows that the model is able to handle other scenarios (different trials, institutions, and others)
External validity	Validating results from different contexts. This shows that the model is able to handle other scenarios (different trials, institutions, and others)
Multimodal data	Combining data from multiple heterogeneous sources. This includes combining text, audio, video, and others
Unstructured data	Data that do not follow a specific organization, such as text and images
Curse of dimensionality	When multiple features are present, separating data in the multidimensional space becomes easier. Consequently, overfitting data is a common occurrence
Holdout	Subset of the data that is kept away from the analysis for posterior testing
Cross-validation	Validation protocol that involves splitting data into k-folds to verify if the model is able to generalize from training
Bootstrap	Alternative validation protocol that creates multiple randomized subsets of training data

Table 40.2 Important points to be considered in machine-learning-based studies

Methodical feature	Considerations
Representativeness of the sample	Was the study truly representative of the target population heterogeneity or included a selected group of users?
In the case of supervised machine learning studies, the subjects in different groups are comparable based on the study design or analysis	Did the study control for the most important confounding factors?
Assessment of the outcome	Independent blind assessment, medical record, or self-report?
Machine learning approach	Was the machine learning algorithm used to analyze data clearly described and appropriate? Were metrics of performance presented?
Class imbalance	How did authors address the class imbalance problem?
Test dataset	Was the test dataset “unseen?”
Feature selection and hyperparameter tuning	Did the study describe both feature selection and hyperparameter tuning?
Missing data	Did the study describe how authors handled missing data, including if they were inputted or removed?

Table 40.3 Evaluation metrics for machine learning model performance

Term	Definition
F1-score	A harmonic mean of precision and recall, where precision is the proportion of true positives that are correctly identified as such, and recall is the proportion of all positive cases that are correctly identified
AUC-ROC curve	A plot of the true positive rate (TPR) against the false positive rate (FPR) at different thresholds of a binary classifier. The area under the curve (AUC) is a measure of the overall performance of the classifier
Confusion matrix	A table that shows the number of correct and incorrect classifications made by a classifier
Calinski–Harabsz index	A measure of the separation between clusters. A higher Calinski–Harabsz index indicates better separation

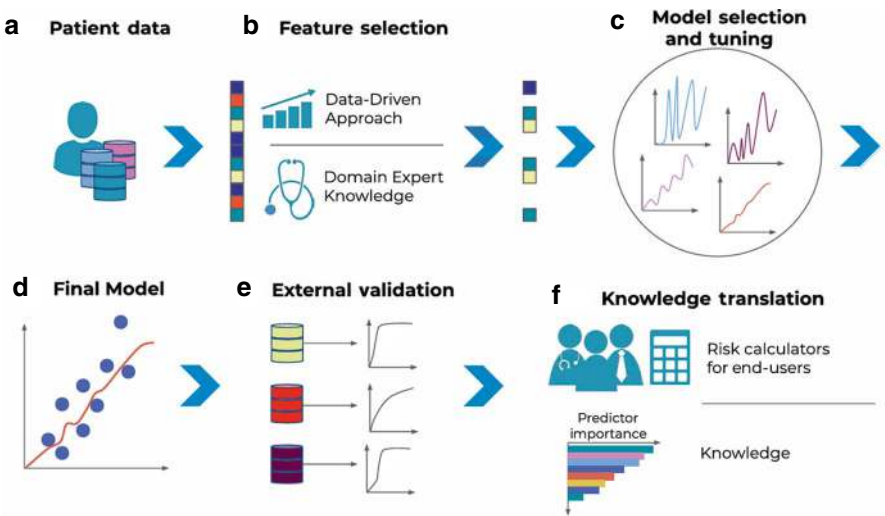


Fig. 40.1 Essential steps in building machine learning models. **(a) Data acquisition:** Patient data from diverse sources and biological levels are integrated. **(b) Feature selection:** To address the issue of data dimensionality, key features are chosen for further analysis through a twofold approach: data-driven selection via feature selection algorithms that automatically extract informative features, and hypothesis-driven selection where domain experts leverage their knowledge to identify relevant features for inclusion. **(c) Model generation:** Candidate models are created using the chosen algorithm. **(d) Model selection:** The best-performing model is chosen based on metrics like accuracy or ROC AUC. **(e) Model validation:** External data (ideally from different institutions) verifies the model’s generalizability. **(f) Knowledge translation:** Insights from the model are used to create practical tools like risk calculators (adapted from Passos IC, et al. (2019) [7])

40.3 How Will Machine Learning and Big Data Analytics Contribute to the Field of Bipolar Disorder?

This section delves into the promising world of machine learning and its potential to redefine bipolar disorder diagnosis. Recent research has highlighted the exciting applications of machine learning in this field, showcasing key studies that demonstrate the latest advancements and diverse methodologies in machine learning-based bipolar disorder diagnosis. Traditionally, statistical methods were the gold standard for assessing bipolar disorder data, despite their lack of precision in real-world scenarios [7]. In contrast, artificial intelligence provides a novel approach to improving diagnosis, developing individualized treatment options, and predicting clinical outcomes [17]. Below, we discuss the primary bipolar disorder-related topics that benefit from machine learning techniques.

40.3.1 *Diagnostic Studies*

Structural and functional neuroimages are promising and widely studied biomarkers for the diagnosis of psychiatric disorders, as recently shown in numerous scientific papers. A recent study applied support vector machine (SVM) to magnetic resonance imaging (MRI) for the identification of bipolar disorder in 44 bipolar patients and 36 healthy controls. Voxel-based morphometry (VBM), a data-driven and well-established technique for quantifying focal anatomical differences in the brain during the resting-state condition, was employed as the primary imaging analysis method [18]. The trained SVM algorithm could then diagnose bipolar disorder with an accuracy of 87.5% (95% CI: 72.5–95.3%), sensitivity of 86.4% (95% CI: 64.0–96.4%), and specificity of 88.9% (95% CI: 63.9–98.0%). These findings underscore the potential of neuroimaging biomarkers in psychiatric diagnosis.

Peripheral biomarkers consist of another favorable diagnostic feature developed with machine learning. A recent study by Fernandes et al. applied a probabilistic multi-domain data integration model to assess samples of peripheral blood of a total of 416 patients to predict diagnosis of bipolar disorder. Twenty-seven blood-based biomarkers and 19 cognitive biomarkers were selected for final analysis, resulting in a sensitivity of 88%, a specificity of 71%, and an AUC accuracy of 79.73% [19]. Another study from Wollenhaupt-Aguiar B et al. used machine learning techniques combined with peripheral biomarkers samples to differentiate patients with bipolar depression from patients with unipolar depression. The serum levels of interleukin-4, thiobarbituric acid reactive substances, and interleukin-10 accomplished to differentiate both disorders with a ROC curve of 0.69, with 0.62 sensitivity and 0.66 specificity [20]. Intriguingly, a Chinese study directly compared 80 depressed patients using graph theory and functional connectivity, two functional neuroimaging techniques, to explore a distinct approach for differentiating bipolar from unipolar depression using neuroimaging and clinical data. The bipolar group showed increased functional connectivity between the right mediodorsal thalamus, bilateral dorsolateral prefrontal cortex, and left ventromedial prefrontal cortex. This pattern distinguished the bipolar group from the unipolar group with an accuracy of 87.5% [21].

Considering multimodal approaches to bipolar disorder diagnosis, a study designed a machine learning algorithm for early identification of the disorder in young adults using a 22-year birth cohort. A total of 3748 subjects were assessed at birth and at 11, 15, 18, and 22 years of age. The algorithm was employed to predict bipolar disorder development by age 22 using data collected up to age 18. The model incorporating 18-year variables showed the best performance metrics, including an AUC of 0.82, balanced accuracy of 0.75, sensitivity of 0.72, and specificity of 0.77. Suicide risk, generalized anxiety disorder, parental physical abuse, and financial problems were key variables in bipolar disorder detection [22].

40.3.2 Prediction of Poor Clinical Outcomes

As a significant advancement, numerous studies have explored the application of machine learning techniques to comprehend suicidal tendencies, the recurrence of mood episodes, and challenges related to functional impairment. A study explored the relationship between suicide attempts and circulating biomarkers of intestinal permeability and systemic inflammation in patients with bipolar disorder and major depressive disorder with and without a history of attempting suicide [23]. Among the included patients were 137 with bipolar disorder and 168 with major depressive disorder, with 133 of them having previous suicidal attempts. They analyzed circulating levels of intestinal fatty acid binding protein (IFABP), calprotectin, apolipoprotein E (ApoE), lipopolysaccharides binding protein (LBP), lipopolysaccharides (LPS), soluble beta-2-microglobulin (B2m), and C-reactive protein (CPR). There was a significant association between higher levels of calprotectin and LBP comparing SA and NSA patients. Additionally, a lower level of IFABP was found in the SA group. The results suggest that a pro-inflammatory process at a systemic level and a dysregulation of the gut–brain axis may be a possible underlying factor in the physiopathology of mood disorders and suicide [23].

Interestingly, another study analyzed the feasibility of text classification to predict individual suicidal behavior using a machine learning algorithm applied to Virginia Woolf's diaries and letters. They compared 46 text entries from the 2 months before the writer's suicide with 54 random texts from other periods of her life. The model showed a balanced accuracy of 80.45%, sensitivity of 69%, and specificity of 91%. The Kappa statistic was 0.6, which means a good agreement and the p-value of the model was 0.003. The area under the ROC curve (AUROC) was 0.80. In other words, the model exhibited good performance when used for classifying Virginia Woolf's diaries and letters [24].

Impairment of occupational and cognitive performance is also frequently described clinical outcomes. In this context, a recent study developed a random forest model, a supervised machine learning algorithm, to predict such outcome using a Brazilian cohort. The sample consisted of 283 young adults with mood disorders between 18 and 24 years of age. The test AUC of the random forest model was 0.68, therefore demonstrating acceptable performance to predict functional impairment at the 5-year follow-up. Furthermore, the most important variables in predicting functional impairment were sexual abuse, severity of depression, anxiety, and somatic symptoms, physical neglect, emotional abuse, and physical abuse [25].

Another study used machine learning and functional neuroimaging techniques to predict suicidal behavior in 288 participants, including 75 with bipolar disorder and suicide attempts, 101 with bipolar disorder and no suicide attempts, and 112 healthy controls [26]. They have trained a two-level k-nearest neighbors (k-NN) model, a supervised algorithm not only used for classification or prediction of outcomes but also for mining medical imaging data, to assess a resting-state functional magnetic resonance imaging (rs-fMRI) to measure intrinsic brain activity of participants. A positive correlation between the brain activity in the right anterior cingulate cortex,

left thalamus, and right precuneus and the prevalence of suicide attempters were found, resulting in an accuracy of 83.52%, a sensitivity of 78.75%, and a specificity of 87.50%. The trained model was promisingly replicated in an independent cohort with 72.72% accuracy.

40.3.3 Selection of Treatment

Increasing evidence indicates that precision psychiatry is becoming a cornerstone of medical care. This approach ensures the precise prescription of medication, tailored to each patient's needs in terms of dosage and timing, particularly for those grappling with psychiatric disorders [27]. These models can be shown as easy-to-use calculators and integrated into electronic medical records systems for clinical use.

A study in the field of bipolar disorder that illustrates such a concept used transdiagnostic genetic and clinical data to predict lithium response in patients with bipolar disorder. Polygenic risk scores were also computed for schizophrenia and major depressive disorder, and then combined with clinical variables using a cross-validated machine learning regression approach. Unimodal, multimodal, and genetically stratified models were trained and validated using ridge, elastic net, and random forest regression on 692 patients with bipolar disorder from ten study sites. Moreover, all models were tested in a set of 342 patients. The best-performing non-linear model used only clinical variables and explained 8.1% of the variance in lithium response. A genomic stratification improved the model performance to 13.7% [28].

Under the same heading, another study developed a machine learning model to predict lithium responsiveness using clinical data from the largest existing sample of direct interview-based clinical data from lithium-treated patients, which consisted of 1266 individuals. The authors showed an AUC of 0.80 using a random forest model and 180 clinical predictors to classify treatment responsiveness. The most informative features to predict lithium responsiveness were completely episodic clinical course and proportion of life affected with primary insomnia, respectively [29].

40.3.4 Prediction of Transition to Bipolar Disorder

An increasingly significant area within the application of machine learning to psychiatric disorder assessment revolves around predicting transitions into disorders or unfavorable outcomes. Specifically in bipolar disorder, much of the scientific literature concentrates on forecasting suicidal tendencies and relapses in mood episodes. This study, encompassing 1022 subjects with bipolar disorder, was undertaken to discern the psychosocial factors correlated with the age at which bipolar disorder manifests (AAO). Employing the least absolute shrinkage and selection operator

(LASSO), a machine learning regression used to predict outcomes, they identified 28 factors to predict AAO. Six of them predicted an early AAO: childhood abuse, regular cannabis use in the year before onset, death of a close family friend or relative in the 6 months before onset, family history of suicide, schizotypal personality traits, and irritable temperament [30].

A longitudinal study analyzed functional brain activation in children and adolescents at familial risk for bipolar disorder to identify markers of prodromal mood disorders using standard event-related region-of-interest to compare brain activation at baseline between groups. The at-risk youth ($n = 115$) and the group-matched offspring of healthy parents ($n = 58$) underwent functional magnetic resonance while performing a continuous performance task with emotional and neutral distractors. At-risk youth presented with reduced activation to emotional distractors in the right ventrolateral prefrontal cortex at baseline ($p = 0.04$). The at-risk youth who developed their first mood episode during follow-up ($n = 17$) had increased activity in the right ventrolateral prefrontal cortex, right caudate, and right putamen [31].

40.3.5 Data Clustering Using Unsupervised and Semi-supervised Machine Learning

Psychiatric disorders, such as bipolar disorder, display considerable variability due to their diverse clinical manifestations, a phenomenon known as “clinical heterogeneity” [32]. Additionally, the underlying biological causes and environmental exposures of these disorders display considerable diversity, termed “biological heterogeneity” and “environmental heterogeneity” [7]. In this context, data clustering, an unsupervised machine learning method, plays an important role in digesting such heterogeneity by formulating unprecedented similar clinical groups and uncovering novel psychiatric phenotypes. By delimiting more consistent subgroups of psychiatric disorders the disease mechanisms may be better understood and the development of personalized treatments is made possible [32].

A study by Hofman et al. investigated the heterogeneous and overlapping nature of symptom endorsement across depressive, anxiety, and sleep–wake disorders using unsupervised machine learning approaches. By assessing a total of 43 symptoms in a sample of 6602 individuals, the cluster analysis curiously suggested a three-cluster solution named mixed symptoms, depressed affect, nervousness, troubled sleep, and interpersonal problems [33]. Another similar study by Kung et al. [34] identified five subtypes of clinical presentations of depression labeled based on the symptom distribution they presented: Psychotic, severe, mild, agitated, and anergic-apathetic demonstrating the potential of unsupervised learning to identify subgroups within mental health conditions based on patient-reported symptoms.

Notably, Yang et al. [35] and Price et al. [36] showcase the effectiveness of unsupervised classification in depression research, proposing its potential as an alternative to traditional norm-based approaches. While the former attempts to adjust

depression cutoff scores for diverse populations through machine learning-based classifications, the latter aims to assess the validity of traditional clinical diagnoses by employing an unsupervised algorithm to phenotype clustering based on symptoms of depressive and schizophrenic patients. These studies collectively underscore the growing importance of data clustering via unsupervised and semi-supervised machine learning for advancing our understanding and classification of mental health disorders, suggesting that unsupervised clustering of naturalistic data aligns with existing diagnostic constructs.

40.3.6 Digital Phenotyping and Quantum Computing

Data science and digital tools hold promise for faster, automated diagnosis via large-scale medical data analysis. Recently, the COVID-19 pandemic forced a rapid shift toward digital solutions, particularly for remote monitoring and virtual consultations. This accelerated exploration of digital tools opened new avenues for research, including leveraging machine learning and artificial intelligence to analyze vast datasets and support clinical decision-making.

Digital phenotyping is a growing field in mental health research and treatment. It analyzes the digital footprints we leave behind through our phones, wearables, and social media interactions. This vast amount of data offers a window into an individual's daily life, sleep patterns, activity levels, and even language use. Digital phenotyping has the potential to create a more patient-centered approach to mental health by analyzing a patient's digital traces to potentially enable earlier diagnoses and personalized interventions in mental health [37, 38].

However, significant challenges need to be addressed. Privacy concerns, overreliance on data, and the potential for algorithms to misinterpret information are all valid considerations. To maximize the effectiveness of digital phenotyping in mental healthcare, a critical step lies in optimizing the interplay between its data-driven insights and the irreplaceable role of human interaction and empathy.

Although machine learning paired with digital phenotyping offers a promising future for mental health, current algorithms struggle with the heterogeneity of mental health data, making it difficult to create generalizable models. In this context, quantum computing could present itself as a valuable tool for further exploration. Quantum machine learning leverages the unique properties of quantum mechanics to potentially unlock hidden correlations in data that are invisible to classical algorithms [39]. This could lead to breakthroughs in areas like suicide prediction, where current models, despite reaching area under the receiver operating characteristic curve (AUROCs) of 0.8, still face challenges due to data heterogeneity [40, 41]. Quantum machine learning possesses significant theoretical potential, though its practical benefits are still being evaluated. Researchers are actively exploring how to bridge the gap between classical data and quantum computation. This exciting field holds the promise of shaping the future of not only mental health research but also various other scientific endeavors.

40.4 Challenges and Ethical Issues

While machine learning offers exciting prospects for understanding and managing bipolar disorder, its path toward integration into clinical practice presents several significant obstacles and ethical considerations. This section explores the key challenges in developing and implementing machine learning models for bipolar disorder. We will examine issues like robust validation, computational limitations, integrating diverse data, and accurately analyzing rare events.

40.4.1 *Model Validation*

In the rapidly evolving field of machine learning, ensuring the validity and efficacy of developed models presents a crucial challenge. This requires careful consideration of both the changing nature of the data and the diverse factors involved in robust model validation.

During model training, two primary challenges can arise: Overfitting and underfitting. Overfitting occurs when the model becomes overly attuned to the specific characteristics of the training data. This can lead to excellent performance on that data, but poor performance on unseen data, hindering the model's generalizability. Underfitting, on the other hand, happens when the model is too simplistic and fails to capture the underlying relationships within the data. This results in suboptimal performance on both the training and unseen data. This challenge is often referred to as the bias-variance tradeoff. In essence, we aim to develop a model with sufficient variance to capture the intricacies of the data, particularly complex relationships. However, excessive variance can lead to overfitting. Therefore, optimizing the model requires a balance between bias and variance.

Moreover, overfitting not only hinders generalizability but can also lead to misleading conclusions about the data's underlying behavior. By focusing on specific features that may be unique to the training data, the model might identify misleading correlations and report them as novel findings. These findings are unlikely to replicate in new datasets, highlighting the importance of robust validation protocols. Several techniques exist to ensure model generalizability and prevent overfitting. These include bootstrapping, cross-validation, and holdout methods [42]. While the "gold standard" for validation is debatable, cross-validation is a common approach. It involves iteratively training the model on subsets of the data and evaluating its performance on unseen subsets. Finally, the holdout method provides the most robust form of external validation. Here, the data is split entirely into training and holdout sets. The model is trained solely on the training set, and its performance is evaluated on the completely unseen holdout set. Ideally, this holdout set should be collected independently from a new sample or even a different institution.

40.4.2 Computational Power and Quality of Data

There is a direct correlation between the volume of data and the quality of the resulting models. While larger datasets are generally desirable, they must be high-quality to generate reliable models. High-quality data allows models to learn from a wider range of variations, leading to better performance on unseen data (generalizability) and facilitating robust validation protocols, ultimately reducing the risk of overfitting. Although large sets of data are desired, acquiring such data can be expensive and logistically complex. The computational burden of analyzing large datasets imposes another obstacle. Even with sufficient data, performing proper feature selection and hyperparameter optimization becomes increasingly challenging as data size and complexity increase [43]. Interestingly, deep learning shows promise for analyzing various forms of unstructured data, including images, text, and video. However, a significant barrier lies in the computational demands of training deep learning models, particularly convolutional neural networks (CNNs), the main technique utilized for such data.

As mentioned earlier, ensuring the presence of high-quality data, effectively managing missing data, and employing a common set of instruments across various sites are critical measures. Furthermore, collaborative data sharing across institutions allows for the creation of larger, more robust, and consistent datasets. These practices promote data quality and comparability, allowing researchers to build reliable and generalizable models that can significantly advance our understanding and treatment of bipolar disorder.

Another important point that deserves attention is the assessment of rare events, such as suicide. Due to the statistical rarity of these events in short-term studies, even highly accurate models might perform poorly in risk stratification [44]. To address this limitation, researchers can employ resampling techniques during the training phase. These techniques essentially oversample rare events, providing the model with a more balanced representation of the data and potentially improving its ability to predict these critical outcomes.

40.4.3 Multimodality

The multifaceted nature of bipolar disorder requires a comprehensive modeling approach that captures its diverse aspects. Integrating diverse data sources, such as text, images, and sensor data, presents a unique challenge. Existing methods for combining such information might not fully capture the complex heterogeneity of bipolar disorder, potentially limiting the models' outcomes. Unlike traditional models, deep learning does not require predetermined features. This limitation often hinders traditional models from fully capturing the intricate relationships within complex and diverse data (multidimensional heterogeneity). Traditional models are

limited to analyzing data based on features hand-selected by researchers, potentially overlooking crucial hidden patterns or nuances.

Utilizing their ability to automatically extract complex data and nonlinear features directly from raw data, deep learning models offer an advantage in understanding hidden patterns and mechanisms underlying bipolar disorder. This comprehensive view of the underlying factors, exceeding the capabilities of traditional, feature-based approaches, can guide the development of more effective and personalized treatment strategies. Hence, deep learning holds great potential to improve patient outcomes and advance our understanding of bipolar disorder.

While deep learning excels at extracting complex patterns from raw data, it is susceptible to a phenomenon called domain shift. This occurs when the data distribution in real-world applications differs significantly from the training data. Imagine analyzing brain scans. For example, a deep learning model trained on scans from one MRI machine might struggle with scans from a different machine due to variations in protocols and equipment. This difference in data distribution can severely impact the model's performance. The shift becomes even more pronounced when switching modalities, such as moving from MRI to CT scans. In such cases, the model likely requires retraining to function effectively. To mitigate this challenge in clinical applications, researchers must ensure the data used for model deployment comes from a distribution similar to the training data. Deviations from this distribution can significantly compromise the model's predictive power.

40.4.4 Nonstationary Distribution of the Data

A critical challenge in developing reliable machine learning models for bipolar disorder lies in addressing nonstationary data distributions. This refers to situations where the underlying patterns within the data change over time, potentially rendering models built on past data inaccurate for future predictions. For instance, suppose a model was trained to predict suicide attempts in bipolar disorder patients based on their social media posts. Over time, language use and writing styles evolve, potentially altering the relationship between words and suicide risk. This dynamic nature of the data presents a significant hurdle, as the factors influencing the model's accuracy can be hidden and difficult to predict.

Similar challenges arise in various healthcare settings. Recent issues with accurately predicting COVID-19 mortality rates exemplify this, highlighting the vulnerability of machine learning models to sudden changes in data patterns [45, 46]. Such inaccuracies can significantly compromise informed decision-making in critical healthcare situations. Another well-documented case involved a model developed to predict flu epidemics. Initially performing well, it was later discovered to consistently overestimate flu prevalence in subsequent years. This phenomenon, known as data drift, highlights how even well-designed models can be misled by data that does not reflect reality [47].

Addressing nonstationary data distributions is crucial for building reliable and generalizable machine learning models in bipolar disorder research. By employing these strategies, we can increase the trustworthiness of predictions and ensure they remain relevant in the face of ever-changing data landscapes.

40.4.5 Heterogeneity and Phenomenological Assessment

The subjective nature of clinical diagnosis, coupled with potential inconsistencies between evaluators, introduces further complexity. Machine learning algorithms are trained on data used to build the models, and if that data itself is inconsistent or subjective, the resulting model may inherit those limitations. Additionally, bipolar disorder is a heterogeneous disorder, meaning its presentation varies greatly across individuals. Algorithms may struggle to capture this diverse spectrum effectively, potentially leading to inaccurate predictions for certain patients. Therefore, bipolar disorder's inherent heterogeneity presents an additional challenge. Machine learning algorithms typically excel at identifying patterns in large datasets composed of small, cumulative effects. While this might reflect the underlying nature of psychiatric disorders, it could also mask the nuances introduced by heterogeneity. In such a scenario, the algorithm might capture broad symptom clusters, potentially overlooking the unique presentations that define individual cases [48].

40.4.6 Funding Agencies and Lack of Interpretability

Limited funding and the “black box” nature of complex models present additional obstacles. Funding agencies need to recognize the potential of this research and provide adequate support, while researchers must strive to develop more interpretable models that offer insights beyond mere predictions. Explainable AI techniques and efforts toward demystifying model decision-making processes can play a crucial role in bridging this gap and fostering trust in these technologies among clinicians and patients alike.

However, a key challenge with complex models lies in their interpretability. While we may struggle to understand how intricate nonlinear models arrive at their predictions, their ability to model complex phenomena can outweigh the need for complete comprehension. In many clinical applications, complete transparency in the model's decision-making process might not be crucial for the clinician. The primary concern is often the model's effectiveness in predicting specific outcomes. While visualization and interpretability remain valuable, perhaps we should not be overly restricted by human pattern recognition limitations. Instead, we should embrace the potential for improved clinical practice through reliable and proven predictions.

Interestingly, the rise of cloud-based services like software as a service (SaaS) is fueling technological innovation and amplifying data-driven fields. The pay-as-you-go approach could mitigate the financial barrier for researchers, allowing them to access these tools on a project-by-project basis. Consider researchers “renting” computing power or storage for specific studies, bypassing massive infrastructure costs. Similarly, scalable cloud storage could house vast datasets securely, facilitating collaboration and accelerating research breakthroughs. This democratization of cutting-edge technology through cloud services holds immense promise for future psychiatric research.

40.5 Ethical Issues

While the potential of machine learning for bipolar disorder research is undeniable, its application raises critical ethical considerations that demand careful attention.

40.5.1 Data Privacy and Security

As machine learning relies heavily on personal data, ensuring patient privacy and security is crucial. Robust data protection measures and clear communication about data usage are essential to gain and maintain patient trust. Balancing the potential benefits of data sharing for research and development with individual privacy rights requires careful ethical considerations and robust legal frameworks [49].

40.5.2 Algorithmic Bias, Discrimination, and Psychosocial Harm

Algorithms trained on biased data can perpetuate existing inequalities. We need to critically evaluate datasets and algorithms for biases based on factors like gender, ethnicity, or socioeconomic status. Mitigating bias requires proactive measures during model development and ongoing monitoring of performance in diverse patient populations. Furthermore, even accurate predictions of future illness or risk can have unintended consequences. Concerns exist about potential discrimination based on such predictions, affecting access to insurance, employment, or social interactions. Additionally, knowing about future risks might negatively impact a patient’s well-being, leading to anxiety, stress, or even self-fulfilling prophecies. Careful consideration of both potential harms and benefits is necessary before implementing these technologies in clinical practice [50].

40.5.3 Data Lifecycle Management

Refers to a systematic approach, especially crucial in data-driven research, which ensures responsible data handling throughout its lifespan, from creation to secure destruction. Data Lifecycle Management (DLM) guarantees data security, compliance with regulations, and efficient utilization. In these fields, where massive datasets are common, DLM promotes cost-effectiveness by freeing up storage space through secure data destruction when no longer needed. This responsible data stewardship demonstrates a commitment to efficiency, potentially facilitating future research funding [51].

40.6 Conclusion

The high burden of bipolar disorder fuels the need for advanced methods for risk prediction, personalized treatment, and prognosis. This chapter explores how machine learning and big data analysis could revolutionize the field by offering personalized predictive models. Precision psychiatry, through tailoring treatments to individual patients, elevates their active role in managing their health, enabling patient-centered care approaches for complex and co-occurring conditions. However, limitations in data size and challenges with generalizability persist, requiring further validation. Overcoming obstacles requires increased investment in replication studies and applying machine learning across diverse research designs (trials, cohorts, and case-control). Collaborative networks with standardized data collection are crucial, and a shift from individual-focused research to a health systems approach is necessary. Additionally, standardizing devices used for symptom assessment remains a challenge. Despite these limitations, machine learning and big data offer a remarkable opportunity to study “real patients” in their complexities [52]. Universal healthcare systems harbor a vast repository of individual-level data, presenting a unique opportunity to develop novel diagnostic tools. Currently, we underutilize this information and the potential of analyzing its sequence and timing. Traditional statistical techniques struggle to capture the intricate details of bipolar disorder embedded within vast, complex datasets. The emergence of big data and machine learning offers a powerful analytical framework for real-time analysis of these intricate details, ultimately leading to a deeper understanding and potentially improved treatment options for bipolar disorder.

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Chapter 41

Lifestyle Prescription in Bipolar Disorder: A Systematic Review of Clinical Trials



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41.1 Introduction

There is a growing interest in the relationship between lifestyle behaviours, mental health, and psychiatric illnesses [1]. The modification of lifestyle behaviours aimed to treat and prevent these diseases is at the core of *Lifestyle Psychiatry* [2]. This new area of knowledge has focused mostly on depressive disorders and represents a promising horizon in clinical practice.

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Recent clinical practice guidelines, such as the Royal Australian New Zealand College of Psychiatrists (RANZCP) guidelines, establish a stepped approach in the management of depression, where healthy lifestyles represent a first step of “less intensive” interventions before moving to conventional treatments [3]. However, research interest in the role of healthy behaviours for the treatment of other psychiatric illnesses, such as bipolar disorder (BD), is comparatively lower. The present chapter aims to review the contemporary management of BD based on lifestyle-based interventions and help bridge that gap.

BD is a mood disorder characterized by the succession of depressive episodes that alternate with manic/hypomanic episodes in the same patient, along with periods of clinical remission or euthymia [4]. BD is associated with a higher prevalence of medical conditions and premature mortality [5]. Prevalence rates of metabolic syndrome, obesity, type 2 diabetes, and cardiovascular disease are higher among individuals with BD, contributing to a reduction of life expectancy by approximately 12–14 years [6].

Current evidence supports unhealthy lifestyle patterns in individuals with BD compared to healthy controls. For instance, around half of them develop alcohol, cannabis, or other substance use disorders during their lifetime [7], and rates of cigarette smoking are 3.5 times higher than the general population [8]. Moreover, sleep is not only impaired during mood episodes but can also be affected during interepisodic clinical stability [9]. Indeed, BD is associated with unhealthy sleep patterns, poor sleep quality, and disrupted circadian/sleep rhythms [1]. Moreover, patients with BD consume around 200 calories more than the general population [10] and qualitative differences in diet also exist, as patients consume more fats (especially saturated fats), carbohydrates, or sugars [11, 12]. People with BD remain sedentary for more than 10 h/day although adherence to physical activity guidelines is similar to that of the general population [13]. All these behaviours seem to contribute significantly to a higher risk for poor mental health and physical comorbidities, including metabolic syndrome, obesity, and cardiovascular disease.

Mood stabilizers represent the cornerstone of the pharmacological treatment of BD, and, psychological therapies, such as psychoeducation, family therapy, and functional remediation, are the other mainstream therapeutic approaches to BD [4]. However, response to standard treatments is often suboptimal in terms of achieving full clinical remission and functional recovery [14], and medications can increase the risk for cardiometabolic conditions [15]. Thus, new strategies that are effective and safe are warranted for managing BD. There is a growing trend in the use of

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healthy lifestyle behaviours to prevent and treat several mental diseases [1]. Indeed, several systematic reviews support the evidence-based use of specific nutrients, such as S-adenosyl methionine (SAMe), methyl folate, omega-3 polyunsaturated fatty acids (n-3 PUFA), and vitamin D add-on to antidepressant drugs to treat depressive symptoms in BD [16]. Another meta-review [17] found consistent evidence for using nutritional supplements in the adjuvant treatment of depression, e.g. n-3 PUFA. There is also evidence of the efficacy of N-acetylcysteine (NAC) as an adjuvant treatment in mood disorders and schizophrenia [17]. Regarding physical exercise, considerable empirical evidence supports the use of physical activity interventions in the treatment of mood and psychotic disorders [18]. However, other lifestyle behaviours exist beyond diet/nutrition and physical activity (PA).

According to scientific societies of lifestyle medicine, up to seven components can be considered healthy lifestyle behaviours [19]. In this sense, the first instrument that aligns with this definition and allows a comprehensive evaluation of these components has recently appeared. The SMILE-C (Short Multidimensional Inventory Lifestyle Evaluation) questionnaire [20] was developed specifically to enable a multidimensional assessment of the lifestyle of the general population during the COVID-19 pandemic. The SMILE-C comprises seven lifestyle domains: (1) Dietary and nutritional intervention or the use of nutritional supplements or nutraceutical products; (2) avoidance of substance use and abuse, including alcohol, tobacco, and other substances; (3) PA/exercise; (4) stress management strategies; (5) restorative sleep pattern; (6) social support; and (7) environmental exposures, such as exposure to sunlight and natural spaces or time spent engaged in digital devices (screen time). A multidimensional assessment with this scale revealed unhealthy lifestyle patterns in people with BD regardless of the polarity of their mood episodes [21].

Regarding BD, several studies show that cognitive behavioural therapy (CBT) focused on nutrition, physical exercise, and well-being is a feasible and acceptable intervention [22]. Moreover, an intervention to improve sleep and circadian functioning reduced the risk of relapse and improved sleep and overall functioning in people with BD [23]. However, other studies did not reach the same results and, thus it cannot be concluded that interventions based on lifestyle modification are beneficial for patients with BD. For instance, a meta-analysis supports the efficacy of n-3 PUFA to improve depressive, but not manic, symptoms [24].

Thus, clarifying the effectiveness of lifestyle-based clinical trials in BD seems relevant for clinical practice. If confirmed, it could be speculated that such interventions would reduce the costs associated with prescribed medications. The prescription of healthy lifestyles by no means suggests withdrawing the use of psychotropic drugs, which are the basis of BD treatment, but instead the likely reduction of unnecessary polypharmacy. As consistently demonstrated in other fields of medicine [25], the implementation of these interventions in clinical practice holds promise to benefit the management of physical comorbidities, especially cardiometabolic conditions. In addition, patients could experience less medication-related side effects. Accordingly, this systematic review of clinical trials of lifestyle-based interventions aims to examine whether current evidence supports the prescription of healthy lifestyle behaviours to individuals with BD.

41.2 Method

A literature search was conducted in two databases (PubMed and Web of Science), without year restrictions, until December 27, 2021. To that end, the criteria of the *preferred reporting items for systematic reviews and meta-analyses* (PRISMA) statement [26] were followed.

To identify candidate studies, the following string of keywords was used: *Bipolar disorder, manic depression cross-referenced with dietary intervention, nutritional intervention, nutritional supplementation, nutraceutical, nutrient, healthy diet, substance use, smoking cessation, alcohol avoidance, drug avoidance, exercise, fitness, aerobic exercise, anaerobic exercise, stretching, strength training, sleep pattern, sleep intervention, sleep hygiene, sleep quality, insomnia, social support, social network, social interaction, stress management, sunlight exposure, blue space, natural environment, green space, screen time, physical activity, exercise therapy, diet therapy, lifestyle intervention, and lifestyle treatment.*

The inclusion criteria were: (a) Studies published in English, (b) clinical trials, and (c) clinical samples consisting only of participants diagnosed with BD based on Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria; (d) studies evaluating the effects of at least one lifestyle behaviour (diet and nutrition, substance use, physical activity, stress management strategies, restorative sleep, social support, and environmental exposures) in mental and physical health outcomes.

We excluded studies that: (a) Were animal studies, (b) grey literature (conference communications and theses), (c) studies without original data (reviews, meta-analyses, editorials, and expert opinions), (d) patients without a DSM/ICD-based diagnosis, (e) observational studies (case-controls, cohorts, and case series), (f) clinical trial protocols, (g) studies that do not assess any healthy lifestyle behaviour, and (h) studies with mixed samples composed of several diseases without providing separate results for patients with BD. No specific criteria applied to the format of the control arms were established. We decided to exclude trials with medications for the treatment of insomnia or addictions, including drugs for smoking cessation, considering that they are not properly “healthy lifestyle” interventions.

Once the records were obtained, the Rayyan bibliographic reference manager (<https://www.rayyan.ai>) was used to proceed with the article selection process. First, duplicate results were eliminated. Next, titles and abstracts of the articles were screened and, for cases without the required information, full-text publications were reviewed. The entire process was carried out by two reviewers independently and blind to each other. Further details of the search strategy are presented in the flow-chart (Fig. 41.1).

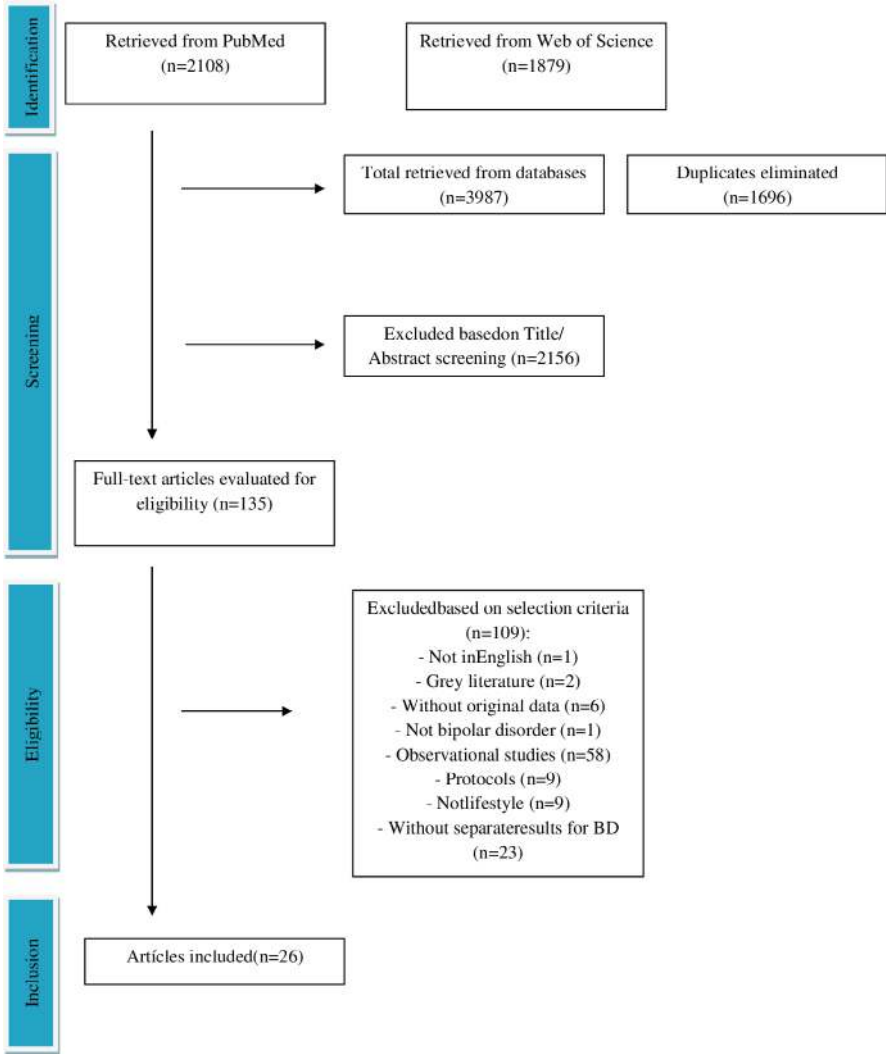


Fig. 41.1 Flowchart of study selection

41.3 Results

A total of 3987 records were identified in the databases (2108 in PubMed and 1879 in Web of Science) as potential studies to be included (Fig. 41.1). Only 26 studies met the selection criteria for this review. The major characteristics of these studies, based on *population, intervention, comparison, outcome, and study design* (PICOS), are presented in Table 41.1, ordered by the appearance in the text below, e.g. lifestyle domains.

Table 41.1 Characteristics of the studies included in the review, sorted by lifestyle domains

Trial (reference)	Population	Intervention	Comparison	Main findings	Type of study
<i>Diet/nutrition</i>					
Kaplan et al., 2001 [27]	n=11; 29.4 (10.7) years	Formulation of vitamins and minerals in capsules (32 capsules daily, divided into four doses) 21 months	No control group	– Reduction of symptoms (HAM-D, BPRS, YMRS) – Reduced need for psychotropic medication – Side effects: nausea (infrequent and transient)	Open trial
Saunders et al., 2021 [28]	Hypomanic (CARS-M ≥ 7) or depressive (MADRS ≥ 6) symptoms in the past month Diet high in n-3 fatty acids and low in n-6 (H3-L6): n=41; 42.7 (13.7) years Control diet: n=41; 44.3 (14.2) years	Diet high in EPA n-3 + DHA (1500 mg/day) and low in LA n-6 (2% energy) 48 weeks	Control diet standardized to the usual American distribution of EPA n-3 + DHA (150 mg/day) and LA n-6 (7% energy)	– H3-L6 >control: reduction in variability of mood, energy, irritability, and pain – The effect of dietary intervention targeting PUFA differed by group over time	RCT
Bernardo et al., 2009 [29]	At least one documented episode of illness (depression, mania, or mixed) in the previous 6 months NAC: n=38; 2 g/day NAC, 44.6 (11.2) years Placebo: n=37; 46.6 (13.8) years	2 g/day of N-acetylcysteine 6 months	Placebo group with inactive product	– No differences for changes in alcohol and tobacco – Decrease in caffeine use in participants treated with NAC at week 2; no differences over subsequent weeks	RCT

Berk et al., 2019 [30]	Current acute depressive episode (MADRS ≥ 20) NAC: n=52: 2000 mg/day NAC, 44.9 (12.5) years CT: n=47: 2000 mg/day NAC + combination nutraceutical therapy, 46.3 (12.7) years Placebo: n=49: 45.4 (11.9) years	NAC: 2000 mg/day N-acetylcysteine CT: 2000 mg N-acetylcysteine + 1000 mg acetyl L-carnitine + 200 mg ubiquinone + 64 mg magnesium + 200 mg ascorbic acid + vitamin D3 250 IU + vitamin E 50 IU + alpha lipoic acid 150 mg + vitamin A 3000 IU + biotin 600 µg + thiamine 100 mg + riboflavin 100 mg + nicotinamide 200 mg + calcium pantothenate 100 mg + pyridoxine hydrochloride 100 mg + folic acid 800 µg + cyanocobalamin 800 µg 20 weeks	Placebo group with inactive product	- No differences between groups (week 16) - Improvement in MADRS, BDRS, SOFAS and LIFE-RIFT: CT $\geq$ placebo (week 20) - CGI: CT $\leq$ placebo (week 20) - Gastrointestinal symptoms: NAC $\geq$ placebo	RCT
Toniolo et al., 2017 [31]	Current depressive episode according to DSM-IV and MADRS ≥ 20 Creatine: n=9: 43.4 (8.4) years Placebo: n=9: 44.1 (10.7) years Subanalysis of Toniolo et al., 2019	6 g/day creatine monohydrate 6 weeks	Placebo group with 6 g/day of cornstarch	- Creatine group improved in verbal fluency performance - No significant differences in the remaining neuropsychological tests	RCT

(continued)

Table 41.1 (continued)

Trial (reference)	Population	Intervention	Comparison	Main findings	Type of study
Toniolo et al., 2019 [32]	Current depressive episode according to DSM-IV and MADRS ≥ 20 Creatine: n=16: 44.5 (8.4) years Placebo: n=11: 43.0 (10.2) years	6 g/day creatine monohydrate 6 weeks	Placebo group with 6 g/day of cornstarch	- No significant differences in MADRS - Clinical remission (MADRS ≤ 12) was higher with creatine - Two patients in creatine group switched to mania early - No clinically relevant side effects	RCT
<i>Sleep</i>					
Esaki et al., 2020 [33]	Clinical remission Orange glasses (BB): n=21: 44.1 (11.8) years Placebo: n=22: 41.1 (10.4) years	Use of glasses that block blue light, from 20:00 until bedtime 3 weeks	Placebo group with clear lens glasses	- No differences in sleep quality, actigraphy parameters and mood symptoms - MEQ changed to advanced pace in the BB group and to delayed pace in placebo group	RCT
Phelps, 2008 [34]	n=21	Wearing glasses with amber-tinted lenses to block blue light, from 8 pm until bedtime	No control group	- More than half of participants responded (CGI) - Two participants discontinued wearing the glasses in less than 5 days because they made them fall asleep earlier than desired - Most people relapsed if they stopped wearing glasses (self-reported sleep pattern) - Some patients were able to eliminate or reduce medication	Open trial

Sit et al., 2018 [35]	Current moderate or severe episode of major depression (SIGH-ADS ≥ 20); no hypomania or mixed symptoms (MRS ≤ 4) Bright white light: n=23; 45.7 (14.3) years Red placebo light: n=23; 43.7 (15.0) years	Daily light therapy sessions between 12.00 pm and 14.30 pm with bright white light of 7000 lux 6 weeks	Placebo group with daily light therapy sessions between 12.00 pm and 14.30 pm with 50 lux dim red light	Bright white light: higher remission rates, and lower scores on depression scales – Improved sleep quality in both groups	RCT
Harvey et al., 2015 [23]	Euthymia (YMRS ≤ 12 , IDS-C ≤ 24) CBTI-BP: n=30; 37.7 (12.4) years Psychoeducation: n=28; 35.5 (9.3) years	CBTI-BP: Sessions focused on case formulation, goal setting, motivational interviewing, sleep education, behavioural module, cognitive module, module to improve daily functioning and relapse prevention 6 months	Psychoeducation: Information is provided but does not facilitate or plan a behavioural change	CBTI-BP: Fewer days of bipolar episode, lower rate of relapse of mania and mood disorders, as well as a reduction of insomnia severity and higher rates of post-treatment insomnia remission Both groups improved in sleep measures and functional impairment	Pilot RCT
Kaplan et al., 2013 [36]	Euthymia (absence of current diagnosis of mania/hypomania and depression, according to DSM-IV and confirmed with a score ≤ 24 in IDS-C and ≤ 12 in YMRS) n=15; 38.1 (11.5) years	CBTI, with stimulus control and sleep restriction 8 weeks	No control group	– Decrease in severity of self-reported insomnia – Improvement in sleep efficiency through sleep diary (not significant)	Open trial

(continued)

Table 41.1 (continued)

Trial (reference)	Population	Intervention	Comparison	Main findings	Type of study
Kaplan et al., 2018 [37]	Euthymia (IDS-C $\leq$ 24, YMRS $\leq$ 12) RISE-UP; a modified CBTI-BP: n=20; 39.3 (14.2) years Psychoeducation: n=20; 35.4 (8.9) years	CBTI-BP: RISE-UP routine-based cognitive behavioural therapy (refrain from dozing, increase activity in the first hour, shower or wash face and hands with cold water, exposure to sunlight, upbeat music, call a friend) 8 weeks	General psychoeducation on sleep and BD without emphasis on behavioural change	– RISE-UP: Reduction of duration and severity of sleep inertia, high compliance, and increase in morning activity levels – Acceptable and credible (both groups)	Pilot RCT
Sylvia et al., 2014 [38]	Clinical remission n=8; 42.3 (14.4) years	– Two 60-min sessions of psychosocial sleep intervention – Use of a sleep monitoring device (M1) at home 4 weeks	No control group	– M1 and sleep intervention were feasible and well tolerated – Improvement in sleep duration, but more unstable measured with M1 – Improvement in self-reported sleepiness, sleep quality and mood symptoms – M1 is feasible to obtain objective sleep quality and quantity data	Open trial

Sylvia et al., 2021 [39]	n=13: 34.8 (9.9) years	- Four 60-min sessions of CBT for sleep disturbance - Use of a sleep monitoring device (M1) at home 4 weeks	No control group	- High feasibility and acceptability of intervention - After the intervention, participants were more likely to recommend it to others - M1 was easy to understand and use, and did not interfere with participants' sleep - Reduction in suicidal ideation and depressive symptoms (Nonsignificant) improvements in stable sleep percentage and total sleep duration	Pilot trial
<i>Substance use</i>					
Weiss et al., 2007 [40]	Clinical remission IGT: n=31 Group drug counselling (control group): n=31 41.9 (10.9) years	IGT: 20 weekly 1-h meetings, employing a CBT of relapse prevention, that integrates the treatment of the two disorders focusing on the similarities between the recovery and relapse processes in BD and substance use disorder 32 weeks	Group drug counselling: 20 weekly 1-h sessions to approximate treatment provided in community substance abuse treatment programmes. It is focused on substance use only	- Fewer days of substance use in IGT - No group difference in time sick	RCT
Weiss et al., 2009 [41]	Clinical remission IGT: n=31 Group drug counselling (control group): n=30 38.3 (11.1) years	IGT: 12 weekly 1-h sessions 6 months	Group drug counselling: 12 weekly 1-h sessions	- Greater reduction in substance use and risks of mood episodes in IGT - Greater tendency to achieve total abstinence in IGT - Greater tendency to achieve a "good clinical outcome" in IGT	RCT

(continued)

Table 41.1 (continued)

Trial (reference)	Population	Intervention	Comparison	Main findings	Type of study
Goldstein et al., 2014 [42]	At least 1 week of depressive or hypomanic symptoms in the previous 3 months, without complete recovery (8 continuous weeks of remission) n=10: 16.9 years	21 FFT sessions for adolescents, with three modules: psychoeducation, training in improving communication, and problem solving 12 months	No control group	– 6 subjects completed half of the treatment – Reduction in manic and depressive symptoms – Improvement in overall functioning	Open trial
Wenze et al., 2015 [43]	Integrated Treatment Adherence Programme (ITAP): n=14: 47.29 (10.83) years Enhanced Evaluation and Monitoring (EAM): n=16: 46.50 (11.03) years	ITAP: A cognitive behavioural approach that seeks to promote a successful transition from acute care to maintenance treatment 6 months	EAM: A battery of self-reported and graded assessments was administered by interviewers and, based on this information, short feedback letters were sent to them	– ITAP > EAM: improvements in depression, mania, functionality, value-based living, and adherence to treatment	Pilot RCT
Biseul et al., 2017 [44]	n=6: 52.5 (16.3) years	2-h 14 sessions, with a first module (6 sessions) of psychoeducation (IGT), followed by a second module (8 sessions) meditation sessions of relapse prevention therapy based on meditation (MBRP)	No control group	– Improvements in mood, especially depressive symptoms, during the first module – Significant clinical improvement in alcohol and substance use in one-half of participants – 75% of participants reported high levels of satisfaction with group therapy	Pilot trial

Heffner et al., 2020 [45]	Clinical remission ACT-based WebQuit Plus: n=25: 47.7 (10.4) years Smokefree.gov : n=26: 50.2 (11.3) years	WebQuit Plus: Program that helps users plan to quit smoking, develop awareness of smoking triggers, develop acceptance-based coping skills to manage triggers, identify personal values, and self-compassion to endure long-term abstinence. All participants received nicotine patch for 8 weeks. 14 weeks	Smokefree.gov : Multimedia website that includes guidance on setting quit date and preparation, identifying triggers, and staying motivated, interactive content, information on the health effects of tobacco. All participants received nicotine patch for 8 weeks	- No differences in satisfaction between groups - Average number of logins was double for WebQuit Plus - The usefulness of the program skills was higher for WebQuit Plus - Similar abstinence rates at follow-up in both groups	Pilot RCT
<i>Multimodal lifestyle</i>					
Gillhoff et al., 2010 [46]	Control group: n=24: 48.9 (12.0) years Multimodal lifestyle intervention group: n=26: 48.1 (11.5) years	11 group sessions, based on the “Quality of life for people with bipolar disorder” programme, covering healthy lifestyles (weight control and relapse prevention), balanced nutrition, and promotion of weekly physical activity 11 months	Control group (TAU)	- BMI reduction (among female patients only) - No differences in cardiovascular and metabolic parameters	RCT

(continued)

Table 41.1 (continued)

Trial (reference)	Population	Intervention	Comparison	Main findings	Type of study
Goracci et al., 2016 [47]	Clinical remission Healthy lifestyle intervention group (HLI): n=81: 49.45 (12.65) years Control group: n=79: 48.80 (11.53) years	Individual sessions conducted by psychiatrists and dietitians focused on the importance of balance in life, psychoeducation in mood disorders, social rhythm hygiene, sleep hygiene, energy balance, physical exercise, nutritional education, eating and drinking behaviour, losing weight with physical exercise, poor eating habits and sedentary life, damage caused by tobacco, ways to quit smoking 15 months	Control group (TAU)	– HLI> control: lower risk of relapse, greater improvement in CGI, and reduction in PHQ-9 and ESS – HLI > control: greater reduction of weight, BMI and waist circumference – No differences in sleep quality	RCT

Sylvia et al., 2011 [48]	Group 1: n=4: 60.0 (6.7) years Group 2: n=6: 50.2 (10.2) years	– 12 sessions of 1 h during 14 weeks of NEW Tx consisting of three modules: Nutrition/weight loss (nutritional psychoeducation and instructing participants in healthy food choices and portion control), exercise (aimed to increase the level of physical activity in daily life), and wellness (making healthy choices). – After group 1 completed the sessions, the treatment was reviewed, and modifications were made for group 2 28 weeks	No control group	– The two groups added more than 100 min/week of exercise compared to pre-treatment – Group 2 improved quality of life, depressive symptoms, and weight	Pilot trial
Sylvia et al., 2013 [22]	Symptomatic patients (CGI-BP ≥ 3) n=5: 44 (16) years	18 sessions (in 20 weeks) of CBT based on three modules: nutrition, exercise, and wellness 20 weeks	No control group	– Reduction in weight, cholesterol, triglycerides, calories/day, and sugar/day – Improvement of depressive symptoms and functionality – Tripled weekly exercise duration	Pilot trial

(continued)

Table 41.1 (continued)

Trial (reference)	Population	Intervention	Comparison	Main findings	Type of study
Sylvia et al., 2019 [49]	Symptomatic patients (CGI-BP ≥ 3) Nutrition, exercise, and wellness treatment (NEW Tx): n=19; 39.7 (12.5) years Control treatment: n=19; 44.3 (11.9) years	18 sessions, over 20 weeks, of CBT based on three modules (nutrition, exercise, and well-being) 20 weeks	Control group (TAU)	- NEW Tx group: increased weekly exercise duration and overall functionality, and reduced severity of illness and depression - Only the improvements in functionality were significantly greater in group NEW Tx group vs control - No differences between groups in weight loss or mood symptoms	Pilot RCT
Sylvia et al., 2019 [50]	Same sample as in ref. 49	18 sessions, over 20 weeks, of CBT based on three modules (nutrition, exercise, and well-being) 20 weeks	Control group (TAU)	- No significant differences in dropout rates - Moderate-high satisfaction in NEW Tx - Expectations of NEW Tx at baseline as well as manic symptoms at baseline predicted post-treatment satisfaction - NEW Tx is a feasible and acceptable intervention for individuals with BD	Pilot RCT

Abbreviations: *BD* bipolar disorder, *BDRS* bipolar depression rating scale, *BMI* body mass index, *BPRS* brief psychiatric rating scale, *CARS-M* clinician-administered rating scale for mania, *CBTL-BP* cognitive behavioural therapy for insomnia, *CGI* clinical global impression, *CGI-BP* clinical global impression-bipolar disorder, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *ESS* Epworth sleepiness scale, *FFT* family-focused therapy, *HAM-D* Hamilton depression rating scale, *IDS-C* inventory for depressive symptomatology-clinician-rated, *IGT* integrated group therapy, *LA* linoleic acid, *LIFE-RIFT* longitudinal interval follow-up evaluation-range of impaired functioning tool, *MADRS* Montgomery Asberg depression rating scale, *MBRP* mindfulness-based relapse prevention, *MEQ* morningness-eveningness questionnaire, *MRS* Mania rating scale, *NEW* nutrition, wellness, and exercise, *PHQ-9* patient health questionnaire-9, *PUFA* polyunsaturated fatty acids, *RCT* randomized clinical trial, *SIGH-ADS* structured interview guide for the Hamilton depression rating scale with atypical depression supplement, *SOFAS* social and occupational functioning assessment scale, *TAU* treatment as usual, *YMRS* Young Mania rating scale

The total number of participants included in this review was 1070: 640 patients with BD and 430 controls. Sample sizes of the individual studies ranged from 5 (patients only) to 160 participants (patients + controls). The average age of samples ranged from 16.9 to 60 years. Regarding the clinical status of patients, in nine studies the participants were in remission, in three they met euthymia criteria, in another ten they were symptomatic (depressive episode in four studies and depressive or manic episode in six studies), whereas it was not detailed in the remaining trials. In terms of study design, 17 were randomized clinical trials (RCT). The duration of the intervention ranged from 3 to 86 weeks. In none of the studies included in this review the lifestyle intervention was used as monotherapy, but add-on to the usual treatment of patients.

The main results of interventions in each lifestyle behaviour are presented in this section (for further details, see Table 41.1). Six *diet and nutrition* interventions were identified [27–32]. In an open-label clinical trial with 11 participants with BD, and no control group, Kaplan et al. (2001) aimed to assess the efficacy of supplements with micronutrients (vitamins and minerals) in mood stabilization. At the endpoint, manic and depressive symptoms improved significantly, and the number of psychotropic drugs was reduced [27].

In a 12-week RCT, Saunders et al. (2021) randomized patients with hypomanic or depressive symptoms to receive two types of diets—an intervention diet high in omega-3 eicosapentaenoic acid (EPA) and low in omega-6 polyunsaturated fatty acids (PUFA) and a control diet, standardized to the usual American distribution of EPA. The intervention was associated with significantly higher mood stability, and decreased irritability, and pain at a 48-week follow-up [28].

Two trials conducted by the same researchers tested the efficacy of N-acetylcysteine (NAC) [29, 30], a precursor to glutathione involved in the antioxidant system. Bernardo et al. (2009) examined the effect of 2 g of NAC daily on substance use in 75 patients with at least one affective episode in the previous 6 months. Supplementation with NAC was associated with a lower caffeine intake in the second week of treatment only, with no significant effect on other substances [29]. In a subsequent RCT conducted on bipolar depression, Berk et al. (2019) examined the efficacy of NAC monotherapy versus NAC combined with nutraceutical treatment (CT) that can act as a mitochondrial modulator. Compared to placebo, supplementation with NAC plus CT was associated with significant improvements in depressive symptoms and secondary variables like disease severity, and social and occupational functioning 4 weeks after the intervention, but not at week 16 [30].

Toniolo et al. [31, 32] conducted a 6-week clinical trial with add-on treatment with creatine monohydrate, which is considered a mitochondrial modulator that can restore brain bioenergetics. Twenty-seven participants with bipolar depression were randomized to receive creatine or placebo. No significant differences were found in the reduction of depressive symptoms, but a higher proportion of patients treated with creatine reached clinical remission [32]. In a subanalysis, creatine was associated with a significant improvement in verbal fluency, but not in the other 15 cognitive variables analysed [31].

Eight studies focused on *sleep patterns* [23, 33–39]. So far, interventions aimed at improving sleep quality are based on blue light-blocking glasses, light therapies, and CBT for insomnia. Two studies assessed the efficacy of blue light-blocking glasses [33, 34]. Esaki et al. (2020) randomized remitted BD patients and comorbid insomnia to wear such glasses or clear glasses (placebo) over 2 weeks. No differences were observed in sleep quality, sleep actigraphy parameters, and mood symptoms. However, a shift towards a morning-preference circadian rhythm was associated with the intervention, whereas a shift towards a more evening-type circadian rhythm was observed in controls [33]. In an open-label clinical trial, without a control group, Phelps et al. (2008) assessed 21 individuals with BD and comorbid insomnia using blue light-blocking glasses with amber-tinted lenses. More than half of the patients showed a clinical improvement of insomnia, and most participants relapsed after stopped using the glasses. However objective measures of sleep, such as actigraphy, were not used in that study [34].

Sit et al. (2018) assessed the efficacy of adjuvant light therapy for bipolar depression in another RCT. The intervention group received a bright white light of 7000 lux, while the placebo group received a dim red light of 50 lux. Higher rates of clinical remission and lower scores on depression scales were observed in the former group. Sleep quality improved in both groups to a similar degree [35].

Three studies found that behavioural interventions could be an attractive option for addressing the high rates of sleep problems in BD patients [23, 36, 37]. Harvey et al. (2015) compared the efficacy of cognitive behavioural therapy for insomnia (CBTI-BP) and psychoeducation to improve euthymic patients' mood symptoms, sleep quality, and functionality. CBTI-BP was associated with reductions in episode duration, as well as lower rates of relapse in a manic episode and mood alterations. The CBTI-BP group also had a significant reduction in insomnia severity and higher rates of insomnia remission [23]. Kaplan et al. (2013) examined the efficacy of CBT for insomnia (CBT-I), along with sleep restriction and stimulus control, during euthymia. Severity of insomnia significantly decreased, and sleep efficiency showed a trend of improvement. However, this study lacked a control group [36]. In another 8-week RCT, Kaplan et al. (2018), euthymic participants were randomized to RISE-UP therapy (see Table 41.1) and psychoeducation on sleep. The RISE-UP group showed a reduction in the duration and severity of sleep inertia, higher compliance, and an increase in morning activity levels [37].

Sylvia et al. [38, 39] conducted two trials without a control group, evaluating the effectiveness of a psychosocial sleep intervention and an electrocardiogram-based sleep monitoring device. Sleep duration, self-reported sleepiness, sleep quality, and mood symptoms significantly improved [38]. Moreover, suicidal ideation and depressive symptoms were reduced through improvement in sleep quality and duration [39]. Both interventions showed adequate feasibility and acceptability [39].

Six studies focused on *substance use* behaviours associated with BD [40–45]. Weiss et al. (2007) randomized remitted participants to receive integrated group therapy (IGT) or group counselling on drugs (Table 41.1). The number of weeks

with mood symptoms was similar between the two groups, but days of substance use were significantly reduced in the IGT group [40]. Later, these authors tested the efficacy of a shortened version of IGT. Higher rates of reduction in substance use as well as a lower risk for mood relapses were associated with IGT compared to group drug counselling. A trend to achieve total abstinence was also observed in the IGT group [41].

In the only study focused on a specific age group, Goldstein et al. (2014) examined the development and feasibility of a family-focused therapy (FFT) for adolescents with BD without full recovery in the previous 3 months and substance use. A significant reduction in manic and especially depressive symptoms, as well as an improvement in patients' overall functioning, was observed. Regarding substance use, a modest, nonsignificant reduction in cannabis use was found [42].

Moreover, Wenze et al. (2015) randomized 30 dual patients to an 'integrated treatment adherence program' or improved assessment and follow-up. The former group experienced greater and faster improvements in symptoms of depression, mania, and functioning. This trial established the feasibility, acceptability, and preliminary evidence of the efficacy of the intervention during the transition from inpatient to outpatient care [43].

In a small study, without a control group, Biseul et al. (2017) tested HABIT, which is an integrated group therapy, for BD comorbid with SUD. Significant improvements in mood symptoms were found, with a greater reduction in depressive symptoms during the first module. Half of the participants improved their tobacco and alcohol consumption [44].

In another RCT, Heffner et al. (2020) assessed a web-based intervention for smokers with BD, based on acceptance and commitment therapy (ACT). Patients were intervened with either an ACT-based therapy called "WebQuitPlus" or "Smokefree.gov" (Table 41.1). In addition, all individuals received nicotine patches for 8 weeks. No significant differences were found between groups in retention rates and abstinence rates, although the average number of logins was double for "WebQuit Plus". Moreover, the usefulness of the program's skills was also greater for "WebQuit Plus" [45].

Finally, six studies were *multimodal lifestyle interventions* [22, 46–50]. In an RCT, Gillhoff et al. (2010) compared the efficacy of lifestyle intervention and treatment as usual (TAU) on body mass index (BMI) and cardiovascular and metabolic parameters (see Table 41.1). The intervention was associated with a significant reduction in BMI, although only in women, but no effect on cardiovascular and metabolic parameters was observed [46].

In another RCT, Goracci et al. (2016) assessed the efficacy of a multimodal healthy lifestyle intervention, including physical exercise, dietary behaviours, sleep hygiene, and smoking cessation. Sessions were individual and conducted by psychiatrists and dietitians. Patients in the intervention group had a significantly lower risk of relapse as well as improvements in symptomatology and daytime sleepiness, compared to the control group. The intervention was also associated with a greater reduction in weight, BMI, and waist circumference, but groups did not differ in sleep quality [47].

Moreover, four studies from the same team employed the “*Nutrition, Exercise and Wellness Treatment*” (NEW Tx), which is a CBT-based, integrated psychosocial treatment developed to reduce the disproportionate medical burden associated with BD [22, 48–50]. The NEW Tx consists of three modules (Table 41.1). Sylvia et al. (2011) conducted a pilot trial in four individuals, who received 12 one-hour sessions. Afterward, other six patients performed the revised intervention. Altogether, the ten participants added more than 100 min/week of exercise compared to before treatment. Participants in the second group showed significant improvements in quality of life, depressive symptoms, and body weight [48]. In another pilot study, without a control group, Sylvia et al. (2013), examined the NEW Tx in overweight individuals with BD. Participants received 18 individual sessions, attended most sessions, and reported high levels of satisfaction with treatment [22]. In addition, body weight, cholesterol, and triglyceride levels, as well as caloric intake were all significantly reduced. Moreover, depressive symptoms and functionality were improved, and participants tripled the duration of their weekly physical exercise. The NEW Tx was found to be a feasible intervention to reduce medical burden in people with BD [22, 48].

In an RCT, Sylvia et al. (2019) allocated symptomatic individuals into an 18-week NEW Tx intervention and a control condition. Similarly, the intervention increased patients’ weekly physical activity duration and patients’ overall functioning and reduced the clinical severity of depression and BD. However, only the improvements in functionality were significant. In addition, no differences were found in weight loss and mood symptoms [49]. The feasibility and acceptability of NEW Tx, as well as predictors of patients’ satisfaction and expectations of treatment, were examined in the same study sample. Participants in the NEW Tx group reported moderate to high levels of satisfaction. Post-treatment satisfaction was predicted by both expectations about NEW Tx and the presence of manic symptoms at baseline [50].

41.4 Discussion

Relatively few studies have evaluated the effectiveness of lifestyle-modification interventions in people with BD. Of these, a significant proportion have been published in the last 10 years (20 of 26 identified studies, 77%), which suggests that the field is moving forward quickly. However, only 17 studies were RCTs, 5 of which focused on diet/nutrition.

A previous literature review of diet/nutrition- and exercise-based interventions found only six studies up to 2015 [51]. Most, if not all, trials emphasized physical outcomes, such as weight management, at that time. Recently, Simjanoski et al. (2023) performed a review and meta-analysis of 18 RCTs of lifestyle interventions for BD. Like the present review, the study outcomes were related to physical health, mental health, and functionality [52]. This change of focus also reflects a shift in the field—from considering that lifestyle interventions are useful only to manage the

medical comorbidities associated with mental disorders, to thinking that they are also useful to treat mental disorders themselves.

Lifestyle is a heterogeneous field where a huge variety of interventions and outcomes are being evaluated. Given the diversity of lifestyle behaviours reviewed herein, the current evidence on each lifestyle is discussed separately.

Mixed results arose in *diet/nutrition*-based clinical trials. Both micronutrient (vitamins and minerals) supplementation [27] and a diet high in n-3 and low in omega-6 PUFA [28] were effective in reducing BD symptoms. Moreover, supplementation with creatine monohydrate was associated with a higher likelihood of clinical remission, but not overall cognition, during depressive episodes of BD [31, 32]. This converges with the preliminary benefits of creatine monohydrate for cognition and depression in a recent review [53]. Conversely, supplementation with NAC alone or in combination with other nutraceuticals did not show promising results [29, 30]. These inconsistent results were also found regarding the potential cognitive benefits of nutraceuticals in patients with major depression and BD [54]. The absence of dietary intervention trials based on healthy dietary patterns in BD is striking. One such pattern, the Mediterranean diet, has been shown to be effective as an adjunctive treatment for unipolar depression [55]. Certainly, changing a dietary pattern is usually more challenging than adding nutritional supplements to the diet. Advancing our understanding of the neurobiology of BD could facilitate the discovery of therapeutic dietary targets and biomarkers for its early detection. In this sense, oxidative stress, inflammation and immune dysfunction, and gut microbiota seem to be the main mechanisms involved, which in turn would be targets of dietary, nutraceutical, and pharmacological interventions [11, 56].

So far, interventions aimed at improving *sleep quality* in BD are mostly based on light therapies and CBT for insomnia. Blue light-blocking glasses may be a useful adjuvant treatment for improving circadian rhythm disturbances, but not sleep quality in BD [33]. Preliminary evidence supports the use of bright white light as a therapy to improve insomnia and depressive symptoms, but not sleep quality, in BD [35]. Moreover, CBT for insomnia has the potential to improve clinical outcomes among BD patients with comorbid insomnia [23]. Addressing morning sleep inertia through modifications in waking behaviour may be a useful addition to CBT for insomnia [37]. Moreover, there is some evidence from small pilot studies that a brief sleep intervention and a sleep monitoring device may reduce suicidal risk and improve sleep [38, 39]. Based on the results of RCTs only, the evidence was negative for objective sleep measures and inconsistent for sleep quality. The small number of trials found in this review focused on sleep patterns is surprising, given the cardinal role that insomnia plays in the pathophysiology of BD, especially in relapses. Probably, the large pharmacological arsenal for this purpose explains in part this low research interest.

The relationship between BD and *substance use*, and its negative impact on disease course and treatment response have been widely studied [57]. This comorbidity may further compound the disease burden and cognitive dysfunction associated with BD [58, 59]. Therefore, the existence of complementary and

novel therapeutic approaches is essential. All interventions aimed to manage substance use comorbid with BD review are psychosocial therapies. This was an expected finding as clinical trials with pharmacological treatments were excluded from this review. Two RCTs found that IGT seems promising to reduce substance use and improve mood symptoms in individuals with BD comorbid with substance use disorders [40, 41]. Other RCTs found benefits for mood symptoms [43], but no efficacy on abstinence rates [45]. Overall, these results are in line with those of previous reviews of psychosocial therapies, at least regarding smoking cessation [60].

Regarding *multimodal lifestyle interventions*, the NEW Tx was feasible and acceptable for individuals with BD [22, 50]. However, its effectiveness to promote changes in lifestyle and improve mood symptoms in people with BD was not confirmed in an RCT [49]. This concurs with the negative results of another RCT regarding cardiometabolic outcomes [46]. Conversely, another multimodal lifestyle intervention was effective in improving several physical health parameters and reducing the relapse risk of BD [46, 47]. Overall, these interventions should be promoted in clinical practice due to their cost-effectiveness and the absence of contraindications [47].

Based on RCTs only, there is promising evidence that these interventions can improve mood symptoms and reduce substance use in patients with BD comorbid with substance use disorders. However, the efficacy to improve mood symptoms was inconsistent for sleep-based and multimodal lifestyle interventions, and largely negative for nutrition-based interventions.

Of note, lifestyle behaviours do not occur in isolation, but instead are intrinsically related to each other and naturally cluster among individuals [61, 62]. Moreover, contemporary definitions of lifestyle consider it as a multidimensional construct, comprising up to seven different lifestyle behaviours [19, 20]. In our systematic review, we did not find clinical trials aimed to modify separately four lifestyle domains in BD—stress management, social support, environmental exposures, and exercise/PA. Stress management has probably been a target of some of the reviewed therapies but not as an independent lifestyle dimension. Furthermore, our search strategies may have limited the findings of some trials. Contrary to expectations, exercise/PA was not a stand-alone target of clinical trials. In all cases, exercise/PA made part of the six existing studies with multimodal interventions. This is surprising due to the substantial evidence supporting the efficacy of PA in depression [63]. Conversely, interventions addressed to sleep patterns and substance use are widely represented in this review, and mostly employ several psychosocial treatments, such as CBT. The study of the effectiveness of trials focused on environmental exposures does not seem to have yet reached bipolar disorder, although it is beginning to be studied in depression [64, 65].

Since a minimum sample size was not required, some studies had less than ten participants and lacked a control group, whereas other trials recruited more than 100 subjects [47]. Regarding participants' age, only one trial recruited adolescents with BD [42]. This might be due to the lower prevalence of BD in the paediatric population, the need for parental consent, or the lower compliance of

programmes by adolescents. However, as these interventions are better tolerated than standard medications, and youth is a critical period to enhance functional outcomes in BD, more clinical trials during childhood and adolescence are warranted. On the other hand, the clinical status of the sample did turn out to be quite disparate between the different studies, as is usual in the trials conducted in BD. Participants were in a symptomatic phase of BD, especially depression, in one-third of the clinical trials, and in clinical remission in another third, but it is striking that they met strict psychometric criteria of euthymia in three studies only. Notably, several trials did not specify the clinical status of the sample, which is a relevant variable in BD research.

Several common aspects can be mentioned. Overall, lifestyle-based interventions appear to be feasible, well tolerated, and well accepted by individuals with BD. Indeed, the adoption of healthy lifestyles is usually promoted in clinical practice, given the absence of formal contraindications and their relatively good cost-effectiveness. However, all these reasons do not represent a firm rationale to recommend their application in clinical practice unless the efficacy of these strategies is demonstrated more consistently for people with BD. This will require conducting further clinical trials with a methodological rigour comparable to that required for standard treatments of BD, e.g., psychotropic drugs and psychotherapies. Of note, 17 of the clinical trials reviewed here were controlled RCTs. The inclusion of some pilot trials and single-arm trials complicates drawing firmer conclusions about the effectiveness of lifestyle interventions in BD.

Most of the reviewed studies assessed outcomes related to clinical improvement and/or adherence to a healthier lifestyle. Less often, the impact of interventions on physical health variables was evaluated [46–48]. However, unlike lifestyle interventions applied in other fields of medicine [66], the long-term effects of these interventions have been seldom evaluated, especially on hard outcomes such as mortality, disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs).

It is important to bear in mind that lifestyle-based strategies are not intended to replace standard treatments for BD, but rather to constitute add-on therapies, and likely reduce the use of unnecessary polypharmacy [67]. Indeed, lifestyle-based interventions were not used in monotherapy in any of the clinical trials. It is also worth noting the low number of adverse effects reported in trials, unlike anti-BD medications. Moreover, this set of interventions may be efficient since they have a positive cost-effectiveness ratio [47]. However, it should be noted that comparative cost-effectiveness studies with standard therapies are not available yet.

Despite being feasible and accepted by patients, lifestyle interventions do not seem to be offered to patients and are implemented frequently in clinical practice as part of the usual package of care for BD. This may be because individuals with BD can be perceived by clinicians to have low motivation for change [68]. Other reasons may include the lack of strong evidence of effectiveness, especially because changing behaviours may need sustained effort from clinicians and patients. This may also explain why prescribing nutraceutical pills was more common than prescribing PA/exercise and diet. Notably, there was no digital health intervention

addressing lifestyle included in the present review. The heterogeneity in this field is huge, as demonstrated by a scoping meta-review of RCTs that included 72 reviews, none of them targeting people with BD [69]. According to a recent meta-analysis [70], the use of portable electronic devices, such as smart watches, can assist both patients and clinicians towards a behavioural change. The use of this technology can allow patients to self-monitor treatment and enhance compliance with lifestyle-based interventions [71]. These tools can be used to collect real-time evaluations, thus achieving the adjustment in the prescription of healthy lifestyle behaviours in the most convenient way possible.

This review has several *limitations*. First, the literature search was restricted to two databases, so future reviews using a larger number of bibliographic repertoires could provide a wider view of this topic. Second, it is likely that the search terms used in this systematic review did not make it possible to identify all the published trials in the field. Furthermore, lifestyle-based interventions remain a very heterogeneous body of knowledge, for which *Lifestyle Psychiatry* aims to promote a common frame of reference. Third, only studies in English were included, thus incurring a possible linguistic bias. Fourth, we did not assess a possible publication bias, thus overestimating the real effect of the intervention. Fifth, some could consider that sleep strategies such as light therapy are not lifestyle interventions. Lastly, the quality of the studies was not assessed, and most studies included small sample sizes.

In conclusion, the findings of this systematic review provide a complicated picture regarding the effectiveness of lifestyle-based interventions in BD. The heterogeneity in the clinical state, study outcomes, and interventions across the reviewed trials precludes drawing firm conclusions. Overall, the available evidence is nonconclusive regarding the effectiveness of these strategies to improve mood-related and lifestyle-related outcomes among individuals with BD. More rigorous research with larger samples is warranted to evaluate the efficacy of these strategies. In keeping with the multidimensional nature of lifestyle, we firmly recommend that lifestyle behaviours should be assessed and implemented in a comprehensive manner.

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