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Paolo Martelletti
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Novel Synthetic Drugs in Migraine

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Novel Synthetic Drugs in Migraine

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Foreword

The cultural project of the Headache Book Series, now in its seventh year, presents its 14th volume dedicated to *Novel Synthetic Drugs in Migraine*, once more endorsed by the European Headache Federation. The editorial structure of the previous volumes, based on essentiality, easy consultation, extreme updating, is maintained and the volume offers the most current knowledge on the new pharmacological classes of small molecules that now fill the therapeutic armamentarium dedicated to migraine.

The architecture of the volume is firmly anchored to the traditional structure of a scientific book, organized in chapters dedicated to single topics, in this case each of the individual small molecules, preceded by introductory overviews both for the entire class of small molecules and for each therapeutic target, then closed by an overview on the future perspectives appearing on the horizon of these new therapeutic classes.

Rome, Italy — Paolo Martelletti

Preface

Novel Synthetic Drugs in Migraine represents a new chapter in the Headache Book Series saga, an educational project created and endorsed since its conception within the European Headache Federation. This series offers the reader an organized summary of the news in the headaches area, covering the clinical and therapeutic aspects across the board, always with an agile usability. This volume organizes and presents to the reader the latest therapeutic opportunities for the treatment of migraine: gepants and ditans, molecules that are positioned in the management of either the preventative or acute treatment phases, or in a case covering them both.

The complexity of migraine therapy has recently been simplified by the recognition of a strategic target such as the calcitonin gene-related peptide which is currently the focus of preventative therapies. The new pharmacological class of gepants, such as atogepant, rimegepant, ubrogepant, and vazegepant, antagonists of the calcitonin gene-related peptide receptor, aims at the same target of current migraine preventatives and acute therapies but at the same time offers an easier treatment modality for optimal therapeutic adherence in prevention. The other therapeutic class, the ditans, 5-HT_{1F} receptor agonists represented now by lasmiditan, offers a greater safety than the available drug class of the triptans, opening the door to all migraine sufferers who could not have access to previous therapies for the treatment of the acute crisis, which targeted the 5-$HT_{1B/1D}$ receptor.

Therefore, these molecules represent a huge step forward for the management of migraine for a series of reasons: the advantage of oral administration, the safety, the possible use free from hospital or territorial healthcare facilities access. These factors have always represented a barrier in the management of migraine, a disease that affects such a large portion of the general population worldwide that makes it difficult to be managed exclusively within the few dedicated hospital structures.

We are confident that this volume contributes to spread the knowledge on the most recent therapeutic acquaintances for the treatment of migraine to a multidisciplinary medical body of non-experts who, despite dealing with migraine patients daily, has yet to reach the management and therapeutic autonomy in their treatment. Lastly, this book will hopefully contribute to the training of new generations of medical students and multi-specialty residents through the acquisition of the

necessary skills for a correct transversal management of such widespread pathology, migraine. Then, they will be ready for the new challenge that the medical profession offers in the current times: transversal and non-monodisciplinary competence, the ability to reason and decide in terms of systems, not individual diseases.

Rome, Italy — Paolo Martelletti
Lund, Sweden — Lars Edvinsson

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Chapter 1
Novel Pharmacological Targets of Migraine: An Overview

Eduardo Rivera-Mancilla and Antoinette MaassenVanDenBrink

1.1 Introduction

Migraine is a disabling neurovascular disorder, characterized by recurrent and moderate-to-severe uni- or bilateral headache, lasting from 4 to 72 h accompanied by symptoms including nausea, photophobia and/or phonophobia [1, 2]. Worldwide, migraine has an age-standardized prevalence of 14.4% and presents the second-highest specific cause of disability, and the first in those people under 50 years of age. Besides its high social and economic impact, migraine also can drastically affect the quality of life [1–3].

The exact mechanisms contributing to the onset of a migraine attack and its pathophysiology are not yet completely characterized. Over time, the vascular [4] and neurogenic [5] theories have tried to explain the pathophysiology of migraine. As both vascular and neuronal aspects seem to be involved in its pathophysiology, migraine is currently considered as a neurovascular disorder [6]. In this respect, it is well documented that serotonin (5-hydroxytryptamine; 5-HT) [7] and calcitonin gene–related peptide (CGRP) [8–10] seem to play a role in migraine pathophysiology. Therefore, the acutely acting and prophylactic treatments for migraine are focused on targeting serotonergic and/or CGRPergic systems [7, 11–18].

After ergot and its derivatives (i.e. ergotamine and dihydroergotamine), sumatriptan was the first triptan developed and used as abortive treatment of migraine attacks [19]. In general, triptans act as agonists primarily at 5-$HT_{1B/1D}$ receptors, although some of them (e.g. zolmitriptan, rizatriptan and naratriptan) also have moderate affinity for the 5-HT_{1F} receptors (see Ref. [11]). The mechanism of action

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of sumatriptan is mainly at the peripheral level due to its low lipophilicity, a property that does not allow it to cross the blood–brain barrier (BBB) [20]. However, second-generation triptans (i.e. almotriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan) are slightly more lipophilic than sumatriptan and are able of crossing the BBB [21], which might be related to the side effects produced at the central level [22]. Although triptans are considered the gold standard for acute antimigraine treatment [21], they have some clinical limitations, including the following:

1. Even though in clinical practice triptans do not seem to increase the risk of cardiovascular events (i.e. stroke, myocardial infarction, ischemia or mortality) [23], they produce vasoconstrictor effects in coronary arteries which are mediated by activation of 5-HT_{1B} receptor subtype [24, 25]. Therefore they are contraindicated in patients with cardio- and/or cerebrovascular risk [23, 26].
2. They are not effective in about 30–40% of patients with migraine due to their lack of efficacy after 2 h of their administration [27–29].
3. Medication-overuse headache (MOH) may be induced when used too frequently, which may triggered, at least partly, by recurrence of the migraine attach after initial response [30].

Despite the fact that triptans have represented a breakthrough in the acute treatment of migraine for many years, their limitations have led to the development and analysis of new potentially safe and effective pharmacological therapies for migraine. Accordingly, novel synthetic antimigraine drugs have been developed and approved for migraine management including ditans (5-HT_{1F} receptor agonists) [31] and gepants (CGRP receptor antagonists) [32–40] (see Table 1.1).

Certainly, both ditans and gepants are the two novel classes of antimigraine drugs which do not produce vasoconstrictor effects offering potential therapeutic options for patients with migraine with cardio- and cerebrovascular risk [7, 11–15, 17, 41], an important advantage over the triptans. Nonetheless, despite their promising and exciting future in migraine management, clinical studies should evaluate their long-term effects in terms of cardiovascular safety, especially for gepants, for which the mechanism of action involves blocking the CGRPergic system that could cause unwanted (mainly cardiovascular) side effects [18], keeping in mind the important role of CGRP in cardiovascular homeostasis under pathological conditions [42].

1.2 Novel Pharmacological Treatments for Migraine

Migraine is considered a neurovascular disorder in which activation of 5-HT and the trigeminovascular systems play an important role. As previously reviewed by Rivera-Mancilla et al. [43], pathogenesis of migraine involves: (1) hypothalamic and brainstem activation involved in starting, maintaining and ending of the migraine attacks; (2) cortical spreading depression, the underlying mechanism involved in

Table 1.1 Novel drugs for the acute and prophylactic pharmacological treatment of migraine

Drug	Mechanism of action	Indication	Notes	References
Ditans				
Lasmiditan (COL-144, LY573144)	5-HT_1 receptor agonist Inhibition of CGRP release	Acute migraine treatment	FDA approved in October 2019	[31]
Gepants				
Ubrogepant (MK-1602)	CGRP receptor antagonist	Acute migraine treatment	FDA approved in December 2019	[32]
Rimegepant (BMS-927,711)	CGRP receptor antagonist	Acute- and prophylactic migraine treatment	1. FDA approved in February 2020 for the acute treatment of migraine 2. FDA approved in May 2020 for the prophylactic treatment of migraine	[33–37]
Atogepant (MK-8031, AGN-241689)	CGRP receptor antagonist	Prophylactic treatment for episodic and chronic migraine	FDA approved in September 2021	[38, 39]
Zavegepant (Vazegepant, BHV-3500)	CGRP receptor antagonist	Acute migraine treatment	Phase II/III clinical trial (NCT04408794)	[40]

5-HT 5-hydroxytriptamine/serotonin, *CGRP* calcitonin gene-related peptide, *FDA* Food and Drug Administration

migraine aura; and (3) activation of the trigeminovascular system, which is involved in the development of headache and the symptoms during migraine [43]. In addition, the following mechanisms have been describing in relation to migraine: (1) low-circulating 5-HT levels preceding migraine attacks [44], which are restored by an intravenous infusion of 5-HT [45]; (2) release of CGRP via the activation of the trigeminovascular system (which includes the meninges and intracranial blood vessels) inducing cranial vasodilation [9]; and (3) high serum levels of CGRP during migraine attacks [46]. In view of the above mechanisms, the development of the novel antimigraine therapies has focused on targeting the serotonergic and the CGRPergic systems [7, 11–13, 15–18].

Currently, the novel, synthetic and selective antimigraine drugs that will be described in this book have been classified into two groups (see Table 1.1): (1) drugs for the acute treatment of migraine (i.e. ditans, 5-HT_{1F} agonists; and gepants which block the CGRP receptor); and (2) prophylactic or preventive antimigraine drugs (i.e. gepants) [7, 16–18].

1.3 Acute Treatment for Migraine Beyond Ergots and Triptans

The main goal of the acute or abortive therapies for migraine treatment is to abolish or decrease the duration and severity of a migraine attack. In this respect, selection of the acute treatment is mainly based on functional disability produced by a migraine attack as surrogate marker of disease severity, aiming to induce sustained pain-free responses reducing the migraine-related symptoms with minimal side effects produced in patients [47, 48].

As mentioned above, ergots (i.e. ergotamine and dihydroergotamine) were the first drugs used for the acute treatment of migraine due to their vasoconstrictor effects produced, which can be mediated by activation of 5-$HT_{1B/1D}$ receptor subtypes [49, 50]. Although ergots have been used for many years to treat migraine, the wide affinity and interaction with different receptors (i.e. 5-$HT_{1/2/3/4/5/6/7}$, dopamine D_1- and D_2-like and adrenergic $\alpha_{1/2}$ receptors) [51] and their side effects and contraindications (including MHO, nausea, vomiting, paraesthesia, ergotism, etcetera) [48, 52], led to the develop more selective drugs. However, the use of inhalable dihydroergotamine in nasal spray (a new dosage form recently developed), which provides rapid relief from migraine-related symptoms and it is well tolerated, has been approved on September 2021 by the Food and Drug Administration (FDA, USA) [53, 54], and represents a promising treatment for patients with migraine. Within this context, and considering the role of 5-HT in migraine [7], triptans were developed to produce similar cranial vasoconstrictor effects as 5-HT, while avoiding its side effects. Sumatriptan (the first triptan developed) and the second-generation triptans (e.g. almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmatriptan) are agonists targeting mainly 5-$HT_{1B/1D}$ receptor subtypes, while some also display moderate affinity for the 5-HT_{1F} receptor subtype [55]. Triptans can exert their antimigraine effects by producing vasoconstriction in cranial blood vessels trough the activation of these receptors [7, 56, 57]; and/or by modulating the release of CGRP in peripheral and central trigeminal nerves [58]. Nevertheless, as previously described by MaassenVanDenBrink et al., triptans may induce coronary vasoconstrictor effects [24, 25], although in clinical practice triptans do not seem to increase the risk of cardiovascular events (i.e. stroke, myocardial infarction, ischemia or mortality) [23]. Considering that migraine patients might have an increase cardiovascular risk [42], triptans may be contraindicated in patients with high risk of cardio- and cerebrovascular diseases.

Therefore, during the last years, novel synthetic antimigraine drugs have been developed for the acute treatment of migraine including ditans (5-HT_{1F} receptor agonist) [31] and gepants (CGRP receptor antagonists) [32–34, 40] (see Table 1.1).

1.3.1 5-HT_{1F} Agonists: Ditans

Next to triptans, 5-HT_{1D} and 5-HT_{1F} receptor subtypes were the main focus of study in an attempt to develop new drugs for migraine treatment considering that (1) the coronary vasoconstrictor effects of triptans via the activation of 5-HT_{1B} receptors

and their contraindication in patients with migraine with cardio- and cerebrovascular disorders [24, 25]; and (2) the 5-HT_{1D} and 5-HT_{1F} receptor subtypes do not induce vasoconstrictor effects as triptans [59–61]. In this respect, a Phase II clinical trial evaluated the safety and efficacy of PNU-142633, a selective 5-HT_{1D} receptor agonist for the acute treatment of migraine [62]. However, this agonist was not effective in aborting migraine attacks, and in addition seemed to induce cardiovascular-related side effects (i.e. chest pain), so its development was discontinued [62]. However, it is important to note that, although the authors described that 5-HT_{1D} receptors may not be a therapeutic target for the treatment of migraine, this conclusion may be premature considering (among other limitations) that (1) PNU-142633 was designed using the gorilla 5-HT_{1D} receptor clone, which is not structurally identical to the human 5-HT_{1D} receptor, so its affinity for the human receptor might be different, explaining the loss of efficacy in aborting migraine attacks in humans; (2) the clinical trial included a small population size (i.e. 69 patients); and (3) and the chest pain observed in 2/34 patients who received PNU-142633 may not necessarily be mediated via the activation of the vascular 5-HT_{1B} receptors or by another cardiovascular mechanisms [16, 63]. Notwithstanding the above, 5-HT_{1F} receptors became the main focus for the discovery of new antimigraine therapies [64].

The 5-HT_{1F} receptor subtype, a member of the G-protein coupled receptors (i.e. $G_{i/o}$), is considered an inhibitor receptor subtype since its transduction mechanism of action involves the inhibition of adenylate cyclase [65]. In humans, the 5-HT_{1F} receptor is mostly expressed in the main areas involved in the pathophysiology of migraine, including the hypothalamus, the cortex, the locus coeruleus, the upper cervical cord and the trigeminal ganglion [66–68]. Moreover, 5-HT_{1F} mRNA is expressed (in lower levels) in both human cerebral [66] and coronary [59] arteries. Therefore, as previously reviewed by Rubio-Beltrán et al. [11], selective 5-HT_{1F} receptor agonists were developed as a novel option for the acute treatment of migraine, especially for patients with cardio- and cerebrovascular risk [11].

Initially, three compounds were proposed as potential drugs for the acute treatment of the migraine: (1) LY 344864 [69]; (2) LY334370 [70]; and (3) lasmiditan [71]. Of these three therapeutic options, LY 344864 was tested only in preclinical models of migraine [69, 72, 73], while LY334370 [74, 75] and lasmiditan [76–78] were tested in humans. However, despite the promising results in which LY334370 was shown to be effective in the treatment of acute migraine through selective trigeminovascular neuronal inhibition [74], its development was stopped due to the hepatotoxic effects produced in preclinical studies [75, 79]. Accordingly, lasmiditan was considered the most promising drug targeting the 5-HT_{1F} receptors for the acute treatment of migraine [11, 14, 64, 76–78].

Over the years, clinical trials have shown that lasmiditan is effective and ‘safe’ for the acute treatment of migraine by reducing disability- and migraine-related symptoms within 2 h from its oral administration [41, 80]. Nevertheless, unlike triptans and gepants, lasmiditan is capable of crossing the BBB (see Fig. 1.1b) [14], producing side effects on the central nervous system such as nausea, dizziness, fatigue and drowsiness, paraesthesia and muscle weakness [81]. Therefore, prescribing lasmiditan should be careful, considering the following: (1) its depressant

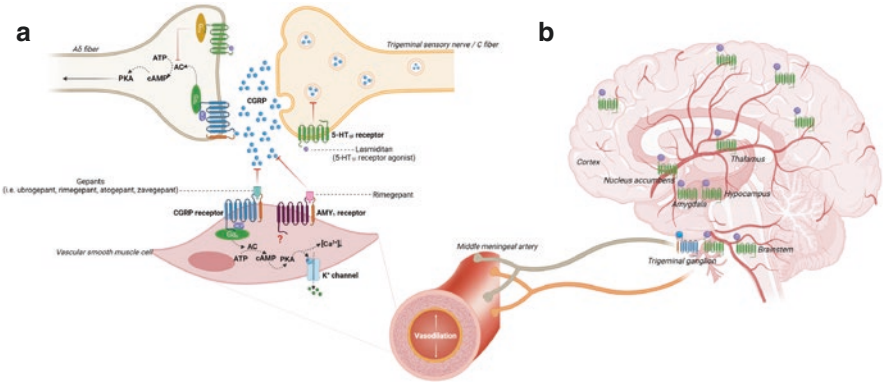

Fig. 1.1 An overview of the mechanisms of action of lasmiditan and gepants. Since 5-HT and CGRP play an important role in the pathophysiology of migraine, the novel treatments for migraine are focused on targeting 5-HT_{1F} and CGRP receptors. This includes the development of lasmiditan (a selective 5-HT1F receptor) and the second- and third-generation of gepants (CGRP receptor antagonist). (**a**) Activation of 5-HT_{1F} receptors located in trigeminal sensory nerves are involved in the modulation of the release of CGRP, while at central level, inhibit cAMP pathway. On the other hand, gepants act at peripheral level by blocking the binding of CGRP to its canonical receptor, even to CGRP-responsive receptors (e.g. AMY_1 receptor) to regulate the vascular tone, while at central level, promote central sensitization via the activation of the cAMP pathway. (**b**) Lasmiditan is able of crossing the blood–brain barrier due to its lipophilic property, exerting its antimigraine therapeutic effects both centrally and peripherally. However, due to its central action, it can also induce unwanted central effects. *Abbreviations*: *5-HT* 5-hydroxytryptamine/serotonin, *AC* adenylate cyclase, *ATP* adenosine triphosphate, *AMY_1* amylin receptor 1, *cAMP* cyclic adenosine monophosphate, *CGRP* calcitonin gene–related peptide, *PKA* protein kinase A, *RCP* receptor component protein. (Created with BioRender.com)

effect at the central nervous system level by interacting with GABAergic receptors (i.e. $GABA_A$ receptors), (2) the tolerability in subjects who are on concomitant preventive treatments; and (3) the possible interaction with other drugs [15, 41, 80, 82]. Evidently, this new therapeutic option is safe in terms of cardio- and cerebrovascular safety [11, 14, 41, 64, 76–78, 80]. However, further studies should evaluate the possible limitations of the use of lasmiditan, especially in the long term, and demonstrate its effectiveness in different populations, including patients with neuropsychiatric and neurological disorders [15] as well as children, adolescents and pregnant women [80].

1.3.2 CGRP Receptor Antagonists: Gepants

As previously described, CGRP plays an important role in the pathophysiology of migraine via the activation of the trigeminovascular system [8–10]. In fact, several authors (see Refs. [15–18, 43]) have described the mechanisms involved in the genesis of migraine, including: (1) the release of CGRP from sensory nerves after

activation of the trigeminovascular system, which results in dilation of cranial blood vessels; (2) an increase of the serum levels of circulating CGRP during migraine attacks; and (3) vasodilation of the middle meningeal artery after an intravenous administration of CGRP, triggering migraine-like headaches. From the above findings, blocking the CGRPergic system has become one of the main study approaches for the development of new pharmacological treatments for both the acute and prophylactic treatment of migraine [13, 15–18].

During the last decades, different drugs targeting the canonical CGRP receptor have been developed. In this respect, gepants, the 'small'-molecule CGRP receptor antagonists, have been shown to have high affinity for the human CGRP receptor, preventing CGRP ligand binding with its receptor located in the trigeminal ganglion and in the vascular smooth muscle cells (see Fig. 1.1) [18]. Currently, gepants are divided into (1) first-generation gepants (initially developed for the acute treatment of migraine; e.g. olcegepant, telcagepant, MK3207, and BI44370TA); (2) second-generation gepants, developed for both the acute (e.g. ubrogepant and rimegepant) and the prophylactic (e.g. rimegepant and atogepant; see Sect. 1.4) treatment of migraine; and (3) third-generation gepants (e.g. zavegepant, formerly called vazegepant) (see Table 1.1).

The first-generation gepants showed to be effective in terms of reducing headaches from severe/moderate to middle headache, as well as migraine-related symptoms [83–86]. Nevertheless, further development of these drugs was ceased due to several reasons, including: (1) pharmacokinetic issues due to low bioavailability in case of olcegepant [83]; and (2) unwanted side effects produced such as hepatotoxicity [84–86]. Currently, some second-generation gepants have been approved for the acute treatment of migraine (i.e. ubrogepant and rimegepant) [32–34], while the third-generation gepants is undergoing Phase III clinical trials (i.e. zavegepant) [40].

Both ubrogepant [87, 88] and rimegepant [89] have shown a favourable tolerability, safety and efficacy profile for the acute treatment of migraine, and are devoid of vasoconstrictor effects in human coronary arteries [90, 91]. Therefore, they are not contraindicated in patients with cardiovascular disease. However, long-term clinical trials should evaluate the effectiveness and safety (in terms of cardiovascular safety) of both ubrogepant and rimegepant considering (1) a direct comparison with different gepants or other drugs used for the treatment of migraine, (2) the recurrence and/or the severity of migraine attacks, (3) potential drug interactions; and (4) to include a heterogeneous population or population with migraine-related comorbidities [87, 88, 91]. In addition, as we will discuss below, rimegepant has also been evaluated and approved as preventive treatment of migraine [35–37].

On the other hand, zavegepant, classified into the third-generation gepants, is the first intranasal gepant developed by Biohaven Pharmaceutical Holding Company Ltd for the acute treatment of migraine. Positive results from a Phase II/III clinical trial showed that zavegepant produced pain freedom and freedom from migraine-related symptoms in addition to having a favourable tolerability profile with no apparent hepatotoxic effects [92]. This intranasal gepant is currently undergoing Phase III clinical trial to evaluate its long-term safety [40].

1.4 Gepants as Prophylactic Treatment for Migraine

The goal of prophylactic antimigraine drugs is to reduce the frequency, duration and severity of migraine attacks to decrease the suffering and disability associated with migraine [18], especially in patients who do not respond to acute therapies and/or suffer from frequent migraine attacks [15, 18]. Besides the gepants described above for the acute treatment of migraine, both rimegepant [35–37] and atogepant [38, 39], which have a longer half-life than ubrogepant (10–12 h for rimegepant, ~11 h for atogepant and 5–7 h for ubrogepant [91, 93]); have been developed, investigated and approved as a prophylactic treatment of migraine. It is important to emphasize that rimegepant is the first and only medication approved by the FDA for both the acute and preventive treatment of migraine [37].

As reviewed by several authors (e.g. see Refs. [15–18, 38, 64, 91]), these gepants have been shown to be effective in preventing episodic and chronic migraine and reducing the number of mean monthly migraine days, in addition to having a good tolerability and safety profile during the clinical trials, at least in the short term. Moreover, studies in vitro using human isolated intracranial (i.e. middle meningeal artery) and coronary arteries showed that rimegepant [94] and atogepant [90] are more effective and potent in antagonizing the vasodilation induced by CGRP in human middle meningeal arteries than in human coronary arteries, which can suggest that both rimegepant and atogepant could have a safety benefit in terms of cardiovascular side effects. Despite their promising future in the prevention of migraine, further clinical trials are required to verify their effectiveness, tolerability and safety in the long term, especially in terms of cardiovascular safety, and to evaluate possible pharmacokinetic alterations due to pharmacological interactions with other drugs.

1.5 Mechanisms of Action of Ditans and Gepants: Is It a Common Pathway?

Knowledge on the trigeminovascular system in migraine has allowed a better understanding of the migraine pathophysiology as well as the development of novel drugs for the treatment of migraine. In fact, and taking into account (1) the involvement of 5-HT and CGRP in the genesis of migraine [7–10] and (2) the vasoconstrictor effects of triptans and their contraindication in patients with cardio- and neurovascular risk [24, 25], the discovery of ditans and gepants has represented a breakthrough and a new era in migraine treatment. Accordingly, blocking the CGRPergic system is an important therapeutic area for the treatment of migraine beside the activation of the serotonergic system since the activation of prejunctional 5-HT_{1F} receptor subtype located in the sensorial nerves can modulate the release of CGRP at peripheral and trigeminal level (see Fig. 1.1a) [7, 11, 14, 16–18, 58], which can suggest that both ditans and gepants might partially exert their effect through the

same pathway. Therefore, the current acute (i.e. ditans and the second- and third-generation gepants) and prophylactic (i.e. rimegepant and atogepant) are focused on targeting 5-HT_{1F} and CGRP receptors, respectively, at both central and peripheral level (see Fig. 1.1a). While, it has been suggested that central actions are not necessary to exert an antimigraine effect of CGRP receptor blockade, this remains to be determined for 5-HT_{1F} receptor agonism [17].

On the one hand, as current representative of the ditans, lasmiditan is a potent and selective 5-HT_{1F} receptor agonist (K_i = 2.1 nM compared to K_i = 1043, 1357, 1053 and 594 nM for the 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1A} and 5-HT_{1E} receptors, respectively) [11, 55, 71]. The 5-HT_{1F} receptor, located (among other sites) in the trigeminovascular system, is coupled to the $G_{i/o}$ G-protein, with a transduction mechanism of action that involve the inhibition of the cyclic adenosine monophosphate (cAMP) pathway by inhibiting the adenylate cyclase (AC); decreasing cAMP production from adenosine triphosphate (ATP) which results in decreasing/inhibiting the phosphorylation of protein kinase A (PKA) (see Fig. 1.1a) [65, 95]. Therefore, one of the antimigraine mechanism of action of lasmiditan is the modulation (by inhibiting) in the release of CGRP from the trigeminal sensory nerves or C-fibres for the regulation of pain pathways (see Fig. 1.1a). This mechanism has been described in preclinical models of migraine as well as in a predictive model of systemic (cardio)vascular side effects [58, 96]. In addition, lasmiditan can cross the BBB into the central nervous system to exert its effects via the activation of the 5-HT_{1F} receptors modulating the central pain pathways and producing its therapeutic effect during migraine attacks (see Fig. 1.1b) [14, 71, 95]. Accordingly, there is a high probability that patients with migraine have unwanted central side effects (i.e. dizziness, nausea, fatigue paraesthesia, etc.) [81] compared to those produced by triptans [97].

On the other hand, the discovery of CGRP as a potent vasodilator playing an important role in migraine pathophysiology led to the development of new treatments targeting CGRPergic system. In this respect, second- and third-generation gepants (i.e. ubrogepant, rimegepant, atogepant and zavegepant) were developed as CGRP receptor antagonists (see Table 1.1 and Fig. 1.1a) for both the acute and prophylactic treatment of migraine. CGRP is a 37–amino acid neuropeptide located in both peripheral and central sensory nervous system, more predominant in C-fibres than in Aδ-fibres in the trigeminovascular system and other structures involved in migraine pathophysiology, where CGRP plays a role as a potent vasodilator and/or neurotransmitter, exercising its effects through the activation of its canonical CGRP receptor (see Fig. 1.1a) [9, 17, 18, 95]. At a central level, CGRP is released from C-fibres (trigeminal sensory nerves) during the onset of migraine attack, which can activate the canonical CGRP receptors located on Aδ-fibres to promote and produce central sensitization (see Fig. 1.1a). In the peripheral nervous system, CGRP can induce vasodilation via the activation of the CGRP receptor, located in vascular smooth muscle cells in human cranial arteries (e.g. middle meningeal arteries) (see Fig. 1.1a). Therefore, one of the main focuses of the novel synthetic antimigraine drugs targeting the CGRP receptor is to reduce vasodilation and neurogenic inflammation [18].

It is important to note that, although CGRP has a high affinity for its canonical receptor (pK_i = 9.7–10.0) it can also bind to other CGRP-responsive receptors (i.e. AM, adrenomedullin and AMY, amylin receptors) with moderate affinity [showing lower affinity for AM receptors (pK_d = 6.0 for AM_1 and pK_i = 6.5–6.8 for AM_2 receptor) than for AMY_1 receptor (pEC_{50} = 8.7–10.7)] (see Ref. [18]). Therefore, these CGRP-responsive receptors might also play a role in migraine pathophysiology. In this respect, there is some evidence that gepants, specifically rimegepant, can antagonize the AMY_1 receptor with a less potency the CGRP receptor [91, 98, 99], however, the mechanisms of action are not yet described (see Fig. 1.1a). Therefore, both CGRP and AMY_1 receptors may help to understand the mechanisms of action of rimegepant in the acute and/or prophylactic treatment of migraine. Further studies are needed to investigate the role and function of this receptor in the pathophysiology of migraine and to analyse the effects of its blockade by gepants.

Finally, since both 5-HT_{1F} and CGRP receptors are located in Aδ-fibres (see Fig. 1.1a) playing a bidirectional role in central sensitization via the inhibition or activation of the cAMP pathway [95], we can suggest that lasmiditan (5-HT_{1F} receptor agonist) and gepants (CGRP receptor antagonists) might partially work on the same pathway. However, as we mentioned above, since lasmiditan can cross the BBB [14], it can produce additional central effects.

1.6 Conclusion

This chapter provides an overview on the role of ditans (a 5-HT_{1F} receptor agonists) and gepants (CGRP receptor antagonists) for the acute and prophylactic treatment of migraine, as well as their mechanisms of action. Besides the monoclonal antibodies targeting CGRP or its canonical receptor, that have been described elsewhere in detail [100], novel antimigraine therapies targeting the 5-HT_{1F} and CGRP receptors including ditans (i.e. lasmiditan) and CGRP receptor blockers (i.e. gepants) have been developed as abortive and preventive treatments for migraine. An interesting feature of lasmiditan and the second- and third-generation gepants is that, unlike the first selective treatments for migraine (e.g. ergots and triptans), they do not cause vasoconstrictor effects. Moreover, these novel synthetic antimigraine drugs have been shown to be effective in reducing migraine attacks, and even preventing them, besides to showing tolerability and safety, at least at the short term. These characteristics represent a great advantage for migraine patients with cardio- and neurovascular risk or for those patients who do not respond to other antimigraine drugs. However, we suggest that further studies (i.e. preclinical and clinical studies) should elucidate (1) the specific mechanism of action of these drugs, including possible interaction with other receptors; (2) pharmacokinetic alteration to evaluate possible drug–drug interactions; (3) the long-term effect of blocking the CGRPergic system in terms of cardiovascular safety, keeping in mind that CGRP is also involve in maintaining cardiovascular homeostasis; and (4) the safety and tolerability in population with cardiovascular comorbidities or CGRP- and/or 5-HT-related pathologies

(e.g. obesity, diabetes mellitus, preeclampsia). Another concern that should be considered is the frequent use of lasmiditan or gepants for the development of MOH. As recently reviewed by van Hoogstraten and MaassenVanDenBrink [101], blockade of the CGRP receptor by gepants besides did not induce MOH, but might possibly even reduce headache in clinical trials of MOH treatments [101]. In contrast, it has been reported in preclinical models that lasmiditan, like triptans, has the potential to develop MOH [102], which can be related to the activation of centrally located 5-HT_{1F} receptors, although this hypothesis should obviously be confirmed or refuted by clinical studies. Therefore, long-term effects of blocking CGRP on MOH, as well as the exact mechanism underlying potential MOH due to the use of lasmiditan should be extensively investigated, specifically in patients with migraine. Finally, the clinical usage and the results of the clinical trials of these novel drugs developed 5-HT- and/or CGRP-targeted therapies will be discussed in the following chapters.

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Chapter 2
Molecular and Cellular Mechanisms of CGRP Antagonists

Kristian Agmund Haanes and Lars Edvinsson

2.1 Introduction

Primary headaches comprise the largest group of neurological disorders; among these migraine prevalence is estimated to 15% of the global population [1]. Although there are many suggested targets and treatments, most of the recent principles relate to the calcitonin gene–related peptide (CGRP) signaling system [2]. The initial starting point for finding and understanding migraine targets and the mechanism of CGRP started with the discovery of neuropeptides and their suggested involvement in migraine [3], which was supported by observed CGRP release under migraine and cluster headache attacks [4, 5]. Originally the link between CGRP and migraine included elements of the neurogenic inflammation theory [6]. This theory was based on tachykinins and CGRP being released and causing downstream vasodilation, mast cell degranulation, and plasma protein extravasation and finally causing pain [6, 7]. This theory has largely been abandoned but did lay the foundation for the development of anti-CGRP pathway drugs. Here in the current chapter we will focus on current suggested molecular and cellular mechanisms of the CGRP antagonists.

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2.1.1 Trigeminovascular System

Early work by *Harold Wolff* showed that the dura mater and its arteries were pain sensitive [8, 9]. Studies that followed showed that these structures are innervated by sensory fibers originating in the trigeminal ganglion (TG) [10]. The TG contains pseudo-unipolar neurons which are mainly C- and Aδ-fibers, and these are involved in mechanical, chemical, and thermic inputs [11, 12]. Further, the TG is rich in glia cells which has been shown to be important in sensory dysfunction and neuropathic pain [13–17]. From the TG, the sensory information is forwarded to second-order neurons in the Trigeminal Nucleus Caudalis (TNC). The nociceptive information from the TG is then processed by the nuclei of the brain stem and forwarded to the thalamus and hypothalamus [18]. The peripheral to central pathway has been dominating in migraine pathophysiology, where it is suggested that the migraine attack starts in the cranial vasculature (by vasodilatation). This view was backed up by intravenous neuropeptide and other vasoactive drug infusion studies [19]. Although the vascular element remains in play, the current theories are more complex and involve a Central Nervous System (CNS) element in the migraine attack, suggesting an origin in the hypothalamus, that leads to anti-dromic effects in the TGV system. A link between the hypothalamus and brainstem/TNC has been shown [20]; however, the missing link between the TNC and the TG still remains to be understood. Irrespective of the theoretical approach, at some point the neurons in TG are activated which leads to release of CGRP. The effects can be blocked by CGRP receptor antagonists or antibodies towards CGRP itself and prevent migraine pain.

2.2 Neuropeptide Signaling

2.2.1 CGRP

CGRP is a peptide containing 37 amino acids and is expressed as two different isoforms: αCGRP and βCGRP [21]. These are synthesized from two separate genes, the CALC I and CALC II. The two isoforms have similar structure and consists of four distinctive domains: (1) Residue 1–7, which contains a disulfide bond between Cystein2 and Cystein7 and is important for receptor activation; (2) the following amino acids; 8–18, forms an α-helix which is important for binding affinity; (3) further amino acids 19–27 forming a β-sheet structure; and finally (4) amino acids 28–37 forming the C-terminus. βCGRP differ from αCGRP by three amino acids and few differences in the pharmacology but different expression profile [22, 23].

Although the CGRP release itself is not a major part of this chapter its origin is important to understand the molecular mechanism of the CGRP pathway antagonists. As mentioned, CGRP is released during migraine attacks [24], and the trigeminal C-fibers and the TG are believed to be the source of the CGRP that is released, with a suggested spillover into the jugular vein which can be measured.

This mechanism has been shown rats [25], cats, and humans [26], suggesting this as a common mechanism among mammals. In the TG, CGRP is expressed in small- to medium-sized neurons, and is often found in a granular pattern [27, 28]. Further, we have recently shown that CGRP packed vesicles also can be observed in boutons/varicosities along the C-fibers and that CGRP can be released directly from the fiber [29].

2.2.2 Amylin

Amylin is also a 37–amino acid peptide hormone that is closely related to CGRP and share a similar secondary structure. Overall 16 amino acids are identical between the two peptides [30], with strong similarities in the N- and C-terminals which have been shown to be important for receptor interactions [31, 32]. We therefore include amylin in this chapter, as there is important research showing overlap between bioactivity between CGRP and Amylin.

Amylin was early reported to be expressed in feline TG neurons, and combined with data showing that amylin can relax cerebral vessels both in vitro and in vivo a role in the TG was suggested [33]. Further, immunohistochemistry have shown that amylin could be expressed in a few small- to medium-sized TG neurons together with CGRP [34]. Using a variety of antibodies, a recent study demonstrated low to no expression of amylin in the TG of mouse, rat, and human [35], suggesting that some earlier studies were hampered by cross-reactivity between CGRP and amylin antibodies [36]. Combined, these observations suggest that there is limited amylin that can be released from/in the TG, but does not rule out the involvement of amylin, as the amylin concentration in plasma (formed largely in the pancreas) is about ten times higher than that of CGRP [37] and the plasma amylin could tentatively be a peripheral source for TG activation.

2.2.3 Neuropeptide Receptors

The CGRP family of receptors include receptors for CGRP, amylin, adrenomedullin, and calcitonin. This chapter will focus in the CGRP and AMY_1 receptors as these are the potential targets for both CGRP and the CGRP antagonists. The other receptors and their involvement in migraine is reviewed in detail elsewhere [38]. Both the CGRP and the AMY_1 receptors are part of a rather unique group of G-protein-coupled receptors, known as the family B (secretin-like) G-protein-coupled receptors (GPCRs) [39], which unlike the family A (Rhodopsin-like) G-protein family consists of two subunits. The largest subunit of the CGRP and AMY_1 receptors consist of a 7-transmembrane (TM) G-protein-coupled receptor named calcitonin receptor-like receptor (CLR) or the calcitonin receptor (CTR), respectively. For these two receptors, the GPCR needs to interact with receptor

activity–modifying protein 1 (RAMP-1) to form heterodimers [40]. Hence the CGRP receptor consist of CLR/RAMP1 and the AMY_1 receptor consists of CTR and RAMP1. The RAMPs themselves are a small single TM-spanning protein that modifies binding characteristics, pharmacology, functionality, and cell trafficking of the specific GPCRs [41]. The need for the RAMP element was initially discovered in early studies where cells transfected with CLR alone could not respond to CGRP [42]. Only when CLR is co-expressed with RAMP1 the functional CGRP receptors is formed [43].

2.2.4 Downstream Activation

The activation of the CGRP receptor (CLR/RAMP) leads to dissociation of the $G\alpha_s$ subunit, which followingly activates adenylyl cyclase. This activation results in ATP being catalytically converted to the secondary messenger cyclic AMP (cAMP). This increase in cAMP has several intracellular effects, with one of the most important is the activation of protein kinase A (PKA) [44]. In addition to well-known targets, PKA can also regulate ion channels essential for nerve signal propagation (more details below), and thereby be involved in sensitization and potentially pain transmission in migraine [45]. Furthermore, when CGRP increases cAMP in Aδ-fibers these can become *hyperexcitable* for other stimuli [46]. Additionally, several gene-related effects can be linked to the activation of the cAMP, including CREB and p38 which have been shown on human and rat trigeminal neuronal cell bodies [47]. In the vasculature cAMP reduces contraction, thereby causing vasodilation, by inhibiting the myosin light chain kinase [48].

The above mechanisms cannot explain how CGRP can activate receptors and lead to pain. One postulate is activation of the hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, known to be involved in neuropathic pain [49]. This channels can be activated by both cAMP and cGMP [50], leading to generation of action potentials. Indeed, it has been shown that the cAMP–HCN pathway and different neuromodulators may alter conduction velocity in the central nervous system [51], and these channels are expressed in the TG [52], supporting the idea that HCN channels could be involved in generating TGV pain signals.

2.3 The Blood–Brain Barrier

CGRP is released from TG neurons both outside and inside the blood–brain barrier (BBB). CGRP release in the extracranial areas and dura mater are outside the BBB, which contrasts to CGRP released from the sensory nerves in the cerebral and pial arteries which is inside the BBB. In regard to the molecular mechanisms of CGRP antagonists in migraine, there are CGRP receptors also expressed in the CNS, meaning that both central and peripheral elements could theoretically be relevant.

Importantly the dura mater, the TG are freely accessible to molecules that are non-BBB penetrating, based on the calculation of permeability surface area–product and experiments with Evans Blue [53, 54]. Regarding central targets, measurements of CGRP antagonists such as the gepants, have shown a minor passage; of around 2% [55]. Despite this apparent permeability of gepants, the CGRP antibodies have nearly no BBB permeability (<0.01%), have similar migraine/side-effect profile (and importantly no CNS side effects), and therefore we believe that the targets for CGRP antagonistic drugs reside outside the BBB. This is also the reason why there are few CNS-related side effects.

2.4 CGRP Antagonists

Although the CGRP antagonists are just now entering the clinic, they have an over two-decade-long history, that started with olcegepant and telcagepant, which were the first small molecules that competitively antagonized the vasodilator effect of CGRP in human arteries [56]. These two drugs entered into several clinical trials, with the olcegepant proven effective when intravenously administrated, but with low oral bioavailability and telcagepant halted because of hepatotoxicity. Following molecular modifications three other gepants have now passed phase III and two are approved by the FDA; these are ubrogepant [57] and rimegepant [58], and these are discussed in details in other chapters. They have all passed extensive clinical studies with significant anti-migraine effects and minor adverse events.

2.5 Molecular Targets

The CGRP antagonists are developed specifically against the CLR/RAMP1 receptor known as the CGRP receptor. As mentioned above, the similarities between the CGRP and amylin comes into play, as the binding site in CLR/RAMP1 and CTR/RAMP1 share similarities. In fact, CGRP has strong affinity for the AMY_1 receptor [23] and when comparing binding affinity of olcegepant between CLR/RAMP1 (for CGRP) and CTR/RAMP1 (for amylin) there are similarities not only in binding characteristics, but also functionally related to changes in cAMP production [59]. For example, the CGRP antagonist Rimegepant, show "only" 30-fold higher specificity for the CGRP receptor compared to the amylin receptor [60]. The interesting discussion is therefore if the gepants interact with amylin receptors are relevant to migraine, which has been suggested in binding studies on TG [59]. This hypothesis was partially tested in a recent study using pramlintide (an amylin analogue), in the intravenous "migraine-trigger" model [35]. Although pramlintide triggered migraine-like attacks in migraineurs, both amylin and pramlintide are weak agonists (around 100 times lower potency) for the CGRP receptor than CGRP itself. Based on this study, it is not clear which receptor was activated, and a study applying erenumab

(CLR/RAMP1 specific blocking antibody) in a clinically relevant dose could lead to a conclusion on whether CTR/RAMP1 receptors are important in migraine pathology. Although amylin receptors could play a part as a CGRP antagonist target, we focus mainly on the potential cellular targets for CGRP, which includes the middle meningeal artery [61], satellite glial cells [62], and importantly the Aδ-neurons [63].

2.6 Cellular Targets

2.6.1 Vascular Targets

CGRP receptors are strongly expressed on the middle meningeal arteries that supply the dura mater but also in the intracranial pial and cerebral arteries. Due to the limited BBB permeability of gepants [55] as well as of CGRP, if at all interacting with the migraine-related vasculature, the most likely target is the middle meningeal artery and its branches. Although nearly all vasodilators given in the peripheral cubital fossa vein results in migraine-like attacks [19], the actual dilation during a migraine attach has been debated [64, 65]. The early studies on CGRP revealed potent vasodilation on cranial arteries that was independent of the endothelium, suggesting a direct increase in cAMP in the vascular smooth muscle cells [66] and which was further shown to also occur in parallel with a reduction in intracellular calcium [67]. Telcagepant, atogepant, and ubrogepant effectively inhibit the CGRP-vasodilatory responses in human meningeal and cerebral arteries [57, 68]. Intracortical administration of either CGRP or amylin causes increased local cerebral blood flow [33]. The monoclonal antibodies against the CGRP receptor showed competitive antagonism with no depression of maximum CGRP induced relaxation in human middle meningeal and cerebral arteries [69, 70], suggesting that CTR/RAMP1 is responsible for the cerebral dilation. This contrasts to the coronary circulation where Shild plots suggest the presence also of CTR/RAMP1 receptors [71]. It is therefore beyond dispute that CGRP antagonists will at least target and prevent CGRP-induced vasodilation of "migraine-related arteries," such as the middle meningeal artery. Whether this is a part of the pain-mitigating mechanisms remains an open question as it has been put forward that the TGV system does not require a peripheral sensory input to be activated [72].

Since there are CGRP receptors on the cerebral arteries (vascular smooth muscle cells), this possible site of action must be considered. The hypothesis that CGRP antagonists could pass through the tight endothelial layer of cerebral arteries was tested in a myograph setup. Here the arteries are perfused, and compounds can be added selectively to the lumen of directly to the smooth muscle layer. CGRP receptor antagonists (olcegepant or telcagepant) could not block CGRP-induced dilation when applied to the lumen [73]. This does not only add to the evidence that CGRP antagonists cannot work centrally, but also that lead us to conclude that cerebral vasculature is a highly unlikely target for these group of blockers.

2.6.2 Trigeminal Targets

2.6.2.1 Satellite Glial Cells

Although this part of the chapter focus mainly on neurons, CLR and RAMP1 have been observed in satellite glial cells [27]. These cells envelope the TG neurons, and may function as gatekeepers for systematically administered drugs, but also involved in complex signaling relationships. One such possibility of intra-TG cross-talk has been suggested to result in a feedback loop, sensitizing neurons [74]. CGRP released from C-fibers in the TG [29] could activate the satellite glial cells, and affect for example local gene expression or release of neurotropic factors.

2.6.2.2 Neuronal Targets

Unlike CGRP, which is expressed mainly in small neurons, the CGRP receptor elements CLR and RAMP1, are expressed together in medium to large (<60 μm) diameter neurons [27, 75]. These larger neuronal bodies typically represent Aδ-fibers, and one can clearly observe the receptor elements throughout the entire length of the neuronal fibers, both in the TG, dura mater, and the root entry zone at the TNC [27, 28, 76]. Based on immunohistochemistry, with clear and strong expression in the Aδ-fibers, the data strongly support that the origin of the migraine pain, and therefore the main target of CGRP antagonist lies in these fibers. As these fibers are the only neuronal fibers in the TGV system that innervate the area where migraine pain is sensed inhibiting CGRP receptors, here most likely mitigates migraine pain [53, 75, 77]. This view is supported by functional data from Burstein and colleagues, which have by using the monoclonal antibodies, shown that they inhibit activation of the trigeminal Aδ-neurons and therefore the response to CGRP [63]. Further it has been demonstrated that CGRP can acutely modulate excitation of TG neurons [47, 78].

2.6.2.3 Potential Antagonistic Effect at the Nodes of Ranvier

The nodes of Ranvier are highly organized structures in which the central, unmyelinated portion of the node is flanked by paranodal and juxtaparanodal regions [79], arising from interactions between axons and myelinating Schwann cells [80]. In these regions we find a wide array of ion-channels [81], which may be putative downstream targets following CGRP receptor activation. As an example, it has in patients with neuropathic pain been shown that an increase in cAMP in the DRG could cause a negative shift of the activation of sodium currents, leading to potential hyperexcitability [82].

As mentioned, RAMP1 and CLR are co-expressed mainly in larger neurons and their associated thinly myelinated fibers, known as the Aδ-fibers [27, 29]. We have

shown that CGRP containing C-fibers run in parallel with the Aδ-fibers and that CGRP containing "boutons" align with adjacent nodes of Ranvier in the Aδ-fibers [29]. We have therefore postulated that this could be a novel target and mechanism of action for CGRP, and therefore also for the antagonists. In this nodal region, CLR/RAMP1, as well as a CGRP receptor antibody that only recognize the fully assembled receptor, showed strong expression [29]. One possibility is that activation of CGRP receptors on the node of Ranvier contributes to sensitization of the Aδ-fibers and explains part of the pain pathophysiology. Alternatively, gradation of the node and internode properties along axons can tune conduction speed and the activation threshold [83]. Functional studies are needed to conclude on the details of the mechanism. This work adds to the hypothesis that the trigeminal system function as a neuronal tuner which could be an important target to understand and thereby elucidate how the sensory input is regulated [84, 85].

2.7 Non-migraine Targets

The clinical trials on anti-CGRP therapy have reported surprising limited side effects considering the CGRPs abundance [86]. The main reported side effects of anti CGPR therapy is related to gastrointestinal disorders and, although not reported as significant side effect, some concerns remain about targets in the cardiovascular system. For the gastrointestinal disorders, constipation is reported in 3–4% of patients [87]. There are some evidence that CGRP per se may reduce gastric emptying [88, 89] and reduce food intake [90, 91], with both local and neurological effects [88, 92]. Importantly it has been shown that a long-acting CGRP peptide analogue could significantly increase levels of circulating Glucagon-Like Peptide-1 (GLP-1) [90]. One could therefore postulate that lowered levels of GLP-1 levels could be associated with the treatment of CGRP receptor antagonist [93]. Thus, it could be worth investigating in light of the importance of GLP-1 signaling on glucose homeostasis and gastrointestinal regulation [94].

Although cardiovascular side effects have not been more frequently reported than placebo in the anti-CGRP treatment studied, all phase II and phase III studies excluded migraine patients with cardiovascular risks [95]. The only study to date on this group, was on erenumab (anti-CGRP receptor antibody) in angina patients, where no negative effects was observed [96]. It is well described in preclinical trials that CGRP is an important vasodilator in cerebral and coronary arteries [97, 98], and with this in mind, they could be targets for the CGRP antagonist. Most likely, compensatory mechanism in the arteries [69, 99] will prevent strong side effects by blocking CGRP signaling. Further, both the anti-CGRP antibodies and CGRP antagonists are competitive, and one could postulate that in a cardiovascular event, the E_{max} effect of CGRP could still be achieved. More research is needed to conclude on the cardiovascular effects.

2.8 Conclusion

CGRP receptor antagonists block the effects of CGRP, which in the TGV system relieves migraine pain. This effect is caused by competitive binding to the CLR/RAMP1 receptor known as the CGRP receptor; however some effect could also be attributed to binding to CTR/RAMP1: the amylin receptor. As CGRP is released during a migraine attack, it activates CGRP receptors mainly on the Aδ-neurons, with potential vasodilation occurring simultaneously at the middle meningeal artery. The current scientific data strongly support that the Aδ-neuron activation is the main causative factor of migraine pain, and therefore the most likely molecular and cellular effect of the CGRP antagonist drugs. Nevertheless, all CGRP receptors outside of the BBB will be blocked by the clinical application of CGRP receptor antagonists, hence vascular effects and side effects must be considered.

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Chapter 3
Atogepant

Anna P. Andreou

3.1 Introduction

Atogepant is the first oral calcitonin gene–related peptide (CGRP) receptor antagonist developed specifically for migraine prevention. The quest for orally acting drugs that target the CGRP receptor is non-trivial, given the well-characterized role of CGRP in migraine biology [1]. The difficulties in designing specific, safe and well-tolerated CGRP antagonists reflect the difficulties of identifying orally bioavailable antagonists that target family B G-protein-coupled receptors (GPCRs), such as the calcitonin receptor-like receptor (CLR), for which the endogenous ligands are large peptides, with a safe metabolism [2].

Atogepant (AGN-241689; also known as MK-8031) is a novel calcitonin gene–related peptide (CGRP) receptor antagonist, developed as an oral tablet for migraine prevention. To date it has received FDA approval for the preventive treatment of episodic migraine in adults, while phase III trials for the efficacy of atogepant in the prevention of chronic migraine are currently underway. Atogepant was initially patented as MK-8031 by Merck Sharp & Dohme Corp, before being acquired by Allergan Inc., which is now part of AbbVie Inc.

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3.2 Chemical Characteristics, Pharmacodynamics and Pharmacokinetics

Atogepant was initially developed as part of a series of highly potent CGRP receptor antagonists that had been optimized to improve the pharmacokinetic profile, with incorporated polar functionality, leading to piperazinone analogues that possessed improved solubility at acidic pH and increased oral bioavailability in monkeys. Further modifications focused on balancing antagonist potency, plasma protein binding, and in vivo clearance [2]. Atogepant is piperidinonylcarboxamideazaindane derivative (Fig. 3.1) and its IUPAC name is (3*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl]-2-oxospiro[1*H*-pyrrolo[2,3-b]pyridine-3,6′-5,7-dihydrocyclopenta[b]pyridine]-3′-carboxamide. Its molecular formula is $C_{29}H_{23}F_6N_5O_3$ with a molecular weight of 603.5 (computed by PubChem 2.1; 2021.05.07-PubChem CID 72163100).

Atogepant is a small molecule with high affinity at human CGRP receptor (K_i = 15–26 pM) and about 100 times lower affinity at human amylin 1 (AMY_1)

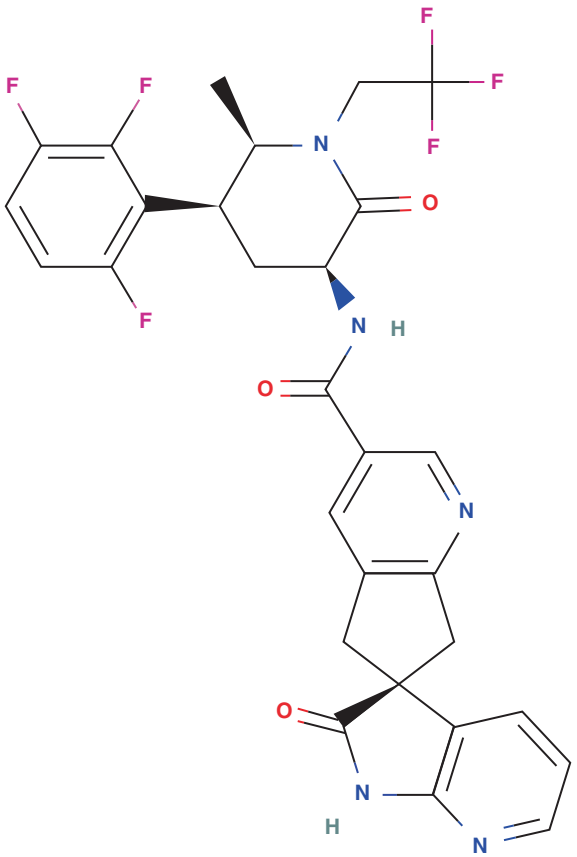

Fig. 3.1 Chemical structure depiction of atogepant (PubChem CID 72163100)

receptor. It has a distinct, but similar structure to that of ubrogepant, another CGRP receptor antagonist in development by the same company for the acute treatment of migraine. However, atogepant has a higher potency and longer half-life than ubrogepant, making it suitable for preventive treatment. Atogepant is rapidly absorbed after oral administration, with a median time to maximum plasma drug concentration (t_{max}) of 1.8 h [3]. Its terminal half-life is estimated around 10–11 h for the 60 mg dose with no evidence of accumulation after once-daily dosing [3]. Steady-state concentrations are typically achieved by day 3 of daily dosing, while the anticipated therapeutic unbound maximum plasma drug concentration (C_{max}) values (< 0.1 μmol/L) [4]. The chemical structure of atogepant is distinct from previous CGRP receptor antagonists, which were associated with elevated serum alanine aminotransferase (ALT) in clinical trials [5–8]. Atogepant is eliminated primarily via hepatic metabolism and biliary secretion. Hepatic metabolism occurs predominantly through oxidation via cytochrome P450 (CYP) 3A4 and to partially via CYP2D6 [9].

3.3 Atogepant in Preclinical Studies

The effects of atogepant were studied in vitro on the relaxation induced by CGRP in human isolated middle meningeal, cerebral and coronary arteries [10]. In this study, atogepant showed a higher potency in antagonizing CGRP-induced relaxations in intracranial arteries compared to the inhibition observed in distal human coronary arteries. The same study showed that atogepant has no de novo vasoconstrictor effects at any of the concentrations studied in human coronary arteries.

The efficacy or mechanisms of action of atogepant or MK-8031 on any of the classical migraine animal models have not been published in peer-reviewed articles. In a preclinical study sponsored by AbbVie Inc., which also has the marketing license of BOTOX (botulinum toxin A) for chronic migraine, atogepant was used in combination with BOTOX in an animal model of cortical spreading depression-induced sensitization of trigeminal fibres. In this study, the combined treatment was found to inhibit high-threshold and wide-dynamic-range neurons with the authors concluding that a dual therapy will be more effective than a monotherapy for the prevention of migraine [11]. Whether such treatment combination will be having added clinical value in a real setting remains to be shown.

3.4 Efficacy of Atogepant in Phase II and Phase III Clinical Trials

A phase II/III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study evaluated the efficacy, safety and tolerability of multiple dosing regimens of oral atogepant in episodic migraine prevention in adults with a mean age

of 40 years old (aged 18–75 years) [12]. Overall, 86% of the participants were females. The average number of migraine days at baseline was 7.7, and 72% of the participants had not tried preciously any other preventive treatment. Patients were randomized to either placebo or atogepant treatment; 10 mg once daily (QD), 30 mg once daily, 60 mg once daily, 30 mg twice daily (BID), and 60 mg twice daily, and treated under double-blind conditions for 12 weeks for the prevention of episodic migraine. The primary efficacy endpoint was the change from baseline in mean monthly migraine/probable migraine headache days across the 12-week treatment period. All active treatment groups demonstrated a statistically significant ($p < 0.05$) reduction from baseline in the primary efficacy parameter (10 mg QD vs. placebo, $\Delta -1.15$; 30 mg QD vs. placebo, $\Delta -0.91$; 60 mg QD vs. placebo, $\Delta -0.70$; 30 mg BID vs. placebo; $\Delta -1.39$; 60 mg BID vs. placebo, $\Delta -1.29$). Secondary outcomes included the number of patients who achieved at least a 50% reduction in mean monthly migraine days and change from baseline in mean acute medication use days. Only the 30 and 60 mg BID groups were associated with a significant outcome over 12 weeks compared with placebo. In a prespecified tertiary analysis, a significant difference in reduction in monthly migraine days was evident at 4 weeks, the first timepoint evaluated, for all dose regimes of atogepant [12].

In a phase III randomized, double-blind, placebo-controlled trial, the efficacy of atogepant in the preventive treatment of migraine was demonstrated in 873 adults (aged 18–80 years) with more than a year's history of episodic migraine [13]. Patients who had responded inadequately to more than four oral medications for migraine prevention (two with different mechanisms of action) were excluded from the trial. The mean monthly migraine day at baseline was 7.5–7.9 days across groups (4–14 days). Atogepant at 10, 30 or 60 mg once daily was compared against placebo. For the primary endpoint over the 12-week treatment period, a significantly ($p < 0.001$) reduction from baseline in the mean number of migraine days per month (least squares mean) was observed for all atogepant doses: 10 mg QD versus placebo, $\Delta -1.2$; 30 mg QD versus placebo, $\Delta -1.4$; 60 mg QD versus placebo, $\Delta -1.7$. Secondary outcomes included the number of patients who achieved at least a 50% reduction in mean monthly migraine days, change from baseline in mean monthly headache days, change from baseline in mean acute medication use days and change from baseline in the role function restrictive (RFR) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at week 12. All three atogepant doses were associated with a significant outcome for these secondary outcomes over 12 weeks compared with placebo [13]. In a secondary analysis, a significant benefit ($p < 0.01$) in the occurrence of a migraine attack was evident as early as day 1 across all atogepant doses, with 10.8–14.1% of patients reporting a migraine versus 25.2% of placebo recipients ($p < 0.01$ for all comparisons). Mean change from baseline in weekly migraine days in week 1 ranged from −0.77 to −1.03 for atogepant versus −0.29 with placebo [14].

3.5 Safety and Adverse Events

Earlier studies on the safety of atogepant identified no apparent formation of reactive metabolites, making it a safe treatment option for migraine. In vitro studies of atogepant showed no inhibition of cytochrome P450 (CYP)1A2 or CYP3A4. However, atogepant displayed weak inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP2C19. Non-potent inhibition of CYP3A4 (IC_{50} > 100 μM) or UDP-glucuronosyltransferase 1A1 in human hepatocytes was shown to be concentration dependent and not time dependent [4]. Additionally, atogepant did not induce CYP1A2 or CYP2B6 in human hepatocyte incubations and did not inhibit P-glycoprotein in vitro [4].

Given the occurrence of hepatotoxicity with earlier gepants, a phase I trial with 28 healthy volunteers examined if multiple doses of atogepant of 170 mg induced changes in ALT levels [3]. Over 28 days of treatment, no participant receiving atogepant had an ALT elevation higher than 1.5 times the upper limit of normal. Overall, changes from baseline in serum ALT levels was not different between atogepant and placebo. All adverse events (AEs) related to atogepant were mild in severity.

In a different phase I study, the pharmacokinetinetics, safety and tolerability profiles of single-dose oral atogepant 60 mg in participants with normal and impaired hepatic function were tested [9]. In this study, the mean half-life of atogepant was shorter in the severe hepatic impairment group (~1 h) compared with the other groups. Compared with participants with normal hepatic function, C_{max} (ng/mL) was 9% higher in participants with mild hepatic impairment, and $AUC_{0-\infty}$ of the plasma mean concentration-time profile of atogepant was 38% higher in participants with severe hepatic impairment. The apparent total body clearance of drug from plasma after extravascular administration (CL/F) was lower in patients with hepatic impairment (ranging from 17.3 to 19.4 L/h) compared to healthy subjects (24.2 L/h). As expected, the free fraction of atogepant in plasma was also higher in hepatic impaired patients compared to healthy volunteers. The atogepant plasma protein binding was not different between the different groups [9]. Despite these difference between healthy subjects and hepatic impaired patients, the authors concluded that overall atogepant was safe and not associated with any clinically relevant change in pharmacokinetics in participants with severe, moderate or mild hepatic impairment. However, given the findings of this study, atogepant may need to be used with caution in clinical practise in patients with hepatic impairment, at least until more data from bigger observational studies are available.

Similarly, in a randomized, double-blind, phase I crossover study the effects of a single supratherapeutic dose of atogepant (300 mg) or placebo were evaluated on the cardiac repolarization in healthy adults [15]. Atogepant was not found to be associated with a clinically relevant prolongation of the Fridericia-corrected QT interval. However, its effects in adults with underlying cardiovascular conditions has not been tested and caution should be used in prescribing atogepant in this patient population.

Given the lack of any significant actions of atogepant on the CYP3A4 in human hepatocytes, the low anticipated therapeutic unbound maximum plasma drug concentration (<0.1 μmol/L) and relative induction score modelling, atogepant is not expected to cause clinically significant drug-to-drug interactions with compounds whose clearance mechanism is predominantly dependent on CYP3A4 [4]. To examine the effect of multiple-dose atogepant 60 mg once daily on the pharmacokinetics of a combination oral contraceptive (ethinyl oestradiol/levonorgestrel; EE/LNG), the metabolism of which includes the CYP3A4, a phase I study in in healthy women taking oral contraceptives was conducted. The incidence of migraine is higher among women and peaks during the reproductive years, when contraceptive medication use is common; hence, the study aimed to address any interactions of atogepant with the pharmacokinetics of oral contraceptive medicines. This small study demonstrated that atogepant does not have a clinically meaningful effect on the exposure of EE/LNG. However, the area under the curve of LNG was increased by 19% after coadministration with atogepant compared with EE/LNG alone. The authors concluded that a change of this magnitude is not expected to affect the contraceptive efficacy of EE/LNG or to have a clinically meaningful effect on safety [4]. In the same study, 14 AEs were considered by the investigator to be related to atogepant. The most common drug-related AEs overall were headache, somnolence, diarrhoea and constipation. All AEs were mild or moderate in intensity and resolved by the end of the study.

Different phase I studies of drug-to-drug interactions (DDIs) trial, aimed to address potential DDIs with commonly used acute painkillers that patients may use as a rescue medication if, while on a preventive treatment with atogepant, a migraine attack occurs. In these studies, coadministration of 60 mg atogepant with 1000 mg acetaminophen or 500 mg naproxen or sumatriptan 100 mg was safe and well tolerated in healthy participants, and no DDIs were observed [16, 17]. Given the vasoconstrictory actions of triptans and the antagonizing actions of atogepant on CGRP-induced relaxations in intracranial arteries caution may need to be taken when both treatments are prescribed. However, in the phase III trials, the acute use of triptans was allowed and no specific AEs to this concomitant use of medications were reported. Preliminary data have also been reported in abstract forms for the lack of DDIs when atogepant is used in combination with drugs that decrease stomach acid production like famotidine and esomeprazole, or with the anti-arrhythmic drug quinidine gluconate [18–20].

In the phase II/II trial, atogepant appeared to be well tolerated with the most common (>5%) treatment-emergent adverse events (TEAEs) across all groups being nausea, fatigue, constipation, nasopharyngitis, upper respiratory tract infection and urinary tract infection. The occurrence of constipation could be related to the blockade of the $CGRP_{\beta}$ downstream pathway in the intestines. No treatment-related serious AEs were reported. In the same trial, 10 cases of the aspartate transaminase (AST) and alanine aminotransferase (ALT) ratio ALT/AST being three times equal or higher to the serum upper limit of normal (ULN) were reported. These were evaluated and adjudicated by a panel of liver experts blinded to treatment allocation. Of those 7 out of 10 cases (6 atogepant, 1 placebo) considered to

be unlikely related, 2 out of 10 cases (1 atogepant, 1 placebo) considered as possibly related, and 1 out of 10 cases (on atogepant) considered probably related. The authors concluded that liver safety profile for atogepant was similar when compared to placebo, with no indications of hepatotoxicity with daily administration over 12 weeks. A higher incidence of TEAEs was found in the 60 mg atogepant groups compared to lower doses of atogepant. The frequency of treatment-related TEAE ranged from 18% to 26% in the patients randomized to atogepant, versus 16% for placebo participants. Eight serious TEAEs were reported during the trial and found to be unrelated to treatment. TEAEs leading to discontinuation were reported in 5% of the atogepant participants and in 2% of the placebo participants.

In the phase III trial, all atogepant doses were well tolerated, the frequency of adverts events reported by participants was similar between the placebo and atogepant groups, and no dose relationship was observed [13]. In the atogepant groups, the most commonly reported AEs were constipation (6.9–7.7% across doses), nausea (4.4–6.1% across doses), upper respiratory tract infection (3.9–5.7% across doses), urinary tract infection (1.4–3.9% across doses), nasopharyngitis (1.8–3.5% across doses) and fatigue (1.4–3.9% across doses). Other AEs included somnolence, sinusitis, gastroenteritis, influenza, sinus congestion and anxiety. Two participants in the 10 mg atogepant group, two participants in the 30 mg atogepant group, one participant in the 60 mg atogepant group and four participants in the placebo group had elevated ALT or AST levels that were at least three times the upper limit of the normal range, with no serious cases of liver disease reported. The incidence of discontinuation due to adverse events was similar across the trial groups. The study also showed slightly higher increased blood creatine kinase (CK) levels in the atogepant groups (0.9–3% across doses) compared to placebo (0.9%). The appearance of CK in blood has been generally considered to be an indirect marker of muscle damage, particularly for diagnosis of medical conditions such as myocardial infarction, muscular dystrophy and cerebral diseases [21]. However, there is controversy in the literature concerning its validity and in the current concept, the increase CK levels in atogepant participants may have no clinical relevance.

Based on a population pharmacokinetic analysis, age, sex, race and body weight did not have a significant effect on the pharmacokinetics (C_{max} and AUC) of atogepant. Therefore, no dose adjustments are warranted based on these factors [20]. However, its actions in children have not been established yet. In the elderly, although the phase III studies included patients up to the age of 80 years old, no sufficient numbers of patients aged 65 years and over were recruited to determine whether they respond differently from younger patients. In general, caution should be used in the use of atogepant in the elderly given the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy [20].

There are no adequate data on the developmental risk associated with the use of atogepant in pregnant women. Similarly, there are no data on the presence of atogepant in human milk, the effects of atogepant on the breastfed infant or the effects of atogepant on milk production. Oral administration of atogepant (5, 15, 125 or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in

decreases in foetal body weight and in skeletal ossification at the two highest doses tested (125 and 750 mg/kg), which were not associated with maternal toxicity. Oral administration of atogepant throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested (125 mg/kg/day), which persisted into adulthood [20]. Oral administration of atogepant (30, 90 or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in foetal visceral and skeletal variations at the highest dose tested (130 mg/kg/day), which was associated with minimal maternal toxicity [20]. In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately twofold higher than that in maternal plasma [20]. Oral administration of atogepant to male and female rats prior to and during mating resulted in no adverse effects on fertility or reproductive performance. Although the plasma exposure of the atogepant doses that induced abnormal foetal development in animals were much higher that of the maximum recommended human dose of 60 mg/day, the use of atogepant in pregnancy and lactation is not approved or recommended.

In both in vitro and in vivo studies atogepant was shown to have no incidence of carcinogenicity or mutagenicity [20].

3.6 Future Developments

Atogepant received its first FDA approval on 28 September 2021 for the preventive treatment of episodic migraine in the USA under the brand name QULIPTA. The approval was based on the phase III, double-blind trial in adults which, as mentioned above, demonstrated that at week 12 there was a 55.6%, 58.7% and 60.8% reduction in the 3-month average of migraine days per month for the 10, 30 and 60 mg atogepant groups, respectively, compared to 29% for the placebo arm ($p < 0.001$). Hence, the recommended dosage of atogepant is 10, 30 or 60 mg once daily, taken without regard to food. Filing and approval from the European Medicines Agency (EMA) are pending.

A number of phase III trials for safety, efficacy and tolerability of atogepant for the prevention of chronic migraine in adults are currently ongoing in the United States, Europe and Asia with outcomes expected in 2022. Recruitment is also underway for another multinational phase III trial that aims to evaluate the safety, tolerability and efficacy of atogepant versus placebo as preventive treatment for episodic migraine in adults who have previously failed two to four classes of oral prophylactic treatments for migraine.

Additionally, the Paediatric Committee of the European Medicines Agency (EMA) has given an opinion on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for atogepant in ages 6–18 years old, with investigational studies expected to be completed by 2029 [22]. The plan includes among other preclinical studies in juvenile rodents to assess toxicity; development of lower-strength tablet/capsule appropriate to the paediatric population from 6 to less than 12 years of age and for those unable to swallow

existing dose form to administer dose higher than 20 mg; randomized, double-blind, placebo-controlled, parallel group study to assess PK, efficacy, safety and tolerability of atogepant as compared to placebo for the preventive treatment of episodic and chronic migraine in paediatric patients from 6 to less than 18 years of age; open-label study to evaluate the long-term safety of daily administration of atogepant for preventive treatment of episodic migraine in paediatric patients from 6 to less than 18 years of age.

3.7 Conclusions

Clinical trials demonstrated that atogepant, currently branded QULIPTA, is a well-tolerated CGRP receptor antagonist for the treatment of episodic migraine in adults. If its safety and efficacy is confirmed in the chronic migraine population, QULIPTA will revolutionize the preventive treatment arena of migraine. As an oral treatment with different dosage formulations, atogepant offers the advantage of rapid treatment adjustments to manage side effects or other health-related events, for example pregnancy in women. Its cost-effectiveness is expected to be higher than that of the available monoclonal antibodies. Its oral formulation offers an additional advantage for the patients who do not favour injectable treatments or who could benefit from a combined treatment with other preventives acting via a non-CGRP-related pathway, for example single-pulse transcranial magnetic stimulation or BOTOX. Real-world evidence on the actual efficacy and safety of atogepant in migraine patients will be valuable, as well as studies on its actual site and mechanism of action in migraine models.

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Chapter 4
Ubrogepant

Martina Curto and Luana Lionetto

4.1 Introduction

Migraine, a complex neurovascular disorder characterized by recurrent episodes of headache [1], is the leading cause of disability in persons under 50 years of age [2], and covers about 14% of the world population with a higher prevalence among females [3, 4]. Pharmacological treatment of migraine includes abortive agents for acute attacks and prophylactic medications, which are usually prescribed when patients report more than four attacks in a month [5]. Among acute attack medications, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and other nonspecific medications are often self-prescribed by migraine patients to control acute attacks with poor response [6, 7]. However, several randomized clinical trials have reported similar efficacy between NSAIDs and triptans, the first-line specific treatments for acute migraine [6, 7]. In fact, about 30–40% of migraine patients do not respond to triptans, and their use is contraindicated in patients with cardiovascular disease requiring other specific acute treatment [8–10]. For this reason, novel targets have been identified to develop additional specific and effective migraine treatments. Calcitonin gene–related peptide (CGRP) plays a key role in migraine pathophysiology through its potent vasodilator action [11, 12]. In fact, it is expressed in sensory neurons, the trigeminal ganglion, and the dorsal medullary ganglia; mediates pain transmission; is involved in neurogenic inflammation (still a topic of

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debate in migraine pathophysiology); and is released from the trigeminal ganglion during migraine headache [13, 14]. Gepants, a novel pharmacological class of CGRP receptor antagonists, have been recently developed and tested in clinical trials to determine their efficacy and safety as new and specific acute migraine drugs, and, in the case of atogepant, also as preventive medications [15]. Ubrogepant belongs to this new drug class effective to alleviate headache attacks without vasoconstrictive side effects [16–18] and has been recently approved by the Food and Drug Administration for clinical use as acute migraine treatment.

4.2 Pharmacology

4.2.1 Chemistry

The International Union of Pure and Applied Chemistry (IUPAC) chemical name of ubrogepant (also known as BHV 3000) is (3*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-5--phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-yl]-2-oxospiro[1*H*-pyrrolo[2,3-b]pyridine-3,6′-5,7-dihydrocyclopenta[b]pyridine]-3′-carboxamide. It approved for oral administration with a dosing of 50 or 100 mg.

4.2.2 Pharmacodynamics

Ubrogepant is a competitive antagonist with high affinity, potency, and selectivity for the human CGRP receptor. It is able to bind to the hydrophobic pocket of CLR-RAMP1, antagonizing initial CGRP binding and subsequent receptor activation [19]. The binding affinity of ubrogepant to native (Ki = 0.067 nM) and cloned human (Ki = 0.070 nM) and rhesus (Ki = 0.079 nM) receptors is similar, with a relatively lower affinity for CGRP receptors of other species (ranging from Ki = 9.6 to 47 nM). In preclinical studies, ubrogepant potently blocked the human α-CGRP-stimulated response to cAMP and exhibited highly selective antagonistic activity against the CGRP receptor compared to other members of the human calcitonin receptor family [20].

4.2.3 Pharmacokinetics and Metabolism

Regarding the pharmacokinetic (PK) data of ubrogepant, the mean reported Tmax is about 0.7–1.5 h, the apparent elimination half-life varies from 3 to 7 h, and metabolism involves mainly the liver CYP3A4 isoenzyme and p-glycoprotein [21]. Plasma concentrations appeared to be dose-dependent [21, 22]. Potential drug interactions of ubrogepant should be considered, as some drugs are metabolized through CYP3A4. There are currently no data on active or toxic metabolites of ubrogepant.

4.3 Clinical Registered Trials

4.3.1 Phase I Trials

Phase I studies are not registered in the clinicaltrials.gov database. However, a phase I study on 22 healthy postmenopausal or oophorectomized women evaluated the effect of multiple doses of ubrogepant on oral contraceptive PK. No results are reported regarding ubrogepant PK, except for a good correlation between whole blood and plasma concentrations in healthy volunteers [23].

4.3.2 Phase II Trials

Two phase II clinical trials have been conducted to evaluate the PK, efficacy, and tolerability of ubrogepant for the treatment of acute migraine. The first multicenter, randomized, double-blind, placebo-controlled study (NCT01657370) [22] was designed to evaluate the effect of demographic or other variables on ubrogepant PK and the correlation between drug levels and efficacy as an abortive agent. Overall, 195 patients were included in the study and assigned to placebo, ubrogepant 1, 10, 25, 50, and 100 mg groups. The primary measures were an assessment of ubrogepant blood concentrations 2 h after drug administration, freedom from pain, and pain relief 2 h after drug administration, and the secondary measures were an assessment of absence of migraine-related symptoms (phonophobia, photophobia, and nausea) 2 h after drug administration, sustained pain relief, and complete relief from migraine from 2 to 24 h after drug administration. The study confirmed that the concentration of ubrogepant is dose dependent.

The higher percentage of patients with migraine pain freedom at 2 h post dose (28.6%) resulted in the ubrogepant 50 mg group; 42.9% of patients reported pain relief 2 h post dose in the placebo and 1 mg groups, while 46.4%, 67.9%, and 70.4% of patients experienced pain relief in 25 mg, 50 mg, and 100 mg groups, respectively [22]. In the second double-blind, placebo-controlled, phase II clinical trial, 834 participants were included and randomized to placebo or different ubrogepant doses. Regarding the two primary endpoints, the results showed that ubrogepant 100 mg alone was statistically significantly superior to placebo in terms of no pain after 2 h (25.5% vs. 8.9%, respectively), but not in terms of pain relief after 2 h. With respect to the secondary outcomes (absence of migraine accompanying symptoms at 2 h, sustained pain freedom and relief 2–24 h and total migraine freedom at 2 h and 2–24 h) ubrogepant 50 and 100 mg demonstrated significant improvements for the majority of them compared to placebo [24]. An additional Phase IIb, multicenter, randomized, double-blind, placebo-controlled trial (NCT01613248) was conducted to investigate the efficacy and safety of ubrogepant [24]. In this study, 834 subjects with migraine disease were enrolled and randomized to ubrogepant 1 mg, 10 mg, 25 mg, 50 mg, 100 mg, and placebo. Significant differences respect to

placebo group were detected in the ubrogepant 25, 50, and 100 mg regarding pain freedom and pain relief at 2 h post-dose. Significant differences were also seen for ubrogepant 50 mg regarding to absence of phonophobia and photophobia at 2 h, sustained pain freedom and sustained pain relief 2–24 and 2–48 h, total migraine freedom at 2 h and at a 2–24 h [24].

4.3.3 Phase III Trials: ACHIEVE I and II and Their Extension Study

Two phase III clinical trials, named ACHIEVE I (NCT02828020) [25] and ACHIEVE II (NCT02867709) [26], were conducted to evaluate the efficacy, safety, and tolerability of oral ubrogepant as treatment for acute migraine in patients with or without aura. The use of prophylactic agents was not included in the inclusion or exclusion criteria in either study. ACHIEVE I is a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the effectiveness of 50 mg or 100 mg of oral ubrogepant for the treatment of acute migraine. A total of 1672 participants were included and 1415 participants completed the study. The primary outcomes were freedom from pain after 2 h, defined as a reduction in headache severity from moderate/severe at baseline to no pain 2 h after the initial dose, and the absence 2 h after the initial dose of the most bothersome migraine-related symptom identified at baseline. Secondary outcomes after the initial dose were considered: (1) pain relief after 2 h; (2–3) sustained pain relief and sustained freedom from pain from 2 to 24 h; and (4) absence of photophobia, phonophobia, and nausea after 2 h. Regarding the absence of pain within 2 h and the absence of the most bothersome symptom associated with migraine, the results showed that both doses of ubrogepant were significantly superior to placebo. The percentage of patients with no pain in the placebo, 50 mg, and 100 mg groups was 11.8%, 18.2%, and 21.8%, respectively, and the percentage of patients with no most bothersome symptom was 27.8%, 38.6%, and 37.7%, respectively. Regarding secondary outcomes, both the 50 and 100 mg doses outperformed placebo in pain relief within 2 h and in sustained pain relief from 2 to 24 h. However, only ubrogepant 100 mg showed sustained analgesia for 2 to 24 h and no photophobia significantly higher than placebo [25].

The second phase III trial, named ACHIEVE II, is a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the effectiveness of 25 mg or 50 mg of oral ubrogepant for the treatment of acute migraine. A total of 1686 participants was enrolled in the study and 1454 completed it. The primary and secondary outcomes of the study were the same as in the ACHIEVE I study. Ubrogepant 25 and 50 mg were significantly superior to placebo in the absence of pain after 2 h, and the absence of the most bothersome symptom associated with migraine was significantly superior to placebo for the 50 mg dose alone. Regarding secondary outcomes, the 25 mg dose was similar to placebo, and the 50 mg dose was superior to placebo for all secondary outcomes.

Notably, in contrast to results obtained in the ACHIEVE I study, ubrogepant 50 mg was superior to placebo in pain relief within 2 h, sustained pain relief and sustained pain freedom from 2 to 24 h, and the absence of photophobia and phonophobia [26].

The extension study (NCT02873221), multicenter, randomized, open-label (UBR-MD-04) enrolled 1254 patients who had completed one of the ACHIEVE I or ACHIEVE II trials. These patients were given ubrogepant doses of 50 and 100 mg and could take a second dose or a rescue drug if they did not respond to the first dose or if they had a migraine relapse. The study was designed to evaluate the long-term safety and tolerability of intermittent treatment with ubrogepant for the acute treatment of migraine (with or without aura) with respect to usual a standard therapy for 1 year. The primary outcome of the study was the occurrence of at least one treatment-emergent adverse event (TEAE) over 56 weeks of treatment, while the secondary outcomes were the assessment of clinically significant changes in laboratory tests, electrocardiogram (ECG) or vital signs and the occurrence of suicidal ideation or behavior [27]. Results after 1 year reported pain freedom at 2 h after the initial dose in ≈24% of ubrogepant-treated (50 or 100 mg) attacks and pain relief at 2 h post-dose in ≈67% of ubrogepant-treated attacks [28]. Safety and tolerability data are discussed in Sect. 4.5.

4.3.4 Post-marketing Studies

Since ubrogepant became available for prescription, one real-world study has been conducted with the aim of evaluating its safety and efficacy in patients affected mostly by chronic migraine, frequently affected by complex medical comorbidities requiring the concurrent use of multiple medications. In this study, all patients treated with ubrogepant were contacted 1–3 months after the prescription to answer a list of standardized questions. Of 106 patients included, 92 were affected by chronic migraine. Headache freedom and headache relief 2-h post dose were reported by about the 20% and the 50% of patients, respectively. Mild-to-moderate adverse events were reported by about the 40% of patients, and included fatigue, dry mouth, nausea, constipation, and dizziness [29].

4.4 Safety and Tolerability

Ubrogepant was generally well tolerated in patients with migraine included in phase I, II, and III trials. In a phase I, randomized, multicenter, double-blind clinical trial, safety and tolerability of ubrogepant 100 mg has been evaluated in 518 participants with respect to placebo. In this study, a treatment-associated adverse event (TEAE) was defined as an adverse event that occurred after the first dose or worsened in severity after the first dose. The incidence of TEAEs was similar in the two groups

(44% and 45% of patients in the ubrogepant and placebo groups, respectively). The most common AEs were headache, oropharyngeal pain, and nasopharyngitis. Severe AEs that occurred in both groups were not considered treatment related. Liver function was evaluated in relation to the incidence of increased liver enzymes. Of the seven cases of increased ALT and/or AST levels, three were considered possibly treatment related (one placebo, two ubrogepant). However, these increases were transient and resolved without treatment [21].

Ubrogepant has also been evaluated in two phase II clinical trials and three phase III clinical trials. In the first phase II study (NCT01657370) involving 195 patients receiving placebo and different doses of ubrogepant, there were no serious adverse events, and approximately 25% of patients reported nonserious adverse events in the placebo and ubrogepant 50 and 100 mg groups [22]. In a second phase II clinical trial, placebo and all doses of ubrogepant showed a similar frequency of adverse events. In particular, nausea and dizziness within 48 h of administration were the most common side effects in the ubrogepant groups, while drowsiness was more frequently observed in the placebo group [24]. In the ACHIEVE I clinical trial, serious adverse events occurred respectively in 0%, 0.64%, and 0.41% of patients in the placebo, ubrogepant 50 and 100 mg groups. No other adverse events were observed in all study groups [25]. Also in the ACHIEVE II trial no serious or other adverse events were reported in the three study groups (placebo, ubrogepant 25 and 50 mg) [26]. The recent phase III extension study to evaluate the long-term (56 weeks) safety and tolerability of oral ubrogepant reported that the overall percentage of participants with at least one TEAE was 65% in the conventional treatment group, 66.3% and 72.6% in the 50 mg and 100 mg ubrogepant groups, respectively. Changes in laboratory tests, EKG and vital signs, and suicidal thoughts or behavior were observed in a similar percentage of patients in the three groups. Similarly, the percentage of patients with serious adverse events during treatment was similar in the three groups (4.08%, 2.23%, and 2.93%, respectively) [27].

4.5 Regulatory Affairs and Clinical Approval

Ubrogepant has been developed by Allergan under license from Merck & Co., for the acute treatment of migraine and approved by the US FDA in December 2019 for the acute treatment of migraines (± aura) in adults [30]. It represents the first drug among oral CRGP antagonists approved for the acute treatment of migraine and is commercialized under the name of Ubrelvy™. The recommended dosage is 50 or 100 mg taken as needed without regard to food. A second dose may be administered at least 2 h after the initial dose if needed, with a maximum dose in a 24-h period of 200 mg. In patients with severe hepatic or renal impairment, the recommended dose is 50 mg; a second dose may be administered at least 2 h after the initial dose if needed [30].

4.6 Conclusions

Ubrogepant, a selective and potent CGRP competitive antagonist belonging to the gepants family, has been recently approved for the oral acute treatment of migraine under the name of Ubrelvy™ 50 and 100 mg. Large phase III trials showed that long-term treatment with ubrogepant did not significantly affect liver function and was not associated with other serious adverse events or with significant cardiovascular changes. Nevertheless, ubrogepant metabolism involves the hepatic cytochrome P450 3A4 isoenzyme, and potential drug–drug interactions or the production of active metabolites have not been investigated yet. The efficacy of the drug has been evaluated in large placebo-controlled trials in which ubrogepant 50 and 100 mg were superior to placebo in terms of 2-h freedom from pain and absence of the most bothersome symptom 2 h after administration. Nevertheless, the therapeutic gain for ubrogepant appears to be lower than the therapeutic benefit of triptans. From this point of view, future studies with active comparators such as triptans or ditans are needed to help physicians balance the risk–benefit profiles of different drugs for the treatment of acute migraine. In fact, compared with triptans or ditans, ubrogepant has shown a more favorable safety profile, a critical issue for migraneurs potentially overusing acute medications.

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Chapter 5
Rimegepant

Andrea Negro

5.1 Introduction

Rimegepant is an oral calcitonin gene–related peptide (CGRP) receptor antagonist developed for the acute and preventive treatment of migraine by Biohaven Pharmaceuticals, under license from Bristol Myers Squibb [1]. The completed phase II and III trials showed its efficacy in terms of pain freedom, pain relief, and freedom from the most bothersome symptoms associated with migraine, with an effect sustained up to 48 h. Significant clinical efficacy has been reported with a rimegepant single dose. In long-term studies rimegepant was well tolerated and the few adverse events were mild or moderate and did not cause trial discontinuation.

Rimegepant 75 mg ODT (Nurtec® ODT; Biohaven Pharmaceutical Holding Company Ltd.) received FDA approval on February 27, 2020, for the acute treatment of migraine with or without aura in adults [2]. On May 27, 2021, FDA extended the indication also for the prevention of episodic migraine [3], making rimegepant the first oral CGRP antagonist approved to prevent migraine.

Rimegepant is the first, and currently the only, medication approved as a dual therapy for both the acute and preventive treatment. Consequently, the daily use of rimegepant could not considered "medication overuse" for rimegepant [4].

This chapter will review available data on pharmacodynamics, pharmacokinetics, metabolism, efficacy, and safety of rimegepant.

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5.2 Introduction to the Compound

In 2012, the gepants' family grew after the addition of a fifth member called BHV-3000 (formerly BMS-927711) and now known as rimegepant (Fig. 5.1).

The IUPAC chemical name of rimegepant is (5*S*,6*S*,9*R*)-5-amino-6-(2,3-difluorophenyl)-5*H*,6*H*,7*H*,8*H*,9*H*-cyclohepta[b]pyridin-9-yl-4-{2-oxo-1*H*,2*H*,3*H*-imidazo[4,5-b]pyridin-1-yl}piperidine-1-carboxylate.

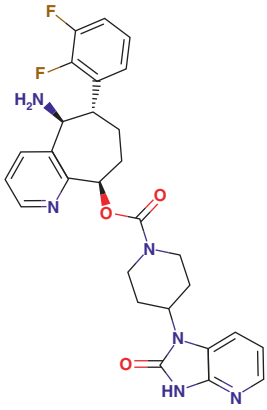
5.2.1 Chemistry

Rimegepant belongs to the class of organic polycyclic compounds known as imidazopyridines that are characterized by an imidazole ring fused to a pyridine ring. These are organic polycyclic compounds containing an imidazole ring fused to a pyridine ring. Imidazole is five-membered ring consisting of three carbon atoms, and two nitrogen centers at the 1- and 3-positions. Pyridine is a six-membered ring consisting of five carbon atoms and one nitrogen center. The presence of a primary amino inside the chemical structure of this compound enhances the pharmacokinetic properties by improving its water solubility (0.0755 mg/mL) [5].

Fig. 5.1 Rimegepant chemical structure

Drug name:	**Rimegepant**
Route of administration:	**Oral**
Pharmacology description:	**CGRP receptor antagonist**
Chemical Formula:	**C28H28F2N6O3**
Type:	**Small Molecule**
Weight	
Average:	**534.568**
Monoisotopic:	**534.219095112**

Chemical structure



5.2.2 Pharmacodynamics

Luo and colleagues described the CGRP receptor antagonism of rimegepant both in vitro and in vivo [6]. The in vitro evaluation of the efficacy of rimegepant was assessed by measuring the inhibition of CGRP-stimulated cAMP release in SK-N-MC cells. Rimegepant showed a complete and competitive receptor antagonism with a half maximal inhibitory concentration (IC50) of 0.14 ± 0.01 nM and an inhibitor constant (Ki) of 0.027 nM. The compound showed low levels of inhibition for CYP3A4 isoform (IC50: 17 μM) and for seven others recombinant hCYP isoforms (IC50 ≥ 20 μM). At 10 and 30 μM, rimegepant caused less than 30% inhibition of the hERG potassium channel α-subunit expressed in HEK-293 cells, and no significant effect was found on L-type calcium or sodium channels expressed in these cells.

The in vivo evaluation was assessed by using a primate model of CGRP-induced facial blood flow. Rimegepant was evaluated by measuring the induced 75–80% reduction of facial blood flow in marmosets after intravenous injection of hαCGRP. The inhibition peaks were strong at 60- and 105-min post-dose with corresponding plasma levels just below 800 nM. In addition, the study also demonstrated good oral bioavailability in rats and cynomolgus monkeys.

Rimegepant does not require dose adjustment in patients with mild-to-severe renal impairment and in patients with mild or moderate hepatic impairment. In clinical trials, plasma concentrations of rimegepant were significantly higher in patients with severe (i.e., Child–Pugh C) hepatic impairment and its use should be avoided in case of severe hepatic impairment [7].

Hypersensitivity reactions have occurred during clinical studies and patients should be made aware of this possibility. Rimegepant should be discontinued immediately if hypersensitivity reaction occurs.

5.2.3 Pharmacokinetics and Metabolism

A phase I, open-label, randomized study evaluated the bioequivalence of two formulations of rimegepant 75 mg—oral tablet and orally dissolving tablet (ODT)—in 35 adult healthy volunteers [8]. The study aimed to investigate the safety, tolerability, and pharmacokinetic features besides to compare the absorption rate and the extent of both formulations. Participants were treated twice with rimegepant ODT administered sublingually without water or rimegepant oral tablet swallowed with water. The median time of maximum plasma concentration (Tmax) was 1.5 h for rimegepant ODT and 2.0 h for rimegepant oral tablet and the difference of time to peak concentration was statistically significant (1.48 h vs. 1.92 h for rimegepant ODT and oral tablet, respectively). Rimegepant showed an absolute oral

bioavailability of approximately 64%. The analysis of the area under the plasma concentration-time curve (AUC) from time 0 to 24 h post-dose (AUC0–*t*), AUC0–∞ and the maximum plasma concentration (Cmax) showed the bioequivalence between the ODT and oral tablet formulations. When administered with a high-fat meal, Tmax is delayed by 1 h, Cmax is decreased by 42–53%, and AUC is decreased by 32–38%. The clinical significance of this difference in pharmacokinetics is unknown.

Another phase I, open-label, randomized study compared the pharmacokinetics of rimegepant during migraine and nonmigraine condition (ClinicalTrials.gov Identifier: NCT01445067) [9]. Forty-eight migraine patients were randomized to receive one of two doses of rimegepant (oral capsule, 300 and 600 mg, once) during an acute migraine attack and during the nonmigraine period. The primary outcome measures of the study were the Cmax, the Tmax, the AUC0–*t* from time 0 to 24 h, the plasma concentration at 0.5 (C0.5 h) and 2 h (C2 h) and the apparent total body clearance (CLT/F). For these pharmacokinetics values, samples were collected for up to 24 h after the dosing. The secondary outcome measures were the same investigated as primary but with a time frame from Day 1 (0 h) to Day 2 (24 h) time points. The results of the study, completed in September 2012, are not available.

5.2.4 Metabolism

At steady state, the volume of distribution is approximately 120 L. Rimegepant is approximately 96% plasma protein-bound but the specific proteins to which it binds have not been elucidated [6]. The elimination half-life in healthy subjects is approximately 11 h [7].

Rimegepant is metabolized by CYP3A4 and, to a lesser extent, by CYP2C9 [7]. Approximately 77% of an administered dose is eliminated unchanged. This finding, together with the fact that specific metabolites of rimegepant have not been characterized and no major metabolites have been detected in plasma, suggest that metabolism is likely to be a minor means of drug elimination. About 78% of the drug dose is recovered in feces and 24% in urine, and unchanged parent drug is the major component in each [7].

5.2.5 Drug Interactions

In phase II and phase III studies, concomitant use of migraine drugs was prohibited and drugs metabolized by CYP3A4 were considered a risk for drug–drug interactions. However, the pharmacokinetics of rimegepant might be potentially affected by interactions with CYP3A4-metabolized molecules.

5.3 Clinical Efficacy

This section will review the clinical studies assessing the efficacy of rimegepant for both the acute and the preventive treatment of migraine (Tables 5.1 and 5.2).

5.3.1 Phase II Studies

A randomized, double-blind, placebo-controlled, phase II study evaluated the efficacy of six doses of rimegepant (10, 25, 75, 150, 300, and 600 mg) for the acute treatment of migraine compared to sumatriptan 100 mg and placebo (ClinicalTrials.gov Identifier NCT01430442) [10]. The primary efficacy outcome was the percentage of patients who were free from pain at 2 h post-dose. Among the rimegepant dosing groups, the 150 mg dose was slightly more effective than the other doses compared to placebo (32.9% vs. 15.3%, $p < 0.001$), but less effective than sumatriptan (35%). The proportions of patients free from pain with rimegepant 75 and 300 mg were 31.4% ($p = 0.002$) and 29.7% ($p = 0.002$) respectively, while no additional benefit was observed with the higher dose of 600 mg (24.4%).

This study also investigated three secondary efficacy outcomes: total migraine freedom at 2 h post-dose (no migraine-associated symptoms), sustained pain freedom (no recurrence of migraine and no use of rescue medication) from 2 to 24 h and from to 2 to 48 h post-dose. Rimegepant 75, 150, and 300 mg, as well as sumatriptan were significantly more effective than placebo in achieving total migraine freedom at 2 h post-dose (27.9%, 25.9%, and 23.4% vs. 11.8%, respectively) and sustained pain freedom from 2 to 24 h (27.9%, 28.2% and 26.1% vs. 7.4%, respectively; sumatriptan 26%). Rescue medications were used more often by subjects in the placebo group (50.7%), followed by 600 mg (41.7%), 10 mg (38.9%), sumatriptan (31.0%), 25 mg (29.0%), 150 mg (25.6%), 75 mg (24.4%), and 300 mg (24.1%) dosing groups.

5.3.2 Phase III Studies

Three phase III clinical trials were conducted in order to evaluate the efficacy of rimegepant as acute migraine treatment in patients with or without aura.

A randomized, double-blind, placebo-controlled, phase III study assessed the efficacy of rimegepant 75 mg oral tablets to treat a single migraine attack (Study 301, ClinicalTrials.gov Identifier NCT03235479) [11]. Preliminary results on 1162 among 1485 enrolled patients were presented as congress communication [12]. Rimegepant was significantly more effective than placebo for both the co-primary efficacy outcomes, percentage of patients with pain freedom at 2 h post-dose

Table 5.1 Rimegepant: clinical trials

ID number [reference]	Official title	Phase	Number enrolled	Primary outcomes	Secondary outcomes	Status
NCT01445067 [9]	Phase I, open-label, randomized, single sequence study with two dose groups to compare the pharmacokinetics of BMS-927711 in migraine subjects during an acute migraine attack and during non-migraine period	I	48	Cmax	Cmax	Completed
				Tmax	Tmax	
				AUC(0–24)	AUC(0–24)	
				C0.5 h	C0.5 h	
				C2 h	C2 h	
				CLT/F	CLT/F	
NCT01430442 [10]	Phase IIb: Double-blind, randomized, placebo controlled, dose-ranging trial of BMS-927711 for the acute treatment of migraine	II	885	2 h PF	Total migraine freedom at 2 h	Completed
					Frequency and severity of AEs	
					2–24 h SPF	
					2–48 h SPF	
NCT03235479 [11, 12]	BHV3000-301: Phase 3: Double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3000 (Rimegepant) for the acute treatment of migraine	III	1485	2 h PF Freedom from MBS at 2 h	Freedom from phonophobia at 2 h	Completed
					Freedom from photophobia at 2 h	
					2 h PR	
					Freedom from nausea at 2 h	
					Rescue medication use at 24 h	
					2–24 h SPF	
					2–24 h SPR	
					2–48 h SPF	
					2–48 h SPR	
					Pain relapse at 2–48 h	
					Freedom from functional disability at 2 h	

NCT03237845 [13]	BHV3000-302: Phase 3: Double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3000 (Rimegepant) for the acute treatment of migraine	III	1499	2 h PF Freedom from MBS at 2 h	2–24 h SPF	Completed
					2–48 h SPF	
					2 h PR	
					2–24 h SPR	
					2–48 h SPF	
					Freedom from photophobia at 2 h	
					Freedom from phonophobia at 2 h	
					Freedom from nausea at 2 h	
					Rescue medication within 24 h	
					FDS at 2 h	
					Pain relapse within 48 h	
NCT03461757 [14]	BHV3000-303: Phase 3, double-blind, randomized, placebo controlled, safety and efficacy trial of BHV-3000 (Rimegepant) orally disintegrating tablet (ODT) for the acute treatment of migraine	III	1811	2 h PF Freedom from MBS at 2 h	2–24 h SPF	Completed
					2–48 h SPF	
					2 h PR	
					2–24 h SPR	
					2–48 h SPF	
					Freedom from photophobia at 2 h	
					Freedom from phonophobia at 2 h	
					Freedom from nausea at 2 h	
					Rescue medication within 24 h	

(continued)

Table 5.1 (continued)

ID number [reference]	Official title	Phase	Number enrolled	Primary outcomes	Secondary outcomes	Status
NCT03732638 [15]	A phase II/III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Rimegepant in migraine prevention	II/III	1629	Change from baseline in mean monthly migraine days (week 9 to end of week 12)	50% reduction from baseline in moderate-to-severe monthly migraine days per month (week 9 to end of week 12)	Completed
					Change from baseline in monthly migraine days (across the 12-week treatment period)	
					Change from baseline in monthly rescue medication use days (week 9 to end of week 12)	
					Adverse events; frequency of AST or ALT elevations; frequency of hepatic-related adverse events and hepatic-related treatment (baseline to end of week 12)	
					Change from baseline in the MSQ role function and MIDAS total score (baseline to end of week 12)	
NCT03266588 [16, 17]	A multicenter, open label long-term safety study of BHV3000 in the acute treatment of migraine	III	1909	Safety and tolerability (over 52 weeks)	Elevated liver function tests Hepatic-related AEs	Completed
NCT03934086 [18]	BHV3000-401: An open-label, intermediate-size, expanded access study of BHV-3000 in the acute treatment of migraine	III	NA	To allow subjects who have completed any rimegepant clinical study to continue to have access to rimegepant during the ongoing safety data		No longer available (results not available)

AUC(0–24) area under the plasma concentration–time curve from time 0 to 24 h; *AEs* adverse events; *C0.5 h* observed plasma concentration at 0.5 h; *C2 h* observed plasma concentration at 2 h; *CLT/F* apparent total body clearance; *Cmax* maximum observed plasma concentration; *FDS* Functional Disability Score; *MBS* nausea, phonophobia or photophobia; *PF* pain freedom; *PR* pain relief; *SPF* sustained pain freedom; *SPR* sustained pain relief; *Tmax* time of maximum observed plasma concentration; *Total migraine freedom* pain freedom, coupled with no symptoms of phonophobia, photophobia, or nausea

Table 5.2 Efficacy endpoints in completed phase II and phase III clinical trials

Rimegepant	Pain freedom at 2 h	Pain relief at 2 h	Freedom from MBS at 2 h	SPF at 2–24 h	SPF at 2–48 h	References
75 mg	31.4 vs. 15.3 (16.1)$^{\#}$	72.1 vs. 51.2 (20.9)*	–	27.9 vs. 7.4 (20.5)*	27.9 vs. 7.4 (20.5)*	[10]
150 mg	32.9 vs. 15.3 (17.6)$^{\#}$	61.2 vs. 51.2 (10.0)^{NS}	–	28.2 vs. 7.4 (20.8)*	28.2 vs. 7.4 (20.8)*	
300 mg	29.7 vs. 15.3 (14.4)$^{\#}$	75.5 vs. 51.2 (24.3)*	–	26.1 vs. 7.4 (18.7)*	26.1 vs. 7.4 (18.7)*	
600 mg	24.4 vs. 15.3 (11.1)$^{\#}$	78.0 vs. 51.2 (26.8)*	–	20.7 vs. 7.4 (13.3)$^{\#}$	20.7 vs. 7.4 (13.3)$^{\#}$	
Sumatriptan 100 mg	35.0 vs. 15.3 (19.7)*	72.0 vs. 51.2 (20.8)*	–	26.0 vs. 7.4 (18.6)*	26.0 vs. 7.4 (18.6)*	
75 mg	19.2 vs. 14.2 (5.0)$^{€}$	–	36.6 vs. 27.7 (8.9)$^{\#}$	14.0 vs. 8.1 (5.9)$^{\#}$	–	[11, 12]
75 mg	19.6 vs. 12.0 (7.6)*	58.1 vs. 42.8 (15.3)*	37.6 vs. 25.2% (12.4)*	12.3 vs. 7.1 (5.2)^{NS}	9.9 vs. 6.0 (3.9)^{NS}	[13]
75 mg	21.2 vs. 10.9 (10.3)$^{¥}$	59.3 vs. 43.3 (16.0)*	27.1% vs. 17.7 (9.4)*	15.7 vs. 5.6 (10.1)$^{¥}$	13.5 vs. 5.4 (8.1)$^{¥}$	[14]

SPF sustained pain freedom
Level of significance (as reported in the original papers): $^{\#}p < 0.002$; $*p \leq 0.001$; ^{NS}p not significant; $^{€}p < 0.03$; $^{¥}p < 0.0005$

(19.2% vs. 14.2%, respectively; $p = 0.0298$) and freedom from the patient's most bothersome symptoms associated with migraine (i.e., phonophobia, photophobia, or nausea) at 2 h post-dose (36.6% vs. 27.7%, respectively; $p = 0.0016$).

Rimegepant was significantly more effective than placebo also for some of the secondary outcomes: percentage of participants with pain relief (56.0% vs. 45.7%, respectively; $p = 0.0006$), freedom from photophobia (34.9% vs. 24.8%, respectively; $p < 0.0005$) and phonophobia (38.6% vs. 30.9%, respectively; $p = 0.0299$) at 2 h post-dose; percentage of participants with sustained pain freedom at both 2 to 24 h (14% vs. 8.1%, respectively; $p = 0.0020$) and 2 to 48 h (11.6% vs. 7.2%, respectively; $p = 0.013$) and with sustained pain relief for both 2 to 24 h (38.9% vs. 27.9%, respectively; $p < 0.0001$) and 2 to 48 h (33.7% vs. 23.9%, respectively; $p < 0.0003$).

The second randomized, double-blind, placebo-controlled, phase III clinical trial enrolled 1186 participants who were randomized to treat a single migraine attack with rimegepant 75 mg oral tablets or placebo (Study 302, ClinicalTrials.gov Identifier: NCT03237845) [13]. This study evaluated the same primary and

secondary outcomes investigated by the above-mentioned trial. The results confirmed the previous findings and showed that, compared to the placebo group, a higher percentage of patients in the rimegepant group was pain-free (19.6% vs. 12.0%, respectively; $p < 0.001$) and free from the most bothersome symptom at 2 h post-dose (37.6% vs. 25.2%, respectively; $p < 0.001$).

Among the secondary outcomes investigated, rimegepant was significantly more effective than placebo for the percentage of participants with pain relief (58.1% vs. 42.8%, respectively; $p < 0.001$), freedom from photophobia (37.4% vs. 22.3%, respectively; $p < 0.001$) and freedom from phonophobia at 2 h post-dose (36.7% vs. 26.8%, respectively; $p = 0.004$). There was no significant difference between rimegepant and placebo in the proportion of patients with sustained pain relief at 2–24 h (42.6% vs. 36.3%) and 2–48 h post-dose (26.5% vs. 22.6%). Similarly, there was no significant difference for sustained pain relief at 2–24 h and 2–24 h post-dose, which was reported by 42.6% and 36.3% of patients treated with rimegepant 75 mg, compared with 26.5% and 22.6% of the placebo group, respectively.

In the third double-blind, placebo-controlled, multicenter phase III trial, 1466 subjects were randomly assigned to receive rimegepant 75 mg ODT or placebo to treat a single migraine attack (Study 303, ClinicalTrials.gov Identifier: NCT03461757) [14]. Rimegepant was superior to placebo for both the co-primary outcomes, freedom from pain (21.2% vs. 10.9%, $p < 0.0001$) and freedom from the most bothersome symptoms at 2 h post-dose (35.1% vs. 26.8%, $p = 0.0009$).

The study investigated 21 secondary outcomes organized into three categories based on time frame. The first category included the outcomes assessed at 2 h post-dose. The second category, the endpoints that reflect early action, evaluated at 60 and at 90 min. The third category, the endpoints that measure the duration of treatment, assessed from 2 to 24 h and from 2 to 48 h post-dose. Rimegepant was superior to placebo for all secondary endpoints, including pain relief (36.8% vs. 31.2%) and ability to function normally at 60 min post-dose (22.3% vs. 15.8%); freedom from pain (15.1% vs. 7.3%), freedom from most bothersome symptom (27.4% vs. 21.5%), and ability to function normally at 90 min post-dose (30.2% vs. 21.3%); use of rescue medications within 24 h (85.8% vs. 70.8%); sustained freedom from pain from 2 to 24 h (15.7% vs. 5.6%) and 2 to 48 h post-dose (13.5% vs. 5.4%); sustained freedom from most bothersome symptom at 2–24 h (27.1% vs. 17.7%) and 2–48 h post-dose (23.2% vs. 16.4%); and sustained pain relief from 2 to 24 h (47.8% vs. 27.7%) and 2 to 48 h post-dose (42.2% vs. 25.2%). Rimegepant was not superior to placebo only for freedom from nausea and pain relapse.

Only one phase II/III randomized, double-blind, placebo-controlled was conducted in order to evaluate the efficacy of rimegepant 75 mg for the preventive treatment of migraine (ClinicalTrials.gov Identifier: NCT03732638) [15]. Adults ($n = 1591$) with at least a 1-year history of migraine and reporting 4–18 attacks were recruited, of whom 747 were randomly allocated either rimegepant ($n = 373$) or placebo ($n = 374$) every other day for 12 weeks (double-blind treatment phase). Rimegepant was superior to placebo on the primary endpoint of change in the mean number of migraine days per month during weeks 9–12 (−4.3 days vs. −3.5 days, respectively; $p = 0.0099$).

Rimegepant was also superior to placebo on some secondary efficacy endpoints: achievement of at least a 50% reduction in the mean number of moderate or severe migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12) (49% vs. 41%, respectively; $p = 0.044$); change in mean number of total migraine days per month over the 3-month treatment period (−3.6 vs. −2.7; $p = 0.0017$); and change in the mean number of migraine days per month in the first 4 weeks of the double-blind treatment phase (weeks 1–4) (−2.9 vs. 1.7, respectively; $p < 0.0001$). The rimegepant and placebo treatment groups did not statistically differentiate with respect to the mean days of rescue medication per month in the last month of the double-blind phase (3.7 vs. 4.0, respectively; $p = 0.39$).

5.4 Safety and Tolerability

This section will review the clinical studies assessing the safety and tolerability of rimegepant for both the acute and the preventive treatment of migraine (Table 5.1).

5.4.1 Phase I Studies

Croop and colleagues conducted a phase I, open-label, randomized study to assess the pharmacokinetics of rimegepant 75 mg ODT and 75 mg oral tablet in 35 healthy volunteers [8]. About 48% of subjects experienced mild adverse events (AEs) such as constipation, headache, back pain, flu-like symptoms, increased alanine aminotransferase (ALT) levels, and increased heart rate. However, none of the AEs required treatment and serious AEs were not reported.

5.4.2 Phase II Studies

Two phase II/III clinical trials were conducted in order to evaluate the efficacy of rimegepant as acute migraine treatment in patients with or without aura.

In a randomized, double-blind, placebo-controlled, dose-ranging, phase II clinical trial comparing six doses of rimegepant (10, 25, 75, 150, 300, and 600 mg) with sumatriptan 100 mg and placebo, the incidence of AEs was similar across the active treatment and placebo groups (ClinicalTrials.gov Identifier: NCT01430442) [10]. However, the single-dose design of the study provides limited information regarding safety and tolerability. The most frequent AEs within 48 h after administration were moderate or mild. The overall incidence of AEs was comparable throughout the placebo and active treatment groups. The most frequent AEs within 48 h after administration were moderate or mild. The most common AE was nausea, which was dose dependent (1.4% in the 10 mg group, 0% in the 25 mg, 3% in each of the

75 and 150 mg dose groups, 4% in the 300 mg, and 8% in the 600 mg groups; 2% in the placebo and sumatriptan groups). Other frequent AEs were dizziness (3% in the 10 mg, 2% in the 25 and 150 mg groups, 1% in the 75 mg, 0% in the 300 mg, and 4% in the 600 mg groups; 2% in the placebo and sumatriptan group) and vomiting (0% of patients in the 10, 150, and 300 mg group, 3% in the 25 mg group, and 2% in the 75 and 600 mg group; 2% in the placebo and 1% in the sumatriptan group). There were no clinically relevant ECG findings, vital sign abnormalities, or physical examination findings. Of note, two patients had increased hepatic enzymes reported as an adverse event. One patient in the rimegepant 75 mg dose group had a report of a mild increase in a hepatic enzyme on day 7 that resolved after 64 days. The second patient was in the placebo group. No deaths were reported and no patients discontinued because of AEs.

The second phase II/III, open-label study assessed the long-term (52 weeks) safety of repeated dosing rimegepant 75 mg (ClinicalTrials.gov Identifier: NCT03266588) [16]. Preliminary results were first posted on July 2, 2020, and were presented as congress communication [17]. Three groups of study participants (= 1908) were randomized into two treatment regimens: individuals with 2–8 (group 1) and 9–14 (group 2) self-reported historical moderate-to-severe migraine days per month preceding enrollment in the group, self-administered rimegepant 75 mg up to once daily as needed (PRN) for 52 weeks; while individuals with 4–14 (group 3) moderate-to-severe migraine days per month self-administered rimegepant 75 mg on a fixed every-other-day schedule and as needed on nonscheduled dosing days (QOD + PRN) for 12 weeks. The co-primary outcomes were the assessment of frequency of AEs, serious AEs and AEs leading to discontinuation and the number of participants with clinically significant laboratory abnormalities; the secondary outcomes were elevations of ALT or AST (>3 the ULN) concurrent with bilirubin elevations (>2 the ULN), hepatic-related AEs and hepatic-related AEs leading to discontinuation. The only AEs occurring in more than 5% of treated participants were nasopharyngitis (7.0% of PRN(2–8), 8.5% of PRN(9–14) and 3.1% of EOD + PRN group), sinusitis (5.5% of PRN(2–8), 5.8% of PRN(9–14) and 2.4% of EOD + PRN group) and upper respiratory tract infection (10.5% of PRN(2–8), 7.9% of PRN(9–14) and 4.20% EOD + PRN group). The frequency of serious AEs was low in all the three groups (2.7%, 3.3%, and 1.0%, respectively) as was the frequency of AEs leading to discontinuation during the treatment period (2.3%, 3.3%, and 2.8%, respectively). The only clinically significant laboratory abnormalities during the treatment period occurring in ≥1% of treated participants were elevation of LDL-cholesterol (3.4%, 3.9%, and 0.8%, respectively) and creatine kinase levels (1.6%, 2.2%, and 1.1%, respectively). Elevations of AST or ALT >3 the ULN concurrent with total bilirubin >2 the ULN were not reported during the treatment period. The incidence of hepatic-related AEs was low in all the groups (1.5%, 2.1%, and 0.0%, respectively) as was the frequency of hepatic-related AEs leading to discontinuation (0.3%, 0.6%, and 0.0%).

Only one phase II/III randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of rimegepant 75 mg with placebo for the preventive treatment of episodic migraine (ClinicalTrials.gov Identifier: NCT03732638)

[15]. The assessment of the safety and tolerability belonged to the secondary outcomes and included the frequency of participants with (1) AEs, serious AEs, and AEs leading to discontinuation of the study; (2) clinically significant laboratory test abnormalities; (3) liver enzymes elevations (ALT or aspartate aminotransferase [AST] elevation >3 the upper limit normal [ULN] concurrently with bilirubin elevations >2 the ULN); and (4) the incidence of hepatic-related AEs and hepatic-related AEs leading to discontinuation of treatment. Participants who received rimegepant and placebo were equally likely to have an AE, with 36% individuals in each treatment group reporting an adverse event. Adverse events occurring in at least 2% of rimegepant-treated participants were nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection. Nearly all AEs were mild or moderate in severity. Treatment-related AEs occurred in 11% of patients who received rimegepant and 9% who received placebo; no treatment-related serious AEs were reported in the rimegepant group. The rate of discontinuation from the study due to an AE was low in both rimegepant (2%) and placebo (1%) groups. Of note, four (1%) participants who were treated with rimegepant and two (1%) who were treated with placebo had increased hepatic enzymes. One participant in the rimegepant group (<1%) had asymptomatic ALT elevation >10 the ULN but alkaline phosphatase and bilirubin levels were always within normal limits. One (<1%) other participant in the rimegepant group had bilirubin levels >2 the ULN and was diagnosed with a hereditary liver disorder (Gilbert syndrome) after genotyping.

5.4.3 Phase III Studies

A randomized, double-blind, placebo-controlled, phase III clinical trial enrolled 1499 participants to treat a single migraine attack with rimegepant 75 mg oral tablets or placebo (Study 302, ClinicalTrials.gov Identifier: NCT03237845) [13]. The most common AEs were nausea (1.8% in the rimegepant 75 mg and 1.1% in the placebo group) and urinary tract infections (1.5% and 1.1%, respectively). Back pain, considered a serious AE, was reported in one participant in the rimegepant group and in two participants in the placebo group. AST and ALT levels were moderately increased in both the rimegepant and placebo groups (2.4% and 2.2%, respectively), but <3× the ULN, and the total bilirubin level did not increase >2× the ULN.

The safety profile of rimegepant 75 mg ODT was confirmed by another placebo-controlled, phase III clinical that enrolled 1466 subjects (Study 303, ClinicalTrials.gov Identifier: NCT03461757) [14]. No cases of serious AEs were reported in treated participants and the most common AEs were nausea and urinary tract infection, both occurring in less than 2% of participants, with no significant differences between treated groups. Liver function tests showed transaminase elevation >3 the ULN in one participant in each treatment group, but there was no sign of hepatotoxicity and no participant in either group had bilirubin elevations >2 the ULN.

An open-label, expanded access study had the purpose to allow subjects who had completed any rimegepant clinical trial to continue to have access to rimegepant while collecting ongoing safety data (ClinicalTrials.gov Identifier: NCT03934086) [18]. The last update was posted on March 3, 2020, but the results are not available.

5.5 Exclusion Criteria

Participants were excluded if they had a history or current evidence of any unstable medical condition that, in the investigator's opinion, would expose them to undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. Participants were also excluded if they had a history of (1) uncontrolled, unstable, or recently diagnosed cardiovascular disease; (2) uncontrolled hypertension or uncontrolled diabetes; (3) major depressive episode within the last 12 months or requiring more than one medication; (4) major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder; (5) pain syndromes, psychiatric conditions, dementia, or significant neurological disorders might interfere with study assessments; (6) gastric or small intestinal surgery or a disease that causes malabsorption; (7) gallstones or cholecystectomy; or (8) HIV disease. Pregnancy or breastfeeding were exclusion criteria in most of the clinical trials because CGRP contributes to the vascular adaptations during pregnancy. Systemic CGRP levels change during gestation, peaking during the third trimester and, therefore, CGRP blockade may negatively affect both the mother and the fetus, especially in the last trimester [19].

5.6 Conclusions

Rimegepant represents perhaps the most significant breakthrough in migraine treatment in the last two decades. Rimegepant is the only compound from the gepants' drug class to have been evaluated and approved for both the acute and preventative treatment of migraine, and this could lead to an innovative therapeutic approach. Migraine patients could control the therapy using the same treatment in a continuous or acute fashion according to their needs.

Future phase IV studies should be designed to evaluate potential drug–drug interactions and investigate the safety of rimegepant during pregnancy.

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Chapter 6
Zavegepant

Matilde Capi, Valerio De Angelis, Donatella De Bernardini, and Paolo Martelletti

6.1 Introduction

Migraine is a complex neurological disease classified by the World Health Organization (WHO) as the third most common disease under the age of 50. In 2016, the Global Burden of Disease (GBD) classified this disease as the sixth most widespread and one of the first causes of disability in the world involving young adults, women in childbearing age, and in working age [1]. Migraine attacks occur with pain from moderate-to-severe intensity associated with symptoms such as nausea, photophobia, phonophobia, and vomiting [2]. In recent years, numerous studies regarding the pharmacological therapy of migraine have been conducted, leading to an increase in the availability of drugs used for acute and preventive therapy. Numerous researches have led to the discovery of the peptide linked to the calcitonin gene (calcitonin gene–related peptide, CGRP), that is responsible in some cases for the transmission of pain signals involved in migraine. CGRP is a neuropeptide, composed of 37 amino acids encoded by the calcitonin gene, with localization in the central and peripheral nervous and trigeminal system with a key role in several

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pathogenic mechanisms of migraine and pain perception such as vasodilation, degranulation of mast cells, neurogenic inflammation, activation of the sensitive signal, peripheral and central sensitization [3]. Based on the scientific discoveries on these new receptors involved in the pathology, new molecules called Gepants have been developed. These drugs are selective CGRP receptor antagonists. This work describes and characterizes a new small molecule called Zavegepant, a structurally unique third-generation CGRP receptor antagonist. Zavegepant, also known as BMS-742413, BHV-3500, or vazegepant, was developed by Biohaven Pharmaceutical under license of Bristol Myers Squibb. It has chemical and physical properties that make it suitable for oral, inhalation, and intranasal administration using the unit dosing system Aptar Pharma approved by FDA. The properties of this molecule such as oxidative stability, low nasal irritation, and great aqueous solubility make it the first and only intranasal antagonist of the CGRP receptor (see Fig. 6.1).

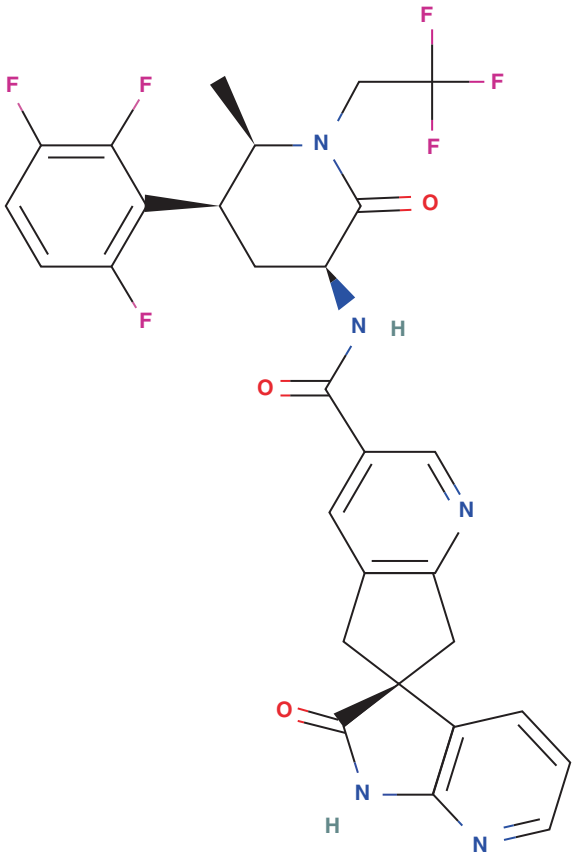

Fig. 6.1 Zavegepant chemical structure

6.2 Preclinical Pharmacology

Up-to-date, preclinical data are limited. Chaturvedula et al. studied the capability of zavegepant as a CGRP receptor antagonist, conducting an inhibition study using SK-N-MC cell membranes. They reported a concentration-dependent inhibition of [125I] CGRP binding to the human CGRP receptor, with a mean Ki of 23 ± 2 pM. The authors measured the drug's functional receptor antagonism by assessing its ability to inhibit CGRP-stimulated formation of cyclic AMP (Kb = 22 pM) in SK-N-MC cells, founding it to be a full competitive antagonist. They conducted radioligand binding tests showing a selectivity for CGRP receptor 10,000-fold greater than that to adrenomedullin receptors 1 and 2, calcitonin, or amylin receptors 1 and 3 among the receptors of the calcitonin receptor family [4, 5]. In ex vivo studies on human intracranial arteries show that zavegepant fully reversed the CGRP-induced dilation, with an EC50 = 880 ± 50 pM. It has also been observed, simultaneously, a shift of the CGRP concentration–response curve rightwards (Kb = 91 pM). Furthermore, zavegepant presented no active constriction, and it is therefore likely to show the absence of the typical cardiovascular effects of triptans.

Zavegepant efficacy has also been tested in vivo studies, conducted on anesthetized marmosets by the intravenous injection with hαCGRP (10 μg/kg), at 45 min intervals (−30, 15, 60, and 105 min), increasing laser doppler facial blood flow. Zavegepant (0.03 mg/kg s.c.) showed a percentage of inhibition of 48%, 80%, and 70% compared to pre-dose control (−30 min) at 15, 60, and 105 min post dose, respectively.

Zavegepant 10 μM showed no significant potential for off-target changes in a wide group of receptors and ion channels. The authors conducted in vitro studies in order to investigate zavegepant safety profile. These studies reported low hepatotoxicity and cardiovascular and genotoxic risks.

Zavegepant was well tolerated in rats when dosed ≤60 mg/kg s.c., and it showed no systemic toxicity after 10 days of administration. Furthermore, no intranasal irritancy was observed when administered at 75 mg/mL at 7 days post dose, but lesions in the nasal olfactory and respiratory epithelium, characterized by epithelial atrophy in a dose-dependent manner, have been observed at higher concentrations. More severe symptoms like inflammation, erosion, ulceration, and necrosis of the olfactory epithelium were observed when zavegepant was administered at 175 mg/mL.

Studies conducted in rabbits a rapid and efficacious intranasal absorption was observed, with a Tmax within 15–20 min post dose. The absolute bioavailability was respectively 13% and 30% at 10 and 100 mg/mL solutions, dependent on the dose concentration. The Cmax parameter was ranged within 0.12 and 2.0 μM (from 10 to 100 mg/mL) [4].

Preliminary results of a phase I clinical trial, conducted to define the pharmacokinetic profile of zavegepant, were only briefly provided in a press release and predicted a suitable pharmacokinetic profile. These results also described that the Tmax was reached in a shorter time than with other small molecule CGRP receptor antagonists [6]. We are still waiting for other information, not available up to date.

6.3 Clinical Trials

6.3.1 Safety and Tolerability

Biohaven summarized and reported the tolerability and safety data regarding the intranasal administration of zavegepant in acute migraine treatment, comparing the results obtained with a placebo group. In a randomized, controlled phase II/III dose-ranging trial (NCT03872453), 2154 participants were recruited and treated with different dosages. Subjects treated with 5 mg (n = 388), 10 mg (n = 394), 20 mg (n = 403), and placebo (n = 403) were analyzed in order to assess treatment adverse events (AEs). The majority of AEs were of low intensity with no hepatic alteration and no bilirubin alteration in patients treated for 1 year with the dosage of 10 mg up to eight times per month [7]. With regard to adverse effects, those most present were dysgeusia (13.5–16.1% in patients vs. 3.5% of placebo group) and nasal discomfort (1.3–5.2% of patients treated with zavegepant vs. 0.2% of the placebo group) [8].

A recent phase II/III, open-label, long-term, safety clinical trial (NCT04408794) examined the long-term effects of intranasal administration of 10 mg zavegepant, up to eight times a month for a 1-year treatment, to 600 enlisted patients suffering from acute migraine. The purpose of the study is to assess safety and tolerability within 52 weeks of treatment, taking into account serious adverse effects and laboratory parameters that could lead to the discontinuation of pharmacological treatment [9].

6.3.2 Efficacy

A recent multicenter, randomized, double-blind, placebo-controlled, phase II/III clinical trial (NCT03872453) is evaluating the efficacy of zavegepant administration compared to the placebo group in acute migraine treatment. Patients enrolled were 2154, suffering from migraine, were treated with different doses of zavegepant (5 mg, 10 mg, 20 mg) and afterwards compared with a placebo group. The primary endpoint is the evaluation of therapeutic efficacy by measuring pain freedom with a Likert scale and using a multiple-choice questionnaire for the most bothersome symptoms (MBS). The secondary endpoints evaluate several parameters including pain relief (at 2 h, 30 min, and 60 min post dose), the ability to return to normal function (at 2 h, 30 min, and 60 min post dose), the probability of resorting to rescue medication (within 24 h of initial treatment), freedom from phonophobia and photophobia (2 h post dose), freedom from nausea (2 h post dose), and incidence of pain relapse (2–48 h post dose) [10].

Biohaven reports preliminary data regarding the dosages 10 and 20 mg of zavegepant. The results show a pain freedom and a freedom from MBS at 2 h with a rapid onset at 15 min of pain relief and return to normal function after 30 min with benefits extended up to 48 h after administration. Data show sustained pain freedom

from 2 to 48 h (5, 10, and 20 mg), pain freedom from 2 to 24 h (5, 10, and 20 mg), sustained pain relief from 2 to 48 h (5 and 10 mg) and sustained pain relief from 2 to 24 h (5, 10, and 20 mg) [7]. Specifically, the results showed that the subjects treated with zavegepant 5 mg (19.6%), 10 mg (22.5%), and 20 mg (23.1%) showed pain freedom at 2 h compared with 15.5% in the placebo group. Zavegepant led to freedom from MBS in 39.0% of those treated with 5 mg ($p = 0.1162$), 41.9% of the 10 mg group ($p = 0.0155$), and 42.5% of those given 20 mg ($p = 0.0094$) compared with 33.7% on placebo.

In a randomized, phase III clinical trial (NCT04571060), the safety profile of intranasal zavegepant was tested versus placebo group in patients affected by moderate or severe migraine. The estimated primary completion date is September 2021 [11]. Data from the clinical trials are available in Table 6.1.

6.4 Conclusion

Gepants have shown good preliminary results, proving themselves to be a promising tool in the acute therapy of migraine. Till date, all gepants studied showed a good safety and efficacy profile, and might be a good alternative in the management of migraine crises, especially in those patients where triptans are not indicated or do not respond to therapy. Given this premise, the benefits of Gepants could represent a valid therapeutic strategy in patients with medication overuse or with cardiovascular comorbidity.

Zavegepant, unlike the other gepants, is the only CGRP receptor antagonist for intranasal administration currently being developed for the acute treatment of migraine. In September 2020, Biohaven evaluated the pharmacokinetic and safety profile of zavegepant. The reported data demonstrated its therapeutic efficacy and safety profile compared to placebo in a phase II/III study in acute migraine

Table 6.1 Clinical trials

Identifier	Title	Subjects	Phase	Treatment	Status	Disease
NCT03872453	Acute treatment trial in adult subjects with migraines	2154	II/III	Zavegepant 10 mg Zavegepant 20 mg Zavegepant 5 mg	Completed	Migraine moderate to severe
NCT04408794	Long-term safety study of BHV-3500 (zavegepant) for the acute treatment of migraine	608	II/III	Zavegepant 10 mg	Active, not recruiting	Acute migraine
NCT04571060	Randomized trial in adult subjects with acute migraines	1400	III	Not available	Active, not recruiting	Migraine

treatment. In this study, zavegepant has been proven statistically superior to placebo on the coprimary endpoints of 2-h freedom from pain and freedom from a patients' most bothersome symptom (either nausea, photophobia, or phonophobia). Since these promising preliminary results, zavegepant is advancing to phase III for the acute treatment of migraine in adults. Up to date, zavegepant has shown a low probability of drug interaction with other drugs as indicated by the value of IC50 (IC50 > 40 μm) estimated in comparison with many CYP including CYP3A4, CYP2D6, CYP2C9, CYP2C19 and CYP1A2. These studies also demonstrated an inhibition of CYP3A4 that was not time-dependent, assuming potentially limited drug interactions [2]. These new approaches allow a specific and personalized therapy especially for patients who do not respond to standard drug therapy or are suffering from cardiovascular comorbidity. Further clinical studies are needed in order to be able to accurately define the pharmacological profile and the safety and therapeutic efficacy profile.

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Chapter 7
Molecular Mechanisms of 5-HT$_{1F}$ Receptor Agonists

Silvia Benemei

7.1 Serotonin (5-HT) and 5-HT Receptors

In 1937, the discovery in the enterochromaffin cells of the gastrointestinal system of a previously unknown amine, which was named enteramine [1, 2], opened up an unprecedented field of research involving several physiological systems and someway giving birth to neuroscience [3]. Just a few years later, serotonin (*nomen est omen*, *ex post*) was also isolated from beef serum and connoted for its ability to provoke vasoconstriction [4, 5], still being ignored its chemical structure. Soon after, serotonin was identified with 5-hydroxytriptamine, 5-HT [6] and then recognized as the same substance of enteramine [7]. In just a few years, a mess of data has been published regarding serotonin [8] and, up to date, its multifaceted physiological roles have been described in several animal species and in humans, including developmental, cardiovascular, gastrointestinal, endocrine, and cognitive function in addition to sensory perception and complex behavior such as appetite or sex [9]. The definition of the complex family of serotonin receptors, resulting from a long evolutionary road [10], together with the discovery and development of selective agonists and antagonists, have allowed to recognize serotonin system as a potential target to treat and prevent a varied group of unrelated diseases, including migraine.

After the cloning of the first 5-HT receptor [11], a huge of data has been accumulated to characterize the current known 14 different receptor subtypes, grouped into 7 classes (from 5-HT$_1$ to 5-HT$_7$) according to structural, transductional, and operational features, to which has to be added multiple receptors generated by alternative splicing of single genes or editing of the receptor RNA [12]. The 5-HT receptors are members of the G-protein-coupled receptor (GPCR) family and classified as "type A," rhodopsin-like receptors [13]; the 5-HT$_3$ receptor is the sole exception being a

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ligand-gated ion channel. Similar to other GPCRs, 5-HT receptors have been shown to form dimers, either homodimers or heterodimers, possibly influencing signal transduction effector pathways and hence adding complexity to the responses elicited by their activation [10]. Up to date, to the aim of understanding migraine mechanism and treatment, 5-HT_1 receptors subtypes B, D, and F (5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}), which often co-express in the same cells, are the most relevant with major focus given to vascular and neuronal localization. Independent from the subtype, the activation of 5-HT_1 receptors induced by their interaction with an agonist, via the inhibition of adenylyl cyclase, decreases the production of cyclic AMP (cAMP). In smooth muscle cells, including vascular ones, the reduced levels of cAMP provoke cell contraction by the increased phosphorylation of the myosin light chain and the consequent cross-bridging between the myosin heads and the actin filaments. In neurons, the expected outcome of a reduced level of cAMP is membrane hyperpolarization and the consequent inhibition of neuronal firing. It is worth noting that the functional consequences of 5-HT_1 receptor activation in complex neuronal systems depends on the physiological function of the cells they are expressed by.

5-HT_{1B} receptors mediate 5-HT-induced constriction in human cerebral arteries, in which they are intensely expressed by smooth muscle cells [14]; in addition, 5-HT_{1B} receptors are expressed by endothelium and meningeal vessels [15]. Regarding to neural districts, 5-HT_{1B} receptors are expressed in brain presynaptically on axon terminals [16], with high level of expression in basal ganglia, including the substantia nigra and globus pallidus, and, more importantly to migraine, they are expressed in trigeminal ganglia and trigeminal nerves. 5-HT_{1D} receptor is expressed throughout the brain [17] and trigeminal ganglia and nerves, [18], however, it differentiates from 5-HT_{1B} because of its expression in trigeminal fibers projecting peripherally to dural vessels and centrally to trigeminal nuclei [19, 20]. 5-HT_{1F}, which has been first cloned in 1993 [21], is expressed in globus pallidus, substantia nigra, cortex, putamen, hippocampus, spinal cord, spinal trigeminal nucleus, substantia gelatinosa, nucleus of the tractus solitarius, and periaqueductal gray and trigeminal system, including trigeminal ganglia [22, 23]. Actually, all the three receptor subtypes, although with slight differences and variations, are expressed by the trigeminal system, which over the past years has been recognized as fundamental to migraine mechanism. Differential level of expression of receptor subtypes in different districts together with the different pharmacological profile (read affinity and selectivity) [24] may explain some differences emerging between classes of drugs targeting 5-HT receptors with different selectivity, namely 5-$HT1_{B/D/F}$ agonists (i.e., triptans) and 5-HT_{1F} agonists (i.e., ditans).

7.2 5-$HT_{1B/D}$ and 5-HT_{1F} Receptors and Migraine Treatment

Explorative studies about a possible direct role of serotonin in migraine mechanism dates back more than 60 years [25, 26], but the unintentional targeting of its receptors, albeit still not identified, is even earlier, as in 1925 ergotamine was first used to

treat migraine. Some pivotal observations have corroborated the involvement of serotonin and its receptors in migraine (Box 7.1) and the availability of increasingly selective agonists has helped to refine migraine mechanism hypotheses while optimizing patient treatment. Although ergot derivatives, due to their chemical structure, have a broad spectrum of pharmacological actions, their antimigraine activity had been early attributed to their agonism at 5-HT$_1$ receptors [27], which is undoubtedly nonselective and mediates a large part of their side effects, indeed. At that time, the mainstream hypothesis about migraine pathophysiology suggested a vascular mechanism, given the demonstration of a temporal correlation of superficial temporal artery pulsations with the headache and the ability of intravenous ergotamine to abort both the pulsations and the pain at the same time [28]. Even if based on the abovementioned vascular hypothesis that is now considered overtaken by the neurovascular theory, the effort to design a drug able to selectively target 5-HT$_{1B}$ receptors, which were considered the transducers of the antimigraine effects at the level of cranial vasculature, led to the development of triptans, a class of drugs acting on 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors, and in most cases also on 5-HT$_{1F}$ [29]. According to the current knowledge, the putative mechanisms attributable to triptans for their antimigraine effects are (1) the constriction of cranial vessels, (2) the inhibition of nociceptive neurotransmitter release from trigeminal sensory neurons, (3) the inhibition of transmission through second-order neurons of the trigeminocervical complex (TCC) [30–32].

In the last years, some pivotal mechanism of migraine has been unraveled with relevant therapeutic advancements. It has been shown a primary role for calcitonin gene–related peptide (CGRP), which is released from peptidergic sensory neurons and mediates neurogenic inflammation and sensitization phenomena [33]. The role of CGRP has been definitely substantiated by the clinical efficacy of drugs able to block its signaling, namely gepants and monoclonal antibodies anti CGRP ort its receptor [34]. In particular, it has been shown that the decrease of intracellular cAMP levels mainly due to the activation of the 5-HT$_{1D}$ receptors, negatively affects the CGRP release from trigeminal neurons, hence reducing nociceptive transmission [35, 36] and likely mediating the major portion of the antimigraine effect of the triptans. On the other hand, the activation of the 5-HT$_{1B}$ receptors, expressed by both the smooth muscle of intra- and extracranial arteries and the endothelium of the coronaries [37] mediates the most concerning drawback of the triptans, that is cardiovascular safety. According to this scenario, the natural step forward in the development of antimigraine treatment has been the design of drugs devoid of affinity for 5-HT$_{1B}$. The challenging endeavor started from the development of selective 5-HT$_{1D}$ receptor agonists that unfortunately have been proven ineffective in clinical trials [38]. Finally, Selective Serotonin One F Receptor Agonists (SSOFRA) have been developed, including the aminocarbazole LY344864 that binds to the cloned human 5-HT$_{1F}$ receptor with a Ki of 6 nM, and with scarce affinity ($\geq$500 nM) for other serotonergic receptors [39], the 4-(3-indolyl) piperidine LY334370 that have a KD of 0.446 nM for the human 5-HT$_{1F}$ receptor, [40, 41] and the piperidinyl piperidine LY573144 (*ex* COL-144, then named lasmiditan), which lacks the indole core typical of triptans and binds to 5-HT$_{1F}$ receptor, with a Ki of 2.21 nM,

compared to values of 1053 nM, 1043 nM, and 1357 nM for the 5-$HT_{1A/B/D}$ receptors, respectively [42]. Most recently the term "ditan" has been introduced in the place of SSOFRA [43], although the suffix "-ditan" has been used also for a 5-$HT_{1A/1B/1D}$ receptor agonist with a low 5-HT_{1F} receptor affinity, hence being generally applied to novel antimigraine 5-HT_1 receptor agonists different from triptans. In the present chapter, we will use the term "ditans" exclusively referring to the pharmacological class of SSOFRA. Up to date, lasmiditan is the sole molecule of the three mentioned above that moved form bench to bedside, as LY344864 was not clinically tested and the promising clinical development of LY334370 [44] was stopped because potential off-target liver toxicity emerged during preclinical toxicology assays [23].

In experimental animals, ditans have been shown to inhibit plasma protein extravasation (PPE) [39, 42, 45], that modeling neurogenic inflammation, for a certain period, has been considered a predictive assay of antimigraine action of drugs. When the PPE model has been discarded, a possible explanation of the antimigraine effects of ditans has been attributed to the inhibition of the TCC [46]. Relevantly, the activation of 5-HT_{1F} receptors inhibits the activation of second-order neurons in the trigeminal nucleus caudalis in several species [42, 47–51].

As described above, serotonin or receptor agonists interaction with the 5-HT_{1F} receptor on neuronal synapses inhibits the release of CGRP and other molecules possibly involved in migraine (i.e., glutamate), reducing hyperexcitability and modulating pain signaling [52]. The inhibition of the release of CGRP may intervene also through complex cAMP-dependent desensitization processes involving receptors, such as the transient receptor potential channel vanilloid 1 (TRPV1), which is highly expressed by trigeminal neurons [53].

A specific involvement of the 5-HT_{1F} in the release of CGRP was also suggested, although not at trigeminal level, in pithed rats, in which electrical stimulation of primary sensory nerves originating from the spinal cord results in vasodepressor responses mediated by CGRP release [54]. More importantly, LY344864 has been showed in vitro to inhibit CGRP release in rat dura mater, although not in the trigeminal nucleus caudalis or trigeminal ganglia [24], but different results have been obtained with lasmiditan that inhibits CGRP release from all the aforementioned districts [55]. In particular, in anesthetized rats lasmiditan, without producing any changes in blood pressure, significantly and dose-dependently inhibits endogenous (i.e., released CGRP via either capsaicin injection or periarterial electrical stimulation) but not exogenous (i.e., systemically administered) CGRP effects (i.e., dilation of the middle meningeal artery), indicating that it can inhibit dural CGRP release but is not a CGRP receptor antagonist [56]. As pursued, ditans do not have vasoconstrictive properties [57]. The potency of the triptans and ditans to contract the human isolated coronary artery was investigated, and it has been shown that concerning the ability to contract vessels, the potency to bind the 5-HT_{1B} and 5-HT_{1F} receptor has a positive and a negative correlation, respectively [58]. According to second messenger activity after receptor activation, triptans showed varying potency as agonists at the 5-$HT_{1B/D}$ and the 5-HT_{1F} receptors, while lasmiditan activates solely the 5-HT_{1F} receptor [58].

Importantly, lasmiditan, differently from sumatriptan, has been shown not to induce any constriction in either isolated middle meningeal artery or carotid artery, in vivo when administered at clinically relevant doses [58]. These recent data are in accordance with previously identified pharmacological profile of lasmiditan, which in a assay of stimulation of [35S]-GTPγS binding, acted as nanomolar agonist at the 5-HT_{1F} receptor, but elicited no effects at the 5-$HT_{1B/D}$ receptors [42, 59]. Though not relevant to migraine according to our current knowledge, an additional pharmacological effect recently identified for 5-HT_{1F} agonists is the induction of mitochondrial biogenesis [60–62], a potential druggable target for the treatment of different conditions, including spinal cord injury [63], Parkinson's disease [64], and kidney injury [65].

Regarding mechanisms underpinning adverse reactions to ditans, central nervous system interaction with their pharmacological target likely represent the major pathophysiological process. The sole currently authorized ditan, lasmiditan, is a highly lipophilic molecule with a high blood–brain barrier permeability causing high penetration to central nervous system and ensuing interaction to centrally expressed 5-HT_{1F} receptors [42], with expected side effects including somnolence, dizziness, fatigue, and paresthesia. It is worth noting that lasmiditan does not have an affinity for muscarinic, dopaminergic, adrenergic, or histamine receptors or γ-aminobutyric acid A (GABAA) channels at concentrations <10 μM. The only additional activity identified was at the site of the benzodiazepine [3H]-flunitrazepam on the GABAA channel, however with >100-fold-lower affinity than for the 5-HT_{1F} receptor and with no agonist, antagonist, or positive allosteric modulator activity at concentrations up to 100 μM. In clinical trials, adverse events considered signal of abuse potential, such as euphoric mood, feeling abnormal or drunk, and hallucinations, have been reported. In humans, the abuse potential of therapeutic (100 mg, 200 mg) and supratherapeutic (400 mg) lasmiditan has been then investigated in comparison to the short-acting benzodiazepine alprazolam and placebo, as positive and negative control, respectively [66]. Notably, only supratherapeutic dosages of lasmiditan has showed effects comparable to alprazolam, with therapeutic dosages being superimposable to placebo.

Recently, it has been shown that in rodents the 5-HT_{1F} receptor agonist LY344864, differently from the CGRP receptor antagonist olcegepant, induces a significant reduction in mechanical withdrawal thresholds, with an increased expression of CGRP in trigeminal sensory afferents and neuronal activation (c-Fos) in the TCC [67]. This experimental outcome is considered a proxy of potential medication overuse headache (MOH) risk for ditans, which seems superimposable to that of triptans. Although mechanisms of MOH and common addiction are considered different and a role for the 5-HT_{1F} receptor in reward processes has not been conclusively identified, it is worth noting that in rodents the agonist LY344864 significantly attenuated the reinstatement of methamphetamine-seeking behavior. Accordingly, 5-HT_{1F} agonists may have therapeutic potential to prevent relapse in addiction [68].

Box 7.1 Initial Evidence Suggesting a Role of Serotonin in Migraine

- **Perivascular injection of serotonin produces migraine-like symptoms**

Wolff HG. Headache and other head pain. New York: Oxford University Press; 1948.

- **Serotonin decreases in plasma and 5-hydroxyindole acetic acid, the metabolite of serotonin, increases in the urine during migraine attacks**

Sicuteri F et al. Biochemical investigations in headache: Increase in the hydroxyindoleacetic acid excretion during migraine attacks. International Arch Allergy and Immunol. 1961;19:55–58.

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Somerville BW. Platelet-bound and free serotonin levels in jugular and forearm venous blood during migraine. Neurology. 1976;26:41.

- **Serotonin infusion could alleviate migraine attacks in open studies**

Kimball RW et al. Effect of serotonin in migraine patients. Neurology. 10, 107–111.

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Chapter 8
Lasmiditan

Simy Parikh

8.1 Introduction

Migraine is a neurologic disease characterized by disabling moderate-to-severe head pain and associated symptoms [1]. Its pathophysiology is complex; however, research has implicated the neuropeptide calcitonin gene–related peptide (CGRP) and the excitatory neurotransmitter glutamate as having key roles in promoting neuronal sensitization and migraine pain transmission [2].

Antimigraine therapies with triptans and ergot alkaloids have long targeted serotonin receptors, specifically subtypes 1B and 1D. However, these therapies have carried the unwanted side effect of vasoconstriction and cardiovascular risk. Isolation of serotonin 1F receptor messenger RNA (mRNA) from trigeminal ganglion neurons in guinea pigs precipitated investigation of the serotonin 1F receptor as a novel therapeutic target [3]. Antimigraine therapy has now been developed that targets the serotonin 1F receptor, which potentially modulates the release of CGRP and glutamate without resulting in vasoconstriction.

Serotonin Serotonin (5-hydroxytryptamine [5-HT]) is a hormone and neurotransmitter that activates receptors in the cell membrane to achieve its biological effect. The name "serotonin" references its notable vasoconstrictive properties; the term is derived from "sero" for its isolation from blood serum and "tonin" for its ability to contract smooth muscle. Free 5-HT circulates in the vasculature and is concentrated by platelets through the serotonin transporter (SERT). 5-HT may cross the blood–brain barrier by SERT. Monoamine oxidase (MAO) metabolizes serotonin to an inactive metabolite, 5-hydroxyindole acetic acid (5-HIAA).

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There are seven major types for 5-HT receptors (5-HT_1–5-HT_7) [4]. These receptors can be either inhibitory or excitatory and each has additional subtypes. The function of each serotonin receptor subtype varies. Three serotonin (5-HT) receptor subtypes, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} are integral to migraine pathophysiology [5]. See Fig. 8.1.

5-HT_{1B} receptors: $5HT_{1B}$ mRNA is present in smooth muscle as well as blood vessel endothelium. The $5HT_{1B}$ receptor may also regulate the release of other neurotransmitters, such as glutamate, dopamine, and norepinephrine. Agonism of this receptor results in cerebral and systemic vasoconstrictive effects [5, 6].

5-HT_{1D} receptors: 5-HT_{1D} receptor mRNA is detected in trigeminal nerve terminals co-localized with cells containing neuropeptides involved in the migraine pathophysiology, including calcitonin gene–related peptide (CGRP), substance P (SP), and nitric oxide synthase (NOS) [5–7]. 5-HT_{1D} receptors have been found in cerebral blood vessels and in vascular smooth muscle. Agonism of this receptor may reduce CGRP release [6]. It may also result in vasoconstriction [4, 8].

5-HT_{1F} receptors: 5-HT_{1F} receptor mRNA is detected in trigeminal nerve endings co-localized with cells containing CGRP, a neuropeptide that plays a key role in neuronal sensitization, as well as glutamate, a neuro-excitatory neurotransmitter that mediates trigeminovascular nociceptive transmission [9]. Together, CGRP and glutamate promote peripheral and central sensitization [2]. The 5-HT_{1F} receptor is a G-protein-coupled receptor, which inhibits adenylate cyclase and the formation of cAMP and thereby inhibits the phosphorylation of protein kinase A; therefore, 5-HT_{1F} receptor agonists can inhibit release of neuropeptides and neurotransmitters [10]. In the human central nervous system, the 5-HT_{1F} receptor is expressed in structures implicated in migraine pathophysiology, including the trigeminal nucleus caudalis (TNC), trigeminal ganglia (TG), hypothalamus, thalamus, nucleus accumbens, and the cerebral cortex [8, 10–12]. 5-HT_{1F} receptor mRNA has additionally been detected in human tonsils, kidneys, thyroid, testis, and ovaries [8]. The expression of the 5-HT_{1F} receptor in coronary arteries and cerebral blood vessels is low [8, 13]. Importantly, the 5-HT_{1F} receptor is not functionally involved in vasoconstriction [13, 14].

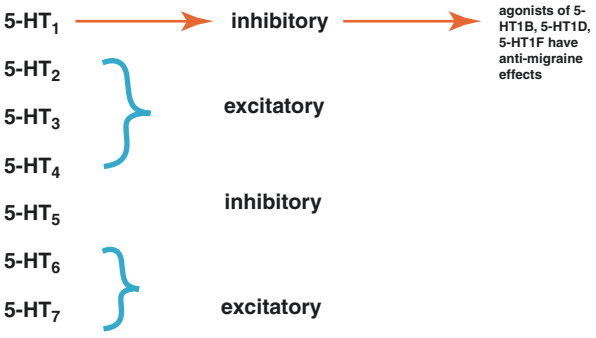

Fig. 8.1 The seven major types for 5-HT receptors

5-HT$_{1B/1D}$ receptor agonists for migraine treatment: Triptans were developed for the acute treatment of migraine, based on the vascular theory of migraine, which hypothesized that cerebral vasodilation was responsible for migraine pain. Triptans were purposefully developed as agonists of 5-HT$_{1B}$ receptors, a receptor which mediates vasoconstriction of the cerebral vasculature. Triptans are agonists at 5-HT$_{1B/1D}$ receptors, with additional affinity for the 5-HT$_{1F}$ receptor [15]. Ergot alkaloids (dihydroergotamine, methergine) are commonly used acute antimigraine treatments that were also initially developed to vasoconstrict cerebral blood vessels; they act as nonspecific 5-HT$_{1}$ receptor agonists [15].

It is now known that the mechanism of their benefit may instead be derived by the ability of triptans and ergot alkaloids to activate presynaptic 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors. Through their agonism at 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors, triptans and ergot alkaloids can suppress the release of CGRP, a neuropeptide with a key role in the propagation of neurogenic inflammation and peripheral and central sensitization [16–19]. 5-HT$_{1B}$-receptor mediated vasoconstriction by triptans and ergot alkaloids is now considered an unnecessary part of their mechanism of action that may result in unintended cardiovascular side effects [16–19].

5-HT$_{1D}$ receptor agonists for migraine treatment: The antimigraine benefits of a selective 5-HT$_{1D}$ agonist, PNU-142663 (Pharmacia-Upjohn) was studied with a randomized, double-blinded, placebo-controlled, parallel-group study [20]. No statistically significant treatment effects were observed at the study's specified time points. Study authors concluded that antimigraine efficacy is not mediated solely through the 5-HT$_{1D}$ receptor subtype. An alternative theory as to why the drug failed points to the drug being developed using gorilla rather than human receptors [20, 21].

5-HT$_{1F}$ receptor agonists for migraine treatment: The potential for the antimigraine efficacy of 5-HT$_{1F}$ receptor agonists is derived from the receptor's co-localization with CGRP and glutamate containing neurons within the TG and its potential for inhibiting glutamate and CGRP release [5, 6, 22]. Importantly, unlike 5-HT$_{1B/1D}$ receptor agonists, 5-HT$_{1F}$ agonists do not result in vasoconstriction and are therefore not contraindicated in those with cardiovascular risk factors [23].

Two selective 5-HT$_{1F}$ receptor agonists have been studied in human trials: lasmiditan and LY334370. A double-blind, parallel-group study demonstrated the efficacy of LY334370, however liver toxicity limited its development [24, 25]. Lasmiditan was ultimately approved for the acute treatment of migraine with or without aura in adults; it has high affinity and selectivity for the 5-HT$_{1F}$ receptor and will be the discussion of this chapter [19].

8.2 Pharmacological Profile

Lasmiditan, or 2,4,6-trifluoro-*N*-[6-[(1-methylpiperidin-4-yl)carbonyl]pyridin-2yl]benzamide, has a unique pyridinoyl-piperidine scaffold instead of the indole core contained by triptans [26]. This differentiating structure allows lasmiditan a novel "ditan" drug classification. Lasmiditan is lipophilic and crosses the blood–brain barrier [8, 26].

Pharmacodynamics Lasmiditan is highly selective to the 5-HT_{1F} receptor. In vitro binding studies demonstrated that lasmiditan has more than a 470-fold selectivity ratio for the 5-HT_{1F} receptor (Ki 2.21 nM) as compared to $5HT_{1B}$ (Ki 1043 nM) and 5-HT_{1D} (Ki 1357 nM) receptors [26, 27]. In vitro studies of human 5-HT_1 receptor subtypes showed that lasmiditan, as compared to triptans, has weak activity at human 5-HT_{1B} and 5-HT_{1D} receptors. Lasmiditan has a high functional selectivity for human 5-HT_{1F} receptor as compared to other 5-HT_1 family receptors [26]. In an assessment of overall selectivity using a panel of 52 binding assays with various receptors, ion channels, and other binding sites, 1 μM lasmiditan blocked binding by less than 50%, with the exception of the benzodiazepine-binding site on the $GABA_A$ receptor (67% inhibition of binding) [26]. Lasmiditan at higher concentrations (5 μM) did not show any significant potential cross-reactivity at other monoaminergic receptors [26].

Lasmiditan has high affinity to the 5-HT_{1F} receptor. As compared to serotonin as an agonist reference standard, lasmiditan displayed approximately fourfold more potency at the 5-HT_{1F} receptor [26].

Pharmacokinetics Lasmiditan's time to maximum serum concentration (t_{max}) following oral administration of 50–400 mg ranges between 1.5 and 2.5 h with a median of 1.8 h [8, 28, 29]. Approximately 55–60% of lasmiditan is plasma protein bound and the oral bioavailability of lasmiditan is approximately 40% [29]. Measurements of lasmiditan concentrations in the brain and plasma 1 h after intravenous lasmiditan administration to rodents showed that lasmiditan crosses the blood–brain barrier [8]; 50.5% of the brain concentration of lasmiditan is unbound [8].

Lasmiditan is metabolized both hepatically and extrahepatically without significant involvement of cytochrome P450 reductase or CYP enzymes [29]. It is a substrate of the transmembrane protein, P-glycoprotein [29]. Its elimination is conducted through ketone reduction metabolism with a minor renal involvement [29]. Lasmiditan's elimination half-life ($t½$) is 5.7 h [29]. The drug does not accumulate with daily dosing [29].

8.3 Preclinical Studies

In vivo studies using rodent models demonstrated that lasmiditan inhibits presynaptic CGRP release in trigeminal nerve terminals [30]. CGRP is a neuropeptide that promotes neuronal sensitization, manifesting clinically as throbbing head pain. Supporting this, orally administered lasmiditan was found to be effective in reducing the downstream effects of neuronal sensitization, including dural plasma protein extravasation and c-fos expression in the TNC [26].

In vivo studies using rabbit saphenous vein rings as a surrogate for human coronary artery showed that lasmiditan does not have vasoconstrictor liability [26, 31].

The comparison of sumatriptan and lasmiditan at similar concentrations showed that, unlike sumatriptan, lasmiditan produced no discernable vessel contractions [26, 31]. Similar in vivo studies of coronary and carotid artery diameters demonstrated that lasmiditan, unlike sumatriptan, does not produce coronary and carotid artery contraction [27].

A preclinical study on rat models suggests that lasmiditan does have the potential to produce medication overuse headache. Results demonstrated the development of drug-induced cutaneous allodynia, which resolved after cessation of drug administration [32].

8.4 Clinical Studies

Two phase III randomized double-blind, placebo-controlled trials, the SAMURAI trial (identifier: NCT02439320) and the SPARTAN trial (identifier: NCT02605174), evaluated the efficacy and safety of lasmiditan for the acute treatment of migraine with and without aura [33, 34]. The SAMURAI and SPARTAN trials were similar in methodology and demographics.

In both trials, participants ≥18 years of age with a diagnosis of episodic migraine with or without aura fulfilling the International Headache Society diagnostic criteria (ICHD-3 beta) 1.1 or 1.2.1, with onset before age 50, were enrolled [33, 34]. Additional inclusion criteria included a Migraine Disability Assessment (MIDAS) score ≥11 [33, 34]. Participants with chronic headache disorders, including chronic migraine and medication-overuse headache, and high risk for seizure were excluded in both studies.

Notably, patients with cardiovascular risk factors (CVRFs) were included in both trials [33, 34]. CVRFs, based on American College of Cardiology/American Heart Association Task Force on Practice Guidelines, included age >40 years, self-report of diabetes, active smoking status, baseline total cholesterol ≥240 mg/dL, baseline high-density lipoprotein cholesterol <40 mg/dL for men or <50 mg/dL for women, and baseline systolic blood pressure ≥140 mmHg, and/or self-reported medical history of high blood pressure at baseline [35–37]. Across both trials, 78.8% had ≥1 CVRF, 41.3% had ≥2 CVRFs, and 20% had CV/cerebrovascular-related history (CCRH), at baseline [35–37]. The rates of risk factors appear to be generally representative of the overall migraine population [37]. In both studies, the majority of participants were female and white, with a mean age of approximately 42.0 (SD 12.0) years [33, 34]. Across both trials, 17.5% used migraine preventive treatment [38].

In both trials, use of a rescue medication 2 h after taking study drug was allowed, with the exception of opioid, barbiturate, triptan, or ergot use within 24 h of study drug administration [33, 34]. Head pain and most bothersome symptom (MBS), defined as photophobia, phonophobia, or nausea, self-identified by the participant, were reported by an electronic diary at baseline and at specific time intervals [33, 34]. Participants also self-reported a global impression of change (PGIC) [33, 34].

The primary efficacy outcomes in both trials were the effect on pain freedom at 2 h and MBS freedom at 2 h in participants who treated moderate-to-severe migraine within 4 h of attack onset [33, 34].

The studies varied in exclusion criteria and doses studied. In SAMURAI, participants were evenly randomized to oral lasmiditan 100 mg (n = 744), 200 mg (n = 745), or placebo (n = 742) [33]. Compared to SPARTAN, the SAMURAI trial had additional exclusion criteria of participants with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension [33]. In SPARTAN, participants were evenly randomized to oral lasmiditan 50 mg (n = 750), 100 mg (n = 754), 200 mg (n = 750), or placebo (n = 751) [34]. Notably, SPARTAN included participants with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension [34].

Efficacy Results of the SPARTAN and SAMURAI trials showed that relative to placebo, lasmiditan resulted in statistically significant improvement of 2 h headache freedom and 2 h freedom from the most bothersome symptom (photophobia, phonophobia, or nausea) [33, 34]. See Table 8.1.

Analyses of secondary outcomes also support the efficacy of lasmiditan. Both SAMURAI and SPARTAN trials showed improvement in the lasmiditan treated group as compared to placebo in (1) pain relief at 2 h, (2) sustained pain freedom at 24 h, (3) total migraine freedom (absence of migraine and migraine symptoms) at 2 h, and (4) migraine-related disability-freedom at 2 h, and a PGIC rating of "very much better" or "much better" at 2 h [33, 34]. All doses of lasmiditan were also shown to result in an improvement in migraine-related functional disability that persisted for 48 h [39].

Table 8.1 Percent participants who achieved the primary endpoints of the Phase 3 SAMURAI and SPARTAN trials. References: [33, 34]

Phase III clinical trials	2 h pain freedom	2 h freedom from MBS	Key differences
SAMURAI			Excluded those with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension
100 mg	28.2% ($p < 0.001$)	40.9% ($p < 0.001$)	
200 mg	32.2% ($p < 0.001$)	40.7% ($p < 0.001$)	
Placebo	15.3%	29.5%	
SPARTAN			Included those with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension Excluded those with increased risk of dizziness/recurrent vertigo, recent drug or alcohol abuse, diabetes mellitus with complications, orthostatic hypotension with syncope, significant renal or hepatic impairment
50 mg	28.6% ($p = 0.003$)	40.8 ($p = 0.009$)	
100 mg	31.4% ($p < 0.001$)	44.2% ($p < 0.001$)	
200 mg	38.8% ($p < 0.001$)	48.7% ($p < 0.001$)	
Placebo	21.3%	33.5%	

Long-term treatment with lasmiditan was found to have sustained efficacy on acute migraine attack treatment as well as on disability as assessed through the Migraine Disability Assessment (MIDAS) [40]. GLADIATOR is a 1-year prospective, open-label, Phase III study that randomized participating completers of the SAMURAI and SPARTAN trials to 100 mg or 200 mg of lasmiditan with assessments at 3, 6, 9, and 12 months of the study [40]. GLADIATOR showed that long-term use of lasmiditan was associated with consistent efficacy for pain freedom across all time quarters for treated attacks at 2 h post-dose for lasmiditan 100 mg (26.9% of treated attacks) and 200 mg (32.4% of treated attacks). MIDAS scores decreased over time, with significant reductions in work or school absenteeism and presenteeism at all-time points during treatment for up to a year, independent of selective attrition [40].

Subgroup analyses of participants of the SAMURAI and SPARTAN trials were done to evaluate the efficacy impact of migraine preventives and CVRFs, as well as of the efficacy and safety of a second rescue dose of lasmiditan. Analyses showed no statistically significant difference in primary or secondary outcomes among those using migraine preventive medications as compared to those not on migraine preventives [38]. Sub-analysis of participants who had received ≥1 dose of study drug showed that the presence of CVRFs did not affect efficacy results [37]. A rescue dose of study drug was provided 2–24 h after the initial dose as a rescue for patients who were not pain-free at 2 h after the initial dose of lasmiditan, or who had mild, moderate, or severe migraine after pain-freedom following the initial dose [33, 34]. Subgroup analysis of the efficacy and safety of a second rescue dose of lasmiditan from SAMURAI and SPARTAN trial data did not demonstrate statistically significant differences in efficacy or treatment-emergent adverse events (TEAEs) with a rescue dose of lasmiditan as compared to placebo [41].

8.5 Safety

There are no serious adverse events or deaths related to lasmiditan use [33, 34]. The majority of TEAEs in the SAMURAI and SPARTAN trials were mild or moderate in intensity; CNS-related; and included dizziness, fatigue, lethargy, nausea, paresthesia, and somnolence [33, 34]. No serious TEAEs related to study drug were reported, and no adverse events resulted in study discontinuation among those patients who used study drug. A sub-analysis of the safety of participants pooled from SAMURAI and SPARTAN showed no notable differences in the rates or types of adverse events (AEs), serious adverse events (SAEs), and TEAEs in the group of lasmiditan-treated patients using migraine preventives compared with those not using preventive treatments [38]. No patients using preventives without lasmiditan experienced SAEs, while 0.2% experienced SAEs with both preventives and lasmiditan [38]. Patients not using preventives experienced SAEs at the same rate (0.3%) with either placebo or lasmiditan treatment [38].

Cardiovascular safety A pooled analysis of the participants enrolled in the SAMURAI and SPARTAN trials who had received ≥1 dose of study drug showed a low frequency of cardiovascular (CV) TEAEs, including cardiac arrhythmias, cardiomyopathy, hypertension, pulmonary hypertension, Torsade de pointes/QT prolongation, and abdominal pain [lasmiditan, 30 (0.9%); placebo, 5 (0.4%)] [35–37]. A subgroup of patients with CV risk factors demonstrated an acceptable safety profile during treatment for up to a year [42].

No drug discontinuations or deaths resulted from CV TEAEs [35–37]. One participant with preexisting hypertension experienced worsening hypertension; symptoms resolved after antihypertensive dose was increased during hospitalization [35–37]. CV TEAEs were not statistically associated with the absence or presence of any CVRFs and there was no differences in efficacy and safety with increasing numbers of CVRFs; palpitations were the only consistent CV TEAE seen across patients with ≥1, ≥ 2, ≥ 3, or ≥4 CVRFs [35–37]. Therefore, the authors of the analysis concluded that lasmiditan has an acceptable safety profile for those with CVRFs [37].

Long-term safety The 1-year GLADIATOR study assessed the incidence of AEs, SAEs, and TEAEs over a longer duration [42]. Interim results over the course of a 288-day median duration (IQR, 98–363 days; $n = 1834$) found that AEs, primarily dizziness, was the discontinuation reason for 11.2% and 14.4% of patients who discontinued 100 mg and 200 mg of lasmiditan respectively [42]. No deaths were reported during the study [42]. Interim results did not observe any new significant safety findings [42].

Treatment-emergent SAE was reported by 48.6% of patients at a higher rate in the 200 mg group (52.0%) than the 100 mg group (45.1%) [42]. However, no SAE occurred in more than one patient [42]. No SAE was considered by the investigator to be related to lasmiditan [42]. Nine patients (0.5%) reported 13 SAEs. In the 100 mg group, SAEs included limb abscess [$n = 1$], carbuncle [$n = 1$], and cellulitis [$n = 1$]. In the 200 mg group, SAEs included bradycardia and sinus node dysfunction [$n = 1$], gastritis [$n = 1$], sinusitis [$n = 1$], acute cholecystitis [$n = 1$], urinary tract infection [$n = 1$], lumbar spinal stenosis [$n = 1$], recurrent thyroid cancer [$n = 1$], and nephrolithiasis [$n = 1$] [42].

In both the 100 and 200 mg treatment groups, dizziness was found to be the most frequent TEAE (15.8% taking 100 mg, 21.3% taking 200 mg), followed in frequency by somnolence, paresthesias, and fatigue in that order. Other TEAEs included nausea, asthenia, hypoesthesia, vertigo, and lethargy [42]. Subgroup analysis of patients treating ≥5 migraine attacks found the frequency of TEAEs to decrease with subsequent treated attacks [42]. Meta-analyses of lasmiditan safety support a dose-related relationship for the rate of TEAEs [43, 44]. Future studies should continue to assess long-term efficacy and safety of lasmiditan.

Impairment and abuse A randomized, blinded, placebo-controlled and alprazolam-controlled crossover study assessing driving performance via a computer-based driving simulation demonstrated a dose-dependent impairment with all doses of

lasmiditan (50 mg, 100 mg, 200 mg) at 90 min after administration, corresponding with lasmiditan's t_{max} [45, 46]. No sustained driving impairment was found at 8 or more hours following administration of 100 mg or 200 mg of lasmiditan in a randomized, blinded, placebo- and diphenhydramine-controlled crossover study assessing driving performance using the Standard Deviation of Lateral Position [45, 46].

There is a low potential for abuse at therapeutic doses of lasmiditan but abuse potential increases at supratherapeutic dosing. An abuse potential study showed that at therapeutic doses (100 and 200 mg) lasmiditan has lower drug-liking scores than alprazolam [47]. However, at supratherapeutic doses (400 mg), lasmiditan drug-liking scores were not significantly different from alprazolam. For this reason, lasmiditan is a Schedule IV drug in the United States.

8.6 Drug Interactions

There are some hypothetical risks for combined therapies with lasmiditan [48, 49]. As lasmiditan's TEAEs appear to be centrally mediated, concomitant use with alcohol or other CNS depressant drugs should be done with caution [29]. There is also a hypothetical risk of serotonin syndrome with the concomitant administration of lasmiditan and other serotonergic drugs [29]. As lasmiditan inhibits P-gp and BCRP in vitro, there is a risk of increasing exposure to drugs that are P-gp or BCRP substrates with concomitant use [29]. Migraine therapies ubrogepant and rimegepant are substrates of BCRP and P-gp transporters; hypothetically, combined use of lasmiditan and gepants may increase exposure of the gepant [50–53]. Clinical drug–drug interaction studies on these risks have not been done [29].

Clinical studies of lasmiditan with common antimigraine therapies sumatriptan, propranolol, or topiramate did not show any significant drug interaction potential [29, 38]. However, an open label, single-center, fixed-sequence study showed that coadministration of lasmiditan and propranolol caused statistically significant decreases in mean hourly heartrate by an additional 6.5 beats per minute as compared to propranolol alone, suggesting that concomitant use of lasmiditan and β-adrenergic receptor antagonists should be done cautiously in those for whom lowered heartrate may be problematic [54]. There was a 3–4 h duration to recovery to pre-dose heartrate [54].

8.7 Conclusion

Lasmiditan is a highly selective 5-HT_{1F} receptor agonist and representative of the novel *ditan* class of medications that has demonstrated efficacy for migraine pain and MBS freedom when used in 100 and 200 mg doses for the acute treatment of

episodic migraine with and without aura. It expands acute migraine therapy to those who have poor tolerability or efficacy to other acute migraine treatment options. The peripheral nervous system is likely lasmiditan's main site of action where it has the potential for inhibiting CGRP and glutamate release, thereby blocking subsequent neuronal sensitization and migraine pain transmission. However, its TEAES of sedation and dizziness signify lasmiditan's ability to cross the blood–brain barrier, highlighting the potential for lasmiditan to also modulate central structures involved in migraine. Notably, lasmiditan's selectivity for the 5-HT_{1F} receptor and favorable cardiovascular safety profile distinguishes it from triptans and ergot alkaloids; lasmiditan provides a much-needed acute migraine therapy option to those with cardiovascular risk.

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Chapter 9
Update on Old and Current Targets for Antimigraine Therapies

Lars Edvinsson and Kristian Agmund Haanes

9.1 Introduction

Migraine is the most prevalent of the primary headaches with prevalence in about 15% in the global population, and seen in about three times more in females and most frequently during the most active ages (18–50 years) [1, 2]. Migraine manifests clinically as recurring attacks with well-described symptoms but without any clear biomarker profile [3]. Most patients have occasional or single attacks which can be handled by ordinary analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] and paracetamol) and triptans (5-hydroxytryptamine, 5-$HT_{1B/1D}$ agonists). However, up to 30% of migraine patients have frequent and severe attacks that require preventive therapy beyond the treatment of acute attacks, sometimes combined with an anti-emetic such as metoclopramide. Several drugs with various targets are approved and recommended for the preventive treatment of migraine (β-adrenoceptor blockers, angiotensin AT_1 blocker, antiepileptics, and antidepressants, inter alia). However, none of these were designed for the purpose of migraine prevention. Several scientifically unresolved issues remain to elucidate their sites of action.

One hypothesis suggests that they may act on neurogenic inflammation and cortical spreading depression [4]. For decades the question of the role of local inflammation, particularly related to the dura mater, the so-called neurogenic inflammation

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theory [5], has long been considered and still is in play [6]. We have addressed this aspect and propose that it might in particular be related to chronification of migraine [7]. The debate is still ongoing as new data is being collected [8–11]. At the molecular level, the potential targets for migraine therapies include the sensory nerves that mainly end in the adventitia of cranial vasculature [12, 13]. Related to the sensory system calcitonin gene–related peptide (CGRP) and substance P containing C-fibers are fairly rich in the cranial vasculature and their receptors are located in the adjacent smooth muscle cells [14, 15]. In this region, the release of CGRP and substance P may act on the vasculature to induce vasodilatation but also activate receptors on the adjacent Aδ-fibers [16]. Notably, CGRP is released from the sensory nerves in the cerebral and pial arteries inside the blood–brain barrier (BBB), but CGRP acting drugs cannot enter here [17]. Therefore, one aspect seems clear; the majority of current antimigraine treatments do not pass the BBB to any significant degree [18, 19]. Others have suggested that the BBB might open in conjunction with a migraine attack. Fairly recent studies have addressed this question; the conclusion suggests that the BBB is not transiently altered during a migraine attack [20–22].

In contrast, we conclude that the migraine therapies can act at the trigeminal ganglion (TG) and the dura mater [23]. The TG is supplied with neurons storing CGRP and others storing CGRP receptors, as well as numerous satellite glial cells (SGCs) [24]. These form an intricate meshwork of possible interactions with neuron-to-neuron and neuron-to-glial connections [25]. We have shown that there are direct interactions between the peripheral nerve fibers at the junctions between the C-fibers and the Aδ-fibers at the nodes of Ranvier [16]. Debate has been heated in discussion whether the gepants, triptans, and monoclonal antibodies have sites of action in the CNS. Our vision is that they do not pass the BBB to any significant degree and experiments with different tracers refute their effects in CNS [18, 19, 23, 26].

9.2 Current Drugs for *Acute* Migraine

9.2.1 NSAIDs and Other Analgesics

The acute treatment of migraine attacks most often rests on nonsteroidal anti-inflammatory drugs (NSAIDs, such as acetylsalicylic acid, ibuprofen, and diclofenac potassium, inter alia) and paracetamol [27, 28]. Despite the frequent and long-term use of NSAIDs, well known for action on the prostaglandin synthase mechanisms, the detailed site of action and how these drugs interact with the pain mechanisms of migraine is still not clarified in detail, but linking to antimigraine effects, it has in recent years been hypothesized that they might involve nitric oxide mechanisms [29]. Further, it is likely that they do not penetrate the BBB and thus they most likely interfere with the prostaglandin synthesis pathways peripherally. Paracetamol and similar drugs have been used for decades and are often

recommended to children. These drugs are usually well tolerated and are considered as first-line treatments and their effects can sometimes be improved with the combination of antiemetics such as domperidone or metoclopramide. These antiemetics are also very complex in their mode of actions and involve, for example, dopaminergic systems. Clearly, understanding the way these drugs act in acute therapy will open for new understanding of pain mechanisms in general.

9.2.2 5-Hydroxytryptamine Receptors in Migraine

When unsatisfactory results of the above first-line acute medication are seen, it is often recommended that patients are given a triptan. Current nomenclature shows that there exist nearly 20 subtypes of 5-HT receptors with different profiles, and the triptans are selective agonist at 5-hydroxytryptamine 1B and 1D (5-$HT_{1B/1D}$) subtype of receptors. Historically migraine was treated with ergotamine, dihydroergotamine (acute therapy), and methysergide (prophylaxis) but these drugs were associated with several and disturbing side effects, because of their action on numerous receptor types [30]. In the mid-1970s, Pat Humphrey started to produce selective agonists for subtypes of 5-HT_1 receptors, with the aim to create selective agonists treatment of migraine; this resulted in the development of triptans, with sumatriptan as the first, that revolutionized the treatment of acute migraine attacks [31]. All of the triptans are a part of the class that share a similar 5-HT_1 receptor selectivity profile (5-$HT_{1B/1D}$) though some subtle important differences do exist among them [32]. Debate has continued as to the antimigraine mechanism from a purely craniovascular constrictor to actions within the brain; currently they are thought to act as presynaptic inhibitors of CGRP release from trigeminal sensory neurons localized outside the BBB [33] and that vasoconstriction is considered more as a "side effect." Experimental studies in anaesthetzed cats early revealed that stimulation of the superior sagittal sinus resulted in a cardiovascular output model were 5-$HT_{1B/1D/1F}$ receptors could inhibit the response [34]. Interestingly, recent in depth immunohistochemistry revealed that there was a fairly rich expression of 5-HT_{1B} and 5-HT_{1D} receptors in the TGV system [35, 36]. Current understanding of the mechanism of action of triptans is the activation of G_i-coupled 5-$HT_{1B/1D/1F}$ receptors, reducing the intracellular cAMP [37]. This leads to reduced CGRP release from C-fibers and potentially reduced neuronal excitability [38].

Since the triptans were developed as cranio-selective vasoconstrictors [39–41], they also cause vasoconstriction in other parts of the vasculature, for example, coronary arteries [42, 43], which has stimulated the search for 5-HT receptor agonists without vasoconstrictive properties. Since triptans also bind to the 5-HT_{1F} receptor [44], this has resulted in the search for a 5-HT_{1F} receptor–specific agonist, which unlike triptans would have little effect on vasoconstriction [45]. The development of a selective 5-HT_{1F} receptor agonist, the first in the class "ditans," is lasmiditan which has been approved by the FDA [46].

Mechanistically lasmiditan as the other triptans acts via an intracellular signaling pathway by being a G_i protein–coupled receptor [47], and therefore the inhibition of CGRP release from the TGV system is similar to the other triptans [48]. However, the expression of 5-HT_{1F} receptor protein and mRNA levels are comparatively low in the trigeminal system while the amount of lasmiditan necessary for clinical effect high (200 mg); this may suggest that 5-HT_1 receptor subtypes should be analyzed in more detail.

9.2.3 Neurokinin Receptors and Blockers

The family of tachykinins or neurokinins consist of substance P (SP), neurokinin A (NKA), and neurokinin B (NKB); the first two are produced by the same gene (preprotachykinin A) and NKB by a different gene (preprotachykinin B) [49]. SP was isolated and sequenced by Susanne Leeman (early 1970s) and following production of antibodies it was observed in peripheral and central nervous systems. The first neuropeptide to be associated with the trigeminal system was SP. Immunohistochemistry revealed it to be localized in several types of neurons and in some endocrine cells [50, 51]. Among neurons, SP was seen in primary sensory neurons of the C-fiber (unmyelinated) type, and associated with nociception [52]. We were the first to demonstrate that both cerebral and meningeal vessels and the dura mater contained SP positive sensory C-fibers [53, 54]. The family of peptides in this group rapidly incorporated neurokinin A and B; however their role in the cranial vasculature was not equally prominent [55]. Another key development was the work of Folkers and Rosell who produced SP antagonists which helped to identify the role of neurokinins in various tissues and conditions [56, 57]. In relation to headache pathophysiology, Mike Moskowitz showed that meningeal (dural) vessels were innervated by fibers from the trigeminal ganglion [58] and suggested that these are involved in the pathophysiology of headaches. A few years later he verified that the SP fibers in dural vessels emanated in the trigeminal ganglion using retrograde tracing [59]. At the same time we showed that SP could be released from cranial vessels [60]. Collectively, the findings provided a background to two decades of SP research with the underlying hypothesis that dural neurogenic inflammation was the key to finding new antimigraine therapies [5].

Recent work has with a set of novel specific antibodies demostrated the detailed localization of SP, NKA, and NKB in the trigeminal system [61]. With potassium depolarization or capsaicin, we observed minor SP release as compared to the pronounced co-release of CGRP. From the immunohistochemical studies, the expression of SP was about one-third of that of CGRP while NKA and NKB were considerably less. These morphological findings point toward a minor role of the neurokinins as compared to CGRP in the TGV system. These observations agree well with the absence of a significant release of SP in migraine and in cluster headache attacks while CGRP showed pronounced release.

There exist three tachykinin receptors and the vasoactive properties of the tachykinins are basically mediated via the neurokinin NK_1 receptor (R). The NK_1R is

found throughout the peripheral and central nervous systems [61], as well as in cranial artery walls, which support a vasomotor role [62]. Early non-peptide NK_1R antagonists were found to block plasma protein extravasation within the dura mater stimulated by electrical stimulation of the trigeminal ganglion [63] and to inhibit the c-fos expression in the TNC in response to the C-fiber stimulant capsaicin [64]. These results lead to the hypothesis that NK_1R antagonists would be beneficial in the treatment of migraine. However, clinical studies with RPR100,893 [65] and LY303,870 [66] were without effect in aborting acute migraine attacks, and possible interaction with CGRP antagonists could be interesting to study.

9.2.4 Gepants

Targeting the CGRP pathway was first suggested by translational work in the 1980s [67], which pointed away from inflammation and drove home the message that non-vasoconstrictors work. The success of drugs blocking the CGRP action or its receptor is a paramount development and patients testify as to their efficacy at the cost of limited side effects [68]. The clinical trials on CGRP receptor blockade were initially directed toward small molecules, called gepants, as a complement to triptans for acute alleviation of migraine attacks. The first drugs were olcegepant and telcagepant, both were successful in trials, but difficulties were preventing their success [69]. At present ubrogepant and rimegepant are approved by FDA for use in the USA, while a third gepant, atogepant, is under study for prophylaxis. The details on these molecules are given in other parts of this volume.

9.3 Targets for *Prophylaxis* of Migraine

Preventive drugs are used to treat aspects of migraine such as frequency, severity, and duration in individuals who are not helped enough by acute medications [70]. European Headache Federation, American Headache Society, and International Headache Society have each produced guidelines for preventive medication of patients that have several days per month of migraine attacks associated with impaired quality of life. Their migraine should be adequately regulated despite optimized acute medication use. Most countries have therapy rationale that includes aspects of effect, side effects, and cost for society.

9.3.1 Beta-Adrenoceptor Blockers

Propranolol, a nonselective beta-blocker, was fortuitously discovered to exert a migraine prophylactic effect in patients treated for angina pectoris [71]. The prophylactic effect of other beta-blocking drugs has been studied as well. Timolol, a

nonselective beta-blocker, atenolol, and metoprolol are selective $beta_1$-blockers which have good antimigraine effects. On the other hand, alprenolol, oxprenolol, acebutolol, and pindolol showed no effect in clinical trials. The mode and site of action remain unclear [71]. The beta-blockers with antimigraine effect have two properties in common: (1) they all lack intrinsic sympathomimetic activity and (2) they all possess a $beta_1$-adrenoceptor blocking effects [72]. The studies confirmed that these blockers are effective prophylactics both in migraine with and without aura. Other beta-adrenoceptor blockers were shown to have minor effect (e.g., atenolol and bisoprolol), putatively in part due to small studies with few subjects. Still the mechanism responsible remains unclear, but one interesting aspect is that the cerebral blood vessels possess relaxant $beta_1$-adrenoceptors [73]. Recent work by Hebstreit and May addressed the enigma of the site of action of metoprolol in patients and healthy controls [74]. There was no effect on trigeminal pain processing, suggesting a peripheral effect of this beta-blocker. Exploratory analysis revealed some enhanced hypothalamic activity under metoprolol in both groups. However, there is some variability in the ability of beta-blockers to pass the BBB; in high doses of metoprolol and propranolol, there are symptoms like vivid dreams that may indicate an action within the CNS.

9.3.2 Angiotensin II AT_1 Receptor Antagonists

A group of hypertension patients noted that their migraine was improved when treated with the angiotensin II AT_1 receptor antagonist candesartan. This resulted in a positive clinical randomized trial [75]. This was followed up by a comparative crossover study comparing candesartan (16 mg), propranolol, and placebo [76]. The two active drugs showed equal effect and were superior to placebo. Candesartan was as good as the beta-blocker with less side effects and better tolerability. The AT_1 receptor blocker group consists of several drugs which are typically used in hypertension and congestive heart failure; despite their frequent use, the effect as prophylaxis in migraine is not studied to any major extent. We are still unclear as how this impacts migraine pathophysiology.

9.3.3 Anticonvulsant Drugs

In this group, two molecules stand out in therapy, topiramate and sodium valproate, which both have proven efficacy for migraine prevention [28, 69, 77, 78]. Clinically, they are difficult to monitor, have lots of moderate-to-severe side effects and often we use the classical method of start-low-go-higher in dosing. Topiramate is often contraindicated due to association with nephrolithiasis, pregnancy, lactation, and glaucoma. Typical contraindications for valproate are liver disease, thrombocytopenia, and females with childbearing potential due to risk of teratogenicity. Topiramate is used due to existence of high-quality evidence and the absence of weight gain. In

meta-analysis of nine RCTs, topiramate was superior to placebo as measured by reduction in monthly number of headache days [79].

Their mechanism of action is largely unknown but considered to have a central mode of action [80]. Topiramate affects glutamatergic and GABAergic transmission, as well as sodium and calcium channels [81]. Andreou and colleagues showed that topiramate may inhibit nociceptive neurotransmission in the trigemino-thalamic pathway [82]. Stimulation of the ventroposteromedial (VPN) nucleus of the thalamus was inhibited after intravenous as well as after local administration of topiramate [82]. This supports a CNS effect of the drug. In support, Hebestreit and May using functional magnetic resonance imaging showed that topiramate may modulate trigeminal pain processing in thalamo-cortical networks in humans [83]. The work of Storer and Goadsby revealed that systemic topiramate partly inhibited stimulus-evoked cell firing in the trigeminocervical complex but local administration did not [84, 85]. Therefore, the authors concluded that topiramate has an effect outside the trigemino-cervical complex [85]. In support, neuronal firing of thalamic neurons reported effects of anticonvulsants in the thalamus [86]. The data has been discussed and related to effects on reducing cortical spreading depression in animal models. The above data, both preclinical and clinical, support the view that topiramate modulates nociceptive trigeminal transmission by attenuation of pain-related activity of the thalamo-cortical network and enhanced the thalamic connectivity to the precuneus, posterior cingulate cortex, and the secondary somatosensory cortex [83]. It is likely that topiramate has several sites of action on pathways within the CNS.

9.3.4 Tricyclic Antidepressant

Amitriptyline is the only drug in this class that is commonly used in migraine prophylaxis. This belongs to the older type of antidepressants, having action on uptake of both noradrenaline and 5-HT. The effect of amitriptyline is comparable with that of topiramate [87]. Among the side effects are weight gain, dizziness, and constipation. It is often considered to use this drug in individuals with comorbidity of depression or sleep disturbances [28]. The more novel selective serotonin uptake inhibitors have been tried but were without effect. Some noticeable contraindications are age <6 years, heart failure, glaucoma, or coadministration with monoamine oxidase inhibitors.

9.3.5 Calcium Channel Antagonists

This group of drugs was introduced as cardiovascular drugs for treatment of cardiac arrhythmias, angina pectoris, and hypertension. Contractile responses of vascular smooth muscle is controlled by regulation of its intracellular Ca^{2+} concentration,

and calcium entry blockers prevent vasoconstriction by interfering with the influx of extracellular calcium into smooth muscle cells and/or inhibition of Ca^{2+} release from intracellular calcium stores [88]. Among calcium entry blockers, flunarizine and nimodipine have been investigated in controlled clinical trials on migraine. Flunarizine was convincingly shown to be effective in the prophylaxis of migraine [89, 90]. Nimodipine was initially showing positive effect, but later studies in larger trials failed to show a positive prophylactic effect [91]. The controlled trials provide support for the use of flunarizine in episodic migraine prevention. Among its side effects are weight gain, fatigue, and constipation. More rare contraindications are Parkinsonism and depression.

The mechanism of action is still a matter of debate because its mode of interaction with calcium ions on cranial blood vessels in humans and animals do not fit the mode of action typical for other calcium entry blockers. Studies on human cranial arteries suggest differences in blocking function of flunarizine [92]. It is a very poor calcium channel inhibitor, and therefore we have postulated that the effect on migraine might be linked to its molecular structure which resembles that of psychotropic drugs.

9.3.6 Onabotulinum Toxin A

Onabotulinum toxin A (BoNT-A) is today well established for the prevention of chronic migraine and approved in numerous countries worldwide. However, the trials did not show effectiveness in episodic migraine [93]. It acts to inhibit the transmission in cholinergic synapses at skeletal muscles and is used in for example torticollis and alike, as well as to alleviate wrinkles in the face. It has also been found useful in order to stabilize bladder function. The traditional story is that women of Los Angeles observed that after cosmetic use of Botox their migraines got better, and this was the background for the trials of BoNT-A. Clinical trials named PREEMPT were positive, and Botox is now approved in numerous countries for chronic migraine [94, 95]. According to the PREEMPT protocol, it is given at 3-month intervals and injected subcutaneously at 31 specified extracranial places on the calvarium.

But what is its mechanism of action? Burstein has made extensive studies and raises the question how extracranial administration can influence migraine pain. One interesting aspect was the discovery that intracranial sensory nerve fibers can communicate with extracranial sensory nerves, also called the “suture pathway.” Interestingly, local extracranial BoNT-A made the suture branches of the meningeal nociceptors, but not the intracranial meningeal nociceptors, mechanically insensitive [96]. Since this experiment was performed acutely on rats, subsequently the group tested a similar approach but with an extended time window of 7 days between application and study. Extracranial BoNT-A suppressed meningeal dural nociceptors’ responses to capsaicin (TRPV1 receptor) and mustard oil (TRPA1 receptor) activation [97]. This work may very well be key in understanding how extracranial BoNT-A might work as prophylactic in chronic migraine.

9.4 Conclusion

The above-mentioned prophylactic drugs are in use worldwide, but Hepp and colleagues studied over a year to what extent the patients remained on their prophylactic drugs. They found out that about 85% stopped the medication within a year either due to lack of effect or of intolerable side effects [98]. Therefore, recent developments of CGRP mechanism medications have provided new hope (see other chapters in this book). Today there are four monoclonal directed to reduce CGRP signaling in migraine. Erenumab is specific for the N-terminals of RAMP1 and CLR. Fremanezumab, galcanezumab, and eptinezumab are all specific for the CGRP peptide itself [68]. Collectively all four antibodies display comparable efficacy which show good tolerability and few side effects [99]. These antibodies are large molecules, 1500 times larger than gepant. Their large size effectively prevents them from entering the brain. The CGRP pathway medications have now paved the way for specific medication in migraine both for acute and prophylactic therapy and improved migraine care. However, novel targets are still needed for the patients that do not respond to anti-CGRP treatments.

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