



# New Oral Drugs for Migraine

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## Abstract

Migraine is a common and disabling neurological disorder, with several manifestations, of which pain is just one. Despite its worldwide prevalence, there remains a paucity of targeted and effective treatments for the condition, leaving many of those affected underserved by available treatments. Work over the last 30+ years has recently led to the emergence of the first targeted acute and preventive treatments in our practice since the triptan era in the early 1990s, which are changing the landscape of migraine treatment. These include the monoclonal antibodies targeting calcitonin gene-related peptide or its receptor. Evolving work on novel therapeutic targets, as well as continuing to exploit drugs used in other disorders that may also have a therapeutic effect in migraine, is likely to lead to more and more treatments being able to be offered to migraineurs. Future work involves the development of agents that lack vasoconstrictive effects, such as lasmiditan, do not contribute to medication overuse, such as the gepants, and do not interact with other drugs that may be used for the disorder, as well as agents that can act both acutely and preventively, thereby utilising the quantum between acute and preventive drug effects which has been demonstrated with different migraine drugs before. Here we discuss the evolution of oral migraine treatments over the last 5 years, including those that have gained regulatory approval and reached clinical practice, those in development and potential other targets for the future.

## 1 Introduction

Migraine is a common and disabling neurological disorder [1]. Often seen as a hidden disability as patients exhibit no abnormal examination findings on the whole when experiencing migraine, this condition is still seen as one of the most disabling diseases [1]. Despite its prevalence, disability and related socioeconomic impact, there remains a therapeutic need for effective and targeted treatments for migraine. Many sufferers remain underserved by currently available therapies, with regards to acute attack abortion and prevention [2]. The first specific drug class to be developed, the triptans (serotonin 5-HT<sub>1B/1D</sub> receptor agonists), were

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## Key Points

Migraine is a frequently disabling condition, yet there remains a paucity of targeted and effective treatments for the condition.

We are currently witnessing first-hand the emergence of the first targeted acute and preventive treatments in our practice since the triptans were developed for clinical use in the 1990s, which are changing the landscape of migraine treatment.

Evolving work into novel therapeutic targets, as well as continuing to exploit drugs used in other disorders that may also have a therapeutic effect in migraine given there are currently no available biomarkers for effective treatment response.

Future work in this area needs to involve the development of agents that lack vasoconstrictive effects and can be used in older patients, those that do not contribute to medication overuse and do not interact with other drugs that may be used for the disorder, as well as those that can act both acutely and preventively to allow the same agent used to abort attacks to have a preventive role in subsequent attack frequency and severity.

first used in the 1990s, and though effective for a number of patients, carry vascular risk and therefore cannot be used in the elderly and those with cerebrovascular and cardiovascular risk [3]. It is clear not every migraineur will respond to triptans [4]. Until recently, other commonly used drugs, both acute and preventive, were non-specific in relationship to migraine, and were developed for use in other disorders such as depression, hypertension and epilepsy. This lack of specificity has had the consequence of broad central nervous system effects, resulting in poor tolerability profiles and limited efficacy [5].

Another issue which can be problematic for migraine patients and their treating clinicians is the development of medication overuse headache (MOH) with use of commonly used acute abortive treatment in migraine, including paracetamol or acetaminophen, opioids and triptans [6]. This contributes to headache-related disability, causes the headache problem to be more refractory to treatment and contributes additional socioeconomic costs, with increased emergency presentations and time off work [7]. Understanding the mechanisms for MOH, and the development of novel therapies that do not contribute to this effect, is important for developing future migraine therapeutics [8].

A further limitation of currently available treatments for migraine is the risk of headache recurrence following initial headache response to treatment, particularly well documented with the triptans [9]. This lack of sustained response to treatment in some individuals and with some drugs is not well understood, but clearly maintenance of treatment effect is an important goal of migraine therapeutics going forward. Children and adolescents remain a poorly served group with regards to migraine management, largely due to a lack of licensed drugs, and a lack of randomised controlled clinical trials in this patient cohort. This leaves a small number of acute treatments available to them, and off-license use of several migraine preventives in practice.

Advances in understanding of the neurobiology of migraine and bench-to-bedside research have led to an exciting time in migraine therapeutics, where we are currently able to offer our patients specific well-tolerated drugs that are safe, efficacious and lack the adverse effect profiles of many of the agents that are conventionally used to treat the disorder. Most interestingly, it has come to light through research into agonists at the 5-HT<sub>1F</sub> receptor, the ditans, that vasoconstriction is not required for the pain response in migraine therapy, and therefore we can hopefully soon start to treat the populations of patients who have been historically undertreated due to concerns about vascular risk [10].

Much of the recent evolution of migraine therapy in our clinical practice has largely been driven by calcitonin gene-related peptide (CGRP) pathway-targeted agents, including the monoclonal antibodies. In the last few years, these have

changed the landscape of migraine prevention by allowing us to offer our patients a safe and effective treatment, which can be administered at home, and has a favourable side effect profile [11]. In addition, it has been suggested that significant haemodynamic and cardiovascular effects are not common with prolonged CGRP inhibition [12, 13]. Whilst the antibodies are administered by subcutaneous injection, or intravenously, oral small molecule CGRP receptor antagonists working on this pathway are in late stages of development, or licensed in many countries, and carry promise for our near future practice, as do other emerging oral treatments for migraine.

There remains a need for further treatment options for migraineurs. Clinical trials in the disorder, even in those testing CGRP-targeted drugs, have never achieved a 100% responder rate, which leaves the challenge for the future open. Interestingly, an excellent responder population, arguably those with a  $\geq 75\%$  reduction in migraine days, has been seen in the antibody trials [14], as well as previous Botulinum toxin studies [15–17]. Importantly, these rates are population-treated estimates. There certainly remains a cohort of patients for whom these new treatments are completely ineffective. This biological and treatment-related heterogeneity in migraine is poorly understood and the factors impacting treatment success are difficult to predict. Biomarkers for treatment response prediction are being explored and need refinement [18, 19]. The lack of clear biomarkers leads to frustrating periods of treatment failure for patients and their clinicians. In addition, the injectable drug formulations are not suitable for everyone, such as children who may be averse to being injected and those who are trypanophobic. For some, self-injecting is difficult and they do not have anyone to help. Increasing the options for treatment and administration, as well as increasing specificity of available treatments and developing prediction models of response are some of the ways that we can tailor treatment for our patients to personalise migraine medicine in the future.

This review will detail the emerging oral treatments for migraine, both those that are currently available, albeit not widely, and those that remain under investigation, as well as potential areas for therapeutic development in the future.

## 2 Currently Available New Treatments That Reached Clinical Practice in Some Countries in the Last 5 Years

The mainstay of acute oral migraine treatment in most places remains with the use of paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs) and the triptans. There is evidence that the combination of an NSAID and triptan can prolong the therapeutic effect and limit rebound headache. A phase III clinical trial of a novel pharmaceutical

product containing meloxicam and rizatriptan presented as formulation-based rapid absorption technology demonstrated a superior, pain-free and most bothersome symptom response at 2 h post-dose compared with placebo, with a 48-h sustained pain-free rate superior to placebo [20]. Similarly, the formulation, AXS-07, was superior to placebo on both pain-free and most bothersome symptom endpoints when administered when pain was mild [21]. Ergotamine is less frequently used in practice, owing to poor oral bioavailability, problematic nausea as a side effect and the superiority of triptans despite the shared vasoconstrictive and medication overuse risk [22]. Dihydroergotamine, which has been used in the treatment of acute migraine since the 1940s [23], has been re-launched, so to speak, with an olfactory delivery device [24]. To avoid unwanted gastrointestinal side effects of NSAIDs, celecoxib has been formulated in a solution with improved bioavailability on regular celecoxib [25], which is effective in acute migraine [26, 27].

More novel, in terms of mechanism, emerging oral treatments that have recently been approved in some parts of the world in the last 5 years are discussed here.

## 2.1 Lasmiditan (Serotonin 5HT<sub>1F</sub> Agonist) Acute Treatment: The ‘Ditans’

The demonstration of selective agonism at the serotonin 5HT<sub>1F</sub> receptor being anti-nociceptive in the trigeminovascular system [28] and the lack of vasoconstrictor actions were important discoveries in migraine therapeutics [29]. The bench work demonstrated that serotonergic drugs could be developed without the adverse side effect of vasoconstriction. The only available drug thus far in this class is lasmiditan (LY573144).

### 2.1.1 Proposed Mode of Action

It is thought that lasmiditan inhibits CGRP release in peripheral and central trigeminal nerve endings [30], although its site of action being the trigeminal ganglion is unlikely given the demonstration of largely serotonin 5HT<sub>1B/1D</sub> receptors in this region [31]. It may also have other neuronal actions due to its blood–brain barrier permeability, which contribute to its nociceptive effect in migraine. Preclinical studies have demonstrated it reduces trigeminovascular activation and reduces superior salivatory nucleus activation in the trigeminal autonomic reflex [32].

### 2.1.2 Trial Evidence in Migraine

The first drug in this class to be tested clinically was LY334370, which was effective but had off-target toxicity that stopped its development [33]. Lasmiditan was developed as an orally available ditan [34, 35]. Its first phase II

study was positive [36], which led to phase III clinical trials of this agent in the acute treatment of migraine [37, 38]. Lasmiditan at all doses led to an increased rate of headache freedom at 2 h post-doses and freedom from the most bothersome symptom relative to placebo. Interestingly, unlike other acute trials of treatment in migraine, these studies both included patients with coronary artery disease, clinically significant arrhythmia and uncontrolled hypertension and were single attack designs, allowing one or two lasmiditan doses only. The presence of pre-existing vascular risk factors had no impact on treatment efficacy, nor did the drug cause a difference in cardiovascular treatment-emergent adverse events relative to placebo [39]. Sub-group analysis also suggested efficacy in those who had previously failed triptan therapy [40, 41], and in those in whom triptans were contraindicated [42]. In an open-label, phase III study using previously recruited trial patients who continued to use lasmiditan, 100–200 mg was effective in 27–32% of attacks with a consistent response, and was generally well tolerated, with dizziness being the most common side effect, and less common ones including fatigue and paraesthesia [43]. The dizziness seems to be dose-dependent and of short duration (median 1.5–2 h), without any influence on drug efficacy [44]. Post-hoc analyses of all three studies have also suggested no increase in adverse events among the elderly compared with younger patients [45]. Post-hoc safety analyses of a trial of consecutive attacks treated with lasmiditan relative to placebo showed treatment-emergent serious adverse events occurred in only two patients taking 100–200 mg relative to one patient with placebo [46]. Dizziness, paraesthesia, fatigue, nausea, vertigo and somnolence were the most common events reported, with the vast majority being mild or moderate in severity and the incidence being highest during the first attack and decreasing with subsequent attacks.

In common with triptans [47], and in contrast to gepants (see below), a second dose of lasmiditan after failure of the initial dose is not more effective than placebo [48]. Again, consistency of response rates are comparable to triptans at two-thirds having pain relief in  $\geq 2/3$  attacks with lasmiditan 100 or 200 mg [49], and sumatriptan 100 mg [50].

This data has led to the United States Food and Drug Administration (US FDA) approving this drug for the acute treatment of migraine in 2019. Unfortunately, a single dose can lead to an impairment with driving which can be unrecognised by the patient, so patients are forbidden from driving for at least 8 h following drug administration [51], which makes emergency use of the drug for some patients unfavourable relative to other currently available options.

Studies in the safety of this drug in children are ongoing (ClinicalTrials.gov identifiers: NCT04396236, NCT04396574).

There is a preclinical suggestion that the ditan class may have an MOH effect akin to the triptans [52], and the

potential for this in clinical practice remains to be evaluated as more widespread clinical use of this agent develops.

Serotonin syndrome, an additive effect of alcohol and possible bradycardia with other medications are all drug–drug interactions and risks that will need to be considered as increased prescribing of this drug within clinical practice occurs [53].

The development of acute migraine therapies that lack vasoconstrictive effects is an appealing therapeutic avenue in migraine, and the ditans hold promise for treatment, particularly in the elderly and those with cardiovascular risk factors.

The phase III clinical trials and sub-studies and their findings for lasmiditan are summarised in Table 1.

### 2.1.3 Ubrogepant, Rimegepant and Atogepant (Small Molecule CGRP Receptor Antagonists): Acute and Preventive Treatment—The ‘Gepants’

As well as the larger monoclonal antibodies, small molecule antagonists at the CGRP receptor have also been developed for the acute and preventive treatment of migraine and are making their way into our clinical practice, after initial concerns regarding hepatotoxicity despite efficacy [54].

#### 2.1.4 Proposed Mode of Action

Whilst it has become well established that blocking the effects of CGRP in migraine has a therapeutic effect, and that CGRP is widely expressed within the central nervous system, including at sites known to be crucial to migraine pathophysiology [55], the sites of action of the small molecule antagonists or the monoclonal antibodies has not been fully elucidated. It has been suggested that neither the gepants nor the CGRP monoclonal antibodies cross the blood–brain barrier in sufficient quantities, and therefore their migraine effect is mediated peripherally in the trigemino-vascular system [56, 57]. Some sites of action which have been proposed include the most peripheral ends of the C- and A $\delta$ -fibres, in part located in the adventitia of intracranial vessels and on the dura, the trigeminal ganglion and the nodes of Ranvier [58]. On the other hand, CGRP receptors are well placed in the trigeminocervical complex [59], ventroposteromedial thalamus [60] and ventrolateral periaqueductal grey [61, 62] to have plausible effect in migraine. Moreover, small amounts of monoclonal antibodies enter the cerebrospinal fluid (CSF) [62], and there is a substantial discrepancy between gepant Ki's (binding affinity between the small molecule and receptor) and CGRP receptor occupancy on brain penetration studies [63, 64], whereas their peripheral effect on the forearm blood flow model of CGRP release in humans is mediated via higher receptor occupancy and a concentration-dependant effect [64].

#### 2.1.5 Trial Evidence in Migraine

Ubrogepant was the first gepant to receive FDA approval in 2019 following two phase III trials demonstrating efficacy relative to placebo with 25–100 mg doses [65, 66]. The initial studies suggested efficacy and tolerability, and subsequent post-hoc analyses have shown consistent responses in triptan non-responders, insufficient responders and those that are triptan naïve [67, 68]. In contrast to the triptans and ditans (see above), a second dose of ubrogepant for primary treatment failure is effective [69]. There seemed to be a favourable side effect profile even amongst those with cardiovascular risk [70]. The acute headache response also seems sustained at 48 h [71]. The use of concomitant migraine prevention did not alter efficacy [72]. Interestingly, a phase III trial assessing the efficacy of ubrogepant in migraine treatment when administered during the prodrome has just been completed, and the results are awaited (NCT04492020). An open-label study is also ongoing looking at the safety of this drug in children and adolescents (NCT05127954). Real-world data are encouraging in terms of efficacy but suggests that adverse events such as fatigue, dry mouth and nausea and vomiting were reported more frequently than in the clinical trials [73]. The trials of ubrogepant are summarised in Table 2.

Rimegepant has also been FDA approved for use as an orally disintegrating tablet at 75 mg in the acute treatment of migraine, following three randomised, phase III, placebo-controlled trials [74–76], which followed a dose-finding phase IIb study in 2014 [77]. The agent has since been European Medicines Agency (EMA) approved. This dose was superior to placebo in headache cessation and treatment of the most bothersome symptom, with nausea and urinary tract infection as the most common adverse events. Interestingly, initial concerns regarding liver impairment with the first drugs developed in this class was not born out [54], with a transaminitis occurring in a single patient in both the active and placebo groups and no elevations in bilirubin more than twice the upper limit of normal reported in one of the rimegepant studies [74]. A further study showed that the drug could also work in the preventive treatment of migraine with alternate day dosing showing superiority to placebo, without significant adverse events [78]. This idea that the same drug could work acutely and preventively for migraine has been historically reported with agents like ergotamine, with intranasal and rectal preparations being used acutely [22], and intravenous dihydroergotamine having a demonstrated preventive effect in migraine [79], yet this bridge between acute and preventive migraine therapy is emerging again. Whilst the CGRP antibodies currently hold UK licensing and National Institute for Health and Care Excellence (NICE) approval for the prevention of migraine only

**Table 1** A summary of the phase III clinical trials and sub-studies of lasmiditan for the acute treatment of migraine, with the salient findings

Study	Study type	Administration	Design	Efficacy of drug	Efficacy of placebo	Other findings <sup>a</sup>
Kuca et al. (2018) [38] (SAMURAI)	Randomised double-blind phase III	Oral	Single attack	100–200 mg 28.2–32.2% PF2h	15.3%	
Goadsby et al. (2019) [37] (SPARTAN)	Randomised double-blind phase III	Oral	Single attack	50–200 mg 28.6–38.8% PF2h	21.3%	
Brandes et al. (2019) [43] (GLADIATOR)	Randomised open-label phase III	Oral	≥1 attack	100–200 mg 26.9–32.4% PF2h	NA	Consistent response across up to 5 attacks in those who treated ≥ 5
Doty et al. (2019) [151]	Post-hoc analysis of [37, 38]	Oral	Single attack	50–200 mg 28.6–35.6% PF2h 17.4–21.2% PF24h 14.9–18.4% PF48h	18.3% PF2h 10.3% PF24h 9.6% PF48h	MBS, total migraine-free and disability-free responses more common in treated groups at all doses (21.7–27% vs 12.9%)
Shapiro et al. (2019) [39]	Pooled analysis of [37, 38]	Oral	Single attack			0.9% with drug vs 0.4% overall cardiovascular treatment emergent adverse events, independent of previous cardiovascular risk factors and similar efficacy
Loo et al. (2019) [48]	Post-hoc analysis of [37, 38]	Oral	Single attack			Some efficacy of a second dose of drug for headache recurrence but not ongoing headache
Loo et al. (2019) [152]	Post-hoc analysis of [37, 38]	Oral	Single attack			No effect of concurrent migraine preventives on drug efficacy or adverse event reporting
Ashina et al. (2019) [153]	Post-hoc analysis of [37, 38]	Oral	Single attack			Symptom relief of headache and other migraine symptoms can start as early as 30 minutes after dose of 100–200 mg
Smith et al. (2020) [154]	Post-hoc analysis of [37, 38, 43]	Oral	Multiple attacks			All doses resulted in an improvement in migraine-related disability which was persistent at 48 h
Tepper et al. (2020) [155]	Post-hoc analysis of [37, 38]	Oral	Single attack			Efficacy of 100–200 mg not influenced by baseline patient characteristics, migraine disease history, delaying treatment > 2 h or co-existent nausea
Lipton et al. (2021) [156]	Pooled analysis from [37, 38]	Oral	Single attack			Pain freedom relative to mild pain at 2 h is associated with freedom from MBS, lower migraine disability and increased patient global impression of change

Table 1 (continued)

Study	Study type	Administration	Design	Efficacy of drug	Efficacy of placebo	Other findings <sup>a</sup>
Ashina et al. (2021) [49] (CENTURION)	Randomised double-blind phase III	Oral	Four consecutive attacks	100–200 mg 14.4–24.4% PF2h in ≥ 2 of 3 attacks	4.3%	Consistent response across attacks with less adverse events after first attack
Tassorelli et al. (2021) [46]	Post-hoc safety analysis of [48]	Oral	Four consecutive attacks	NA	NA	Mild to moderate adverse events of short duration, with reducing frequency over subsequent attacks
Reuter et al. (2022) [41]	Subgroup study of [49]	Oral	Four consecutive attacks			Response independent of previous triptan response
Kregge et al. (2022) [42]	Subgroup study of [37, 38, 49, 157]	Oral	Single/multiple attacks			2-hour pain relief the same for those with and without triptan contraindications and same safety and tolerability profiles

MBS most bothersome symptom, *PF<sub>2h</sub>* pain freedom at × hours

<sup>a</sup>Across all studies, dizziness, fatigue, paraesthesia, sedation, nausea and impaired driving were the most common adverse events reported

[80], there is evidence that if administered intravenously between 1 and 6 h after the onset of a migraine, eptinezumab can be effective at shortening the attack duration relative to placebo [81], as well as being an effective preventive treatment of migraine [82, 83]. Recent work also suggests long-term safety of rimegepant use, even in those with moderate to high cardiovascular risk [84]. An open-label study has suggested a potential preventive effect even with PRN use over a 52-week period with improved quality of life outcomes and no obvious medication overuse effect with more frequent usage of rimegepant [85]. However, this study was open-label and allowed concomitant use of other migraine preventives (amitriptyline and topiramate being the most common), which could have led to some confounding of the results. The rimegepant studies are summarised in Table 3.

Atogepant has been specifically investigated for the preventive treatment for migraine rather than the acute treatment of migraine. This has been the latest drug to gain FDA approval in its class in 2021, and is pre-registration for migraine prevention in the EU, Israel, Kuwait and the United Arab Emirates. Two phase III trials have demonstrated efficacy in headache prevention (a reduction in mean monthly migraine days relative to placebo) over 12 weeks at all doses between 10–60 mg, with adverse effects of fatigue, constipation and nausea [86, 87]. Therapeutic efficacy seems to start early in the course of treatment and is sustained at 12 weeks [88]. A recent study has demonstrated no clinically significant pharmacokinetic interactions between sumatriptan and atogepant when co-administered [89]. A further phase III study is examining the efficacy of atogepant in episodic migraine prevention in those who have failed two to four previous preventives (NCT04740827) [90]. The atogepant studies are summarised in Table 4.

An intranasal gepant, zavegepant, formerly called vazegepant, is under investigation for the acute treatment of migraine (NCT04408794) [91]. Despite low oral bioavailability in rats, efficacy in the nasal delivery formulation has been demonstrated in unpublished phase II/III data [92] and approval has been filed at the FDA, with a decision expected early next year. Further work is under way to alter the molecular structure to try to increase oral bioavailability and increase delivery options of this agent [93]. An oral formulation is currently under investigation (NCT04804033).

Interestingly, preclinical data suggests that targeting the CGRP pathway rather than the serotonergic one is less likely to lead to medication overuse [52]. The efficacy of the monoclonal antibodies targeting this pathway despite the presence of medication overuse, compared with other migraine preventives, is interesting and alludes to the role of this system in the mediation of medication overuse [8]. Again, longer term and more widespread clinical use of these agents will reveal further insights with regard to this in due course. Of note, all the gepants are prone to drug

**Table 2** Summary of the findings of the phase III trials and sub-studies of ubrogepant in the acute treatment of migraine, with the salient findings

Study	Study type	Design	Efficacy of drug	Efficacy of placebo	Adverse events	Other findings
Dodick et al. (2019) [65] (ACHIEVE-I)	Randomised double-blind phase III	Single attack	50 or 100 mg 19.2–21.2% PF2h 37.7–38.6% MBS freedom at 2 hours	11.8% PF2h 27.8% MBS free at 2 hours	Nausea, somnolence, dry mouth	
Lipton et al. (2019) [66] (ACHIEVE-II)	Randomised double-blind phase III	Single attack	25 or 50 mg 20.7–21.8% PF2h 34.1–38.9% MBS freedom at 2 hours	14.3% PF2h 27.4% MBS free at 2 hours	Nausea and dizziness	
Ailani et al. (2020) [158]	Randomised open-label phase III	Multiple attacks			Upper respiratory tract infection	Long-term use of 50 and 100 mg safe and well tolerated
Dodick et al. (2020) [159]	Sub-analysis of [65, 66]	Single attack				Increased rates of normal function, medication satisfaction, patient global impression of change scale at all doses relative to placebo
Goadsby et al. (2021) [71]	Post-hoc analysis of [65, 66]	Single attack				Drug effect within 1–2 hours post dose with effect persistent at 48 hours
Hutchinson et al. (2021) [70]	Post-hoc analysis of [65, 66]	Single attack				No difference in efficacy, adverse events or cardiac events between different cardiovascular risk groups
Blumenfeld et al. (2021) [67]	Post-hoc analysis of [65, 66]	Single attack				No difference in efficacy or tolerability regardless of previous triptan exposure or response
Chiang et al. (2021) [73]	Post-market cohort study	Multiple attacks	Headache relief 47.6% Headache freedom 19%	NA	Fatigue, dry mouth, nausea, vomiting, constipation, dizziness	No difference in response amongst those on a CGRP antibody, although higher rates of adverse events, adverse events in general may be higher than suggested in initial trials
Blumenfeld et al. (2022) [72]	Sub-analysis of [66, 159]	Single attack				Similar drug response despite migraine prevention, with no significant differences across classes of preventives, and similar adverse events

Table 2 (continued)

Study	Study type	Design	Efficacy of drug	Efficacy of placebo	Adverse events	Other findings
Lipton et al. (2022) [68]	Post-hoc analysis of [65, 66]	Single attack				Increased rates of normal function and treatment satisfaction in those with an insufficient triptan response previously compared with placebo

*CGRP* calcitonin gene-related peptide, *MBS* most bothersome symptom, *PFx/h* pain freedom at x hours

interactions when co-administered with CYP34A inducers or inhibitors; inducers such as phenytoin, St John's Wort and carbamazepine may lead to reduced gepant serum levels and loss of efficacy and inhibitors such as ketoconazole and clarithromycin may lead to elevated serum gepant levels [11].

The emergence of these agents in both the acute and preventive treatment of migraine gives us the first targeted oral treatment to use in clinical practice since the development of the triptans in the 1990s. The prospect of these treatments being efficacious, working in the presence of other CGRP-targeted therapies, not interacting with the triptans and not being affected by other migraine prevention, as well as the suggestion that they may not be troublesome in the presence of cardiovascular risk and may not cause medication overuse, provides another novel and exciting treatment opportunity to offer our patients.

## 2.2 Memantine (NMDA Receptor Antagonist): Preventive Treatment

Memantine has recently emerged as a possible preventive option for migraine in the clinic. Classically used in Alzheimer's dementia, it is an NMDA receptor antagonist, therefore inhibiting glutamate, and in Alzheimer's it exerts a neuroprotective and potentially symptomatic action [94]. Glutamate has been hypothesised as having a role in migraine in both animal models of migraine and human migraine [95]. Three randomised, placebo-controlled trials of memantine in migraine prevention have yielded conflicting results [96–98]. A meta-analysis of four studies (one being in chronic tension-type headache) suggested efficacy in reducing headache days, pain intensity and migraine-related disability, though there was no significant effect on medication days and nausea and vomiting [99]. The drug was well tolerated without significant adverse events.

We offer this drug to patients who may have failed other more historically used migraine preventives. It may be particularly useful in those in whom adverse effects with other drugs may have been problematic, given the favourable side effect profile, as well as in the elderly where some of the other migraine preventives can be contraindicated due to other comorbidities or less well tolerated due to adverse effects.

## 2.3 Melatonin: Preventive Treatment

Melatonin is an endogenous hormone responsible for the regulation of the sleep–wake cycle and other circadian rhythms [100], and it is pharmaceutically available for the treatment of insomnia. Given the relationship between migraine and sleep [101], and the postulated role of the hypothalamus in migraine [102], melatonin has been suggested to have



**Table 3** Summary of the findings of the phase trials of rimegepant in the acute and preventive treatment of migraine, and the salient findings

Study	Study type	Design	Efficacy of drug	Efficacy of placebo	Adverse events	Other findings
Marcus et al. (2014) [77]	Randomised phase IIb	Single attack	75 mg 31.4% 150 mg 32.9% 300 mg 29.7% PF2h	15.3% PF2h 100 mg sumatriptan 35% PF2h	Nausea and overall adverse event rate comparable to placebo	Sustained pain freedom from 2 to 24 h for all doses relative to placebo
Lipton et al. (2019) [75]	Randomised double-blind phase III	Single attack	75 mg 19.6% PF2h 37.6% MBS free at 2 hours	12% PF2h 25.2% MBS free at 2 hours	Nausea and urinary tract infection	Liver toxicity did not seem to be a concern
Croop et al. (2019) [74]	Randomised double-blind phase III	Single attack	75 mg 21% PF2h 35% MBS free at 2 hours	11% PF2h 27% MBS free at 2 hours		
Croop et al. (2021) [78]	Randomised double-blind phase II/III	Every other day for 12 weeks	75 mg -4.3 MMD reduction	-3.5 MMD reduction	Nausea, nasopharyngitis, urinary tract infection, upper respiratory tract infection	
Johnston et al. (2022) [85]	Post-hoc analysis of open-label safety study	As needed dosing up to OD for 52 weeks	75 mg -2 MMD reduction with 2-14 doses/month	NA	NA	Improved quality of life outcomes, no clear impact of frequency of dosing on medication overuse headache

MBS most bothersome symptom, MMD mean monthly migraine days, OD once daily, PF2h pain freedom at × hours

a therapeutic role in migraine for several years. Its anti-nociceptive role has been suggested as occurring through a variety of receptor systems, including the  $\mu$  opioid and GABA-B receptors [103], as well as the possibility that it exerts a therapeutic effect on anxiety and sleep, causing a secondary impact on pain perception. Only recently have meta-analyses supported its use in migraine [104, 105] after years of conflicting clinical trial data, perhaps due in some part to the use of different formulations in adults [106–109]. Interestingly, there is randomised controlled data for the use of melatonin in children for migraine prevention [108, 110, 111], and a suggestion of an acute effect [112], although it is difficult to know if this is a true drug effect or the result of sleep induction, given the efficacy in the acute study was better after a nap following the dose [112].

We offer this drug for migraine prevention in both our adult and paediatric clinics. Its beneficial effect on sleep alone is helpful for some patients, and the favourable side effect profile and lack of drug interactions make it attractive compared with some of the more commonly used migraine preventives, especially in children.

### 3 Therapeutic Targets with Future Potential, but not Under Current Investigation

#### 3.1 Orexins: Preventive Treatment—The ‘Rexants’

Orexins, or hypocretins, are hypothalamic transmitters located in neurons known to be depleted in narcolepsy, and implicated in various homeostatic functions such as sleep–wake and temperature regulation [113]. There is a complex relationship between migraine and sleep [114], and narcolepsy is two to four times more common amongst migraineurs, compared with the general population [115]. A dual role for the orexins was demonstrated in a rodent model of trigeminal nociception, with reduced neuronal firing in the trigeminal nucleus caudalis (TNC) following dural stimulation after injection of orexin A into the posterior hypothalamus, whereas it was increased with orexin B [116]. Administration of an orexin A antagonist could revert the effect of orexin A [117]. An intravenous dual orexin receptor antagonist, suvorexant, in a rodent model could reduce trigeminocervical complex (TCC) neuronal activity, middle meningeal artery (MMA) dilatation and cortical spreading depression (CSD) thresholds [118]. In humans, cerebrospinal fluid (CSF) levels of orexin A are higher in chronic migraine compared with healthy controls, and in those with medication overuse [119].

Unfortunately, a dual orexin receptor antagonist, florexant, administered once daily failed a human clinical trial for headache prevention [120]. Further receptor sub-type

**Table 4** Summary of the findings of the phase III and sub-studies trials of atogepant in the preventive treatment of migraine, and the salient findings

Study	Study type	Design	Efficacy of drug	Efficacy of placebo	Adverse events	Other findings
Goadsby et al. (2020) [86]	Randomised double-blind phase IIb/III	Varying OD or BD dosing for 12 weeks	10 mg –4 MMD reduction 30 mg –3.8 MMD reduction 60 mg –3.6 MMD reduction 30 mg BD –4.2 MMD reduction 60 mg BD –4.1 MMD reduction	–2.9 MMD reduction	Nausea and fatigue	
Ailani et al. (2021) [87] (ADVANCE)	Randomised double-blind phase III	Varying OD dosing for 12 weeks	10 mg –3.7 MMD reduction 30 mg –3.9 MMD reduction 60 mg –4.2 MMD reduction	–2.5 MMD reduction	Constipation and nausea	
Schwedt et al. (2022) [88]	Post-hoc analysis of [87]	Varying OD dosing for 12 weeks				Efficacy as early as first full day of treatment and sustained monthly across 3 months
Boinpally et al. (2022) [89]	Open-label randomised crossover	Atogepant, sumatriptan or both				No significant pharmacokinetic interactions of clinical relevance between oral sumatriptan and atogepant
Pozo-Roisch et al. (2022) [90]	Randomised double-blind phase III (PROGRESS)	Two doses for 12 weeks	30 mg BD –7.5 MMD reduction 60 mg QDS –6.9 MMD reduction	–5.1 MMD reduction	Constipation and nausea	≥ 41% of those treated with atogepant had ≥ 50% reduction in the 3-month MMD compared with 26% in the placebo group. Secondary endpoints of changes in quality of life, acute medication use, performance in daily activities and physical impairment all met with significance for both atogepant doses

BD twice daily, MMD mean monthly migraine days, OD once daily, QDS four times daily

selective agents may be a useful migraine therapeutic strategy going forwards.

### **3.2 Metabotropic Glutamate Receptor 5 (mGluR5): Acute and Preventive Treatment**

mGluR5 is one of the type 1 metabotropic glutamate receptors, mostly located postsynaptically and acting in stimulatory pro-nociceptive roles. mGluR5 receptors are located at various sites within the trigeminovascular nociceptive system [121, 122], and may contribute to central sensitisation through regulation of synaptic plasticity in a rodent model [123]. Given the proposed role of glutamate in migraine biology [95], this receptor has become a therapeutic target of interest in migraine.

In a rodent model, a selective negative allosteric mGluR5 modulator (ADX10059, raseglurant), was able to reduce dural vasodilatation and TCC firing in response to meningeal and dural stimulation, respectively. In the same paper, a human study in the acute treatment of migraine found raseglurant to be superior to placebo in 2-h pain freedom [122]. Unfortunately, the drug showed hepatotoxicity in a phase IIb clinical trial in headache prevention, leading to early termination (NCT00820105). Other modulators in this class do not seem to have the same liver effect and hold potential for future investigation [124]. Perhaps the liver toxicity issue can be avoided with other agents whilst keeping the efficacy, as has been demonstrated with the later generation gepants targeting the CGRP pathway.

### **3.3 Neuronal Nitric Oxide Synthase (nNOS) Inhibition: Acute Treatment**

Preclinical data suggests that nNOS inhibition may reduce CGRP and neurogenic vasodilatation [125, 126], as well as allodynia in a rodent model of trigeminovascular central sensitisation [127].

Whilst there have been no clinical trials of a selective nNOS inhibitor in migraine, a combination of an nNOS inhibitor and a triptan seemed to be able to reduce CGRP release in preclinical migraine models [126], but this did not translate to a useful effect in a phase II clinical trial in humans [128].

### **3.4 Acid Sensing Ion Channel 1a/3 (ASIC1a/3): Acute Treatment—The ‘Mambalgins’**

Acid sensing ion channels (ASICs) are widely expressed throughout the central nervous system and have been implicated in several neurological diseases, including migraine [129]. No specific ASIC1a or ASIC3 antagonists exist for trial in humans (it is felt that these receptor subtypes are the most likely involved in migraine biology), and an available

drug, amiloride, non-selectively blocks all the ASIC receptors. A small human study suggested an effect of amiloride in the treatment of migraine aura [130].

Future availability of targeted receptor subtype antagonists may hold future promise for migraine management.

### **3.5 Amylin: Acute and Preventive Treatment**

Amylin, like CGRP, belongs to the family of calcitonin peptides, both sharing the receptor activity modifying protein 1 (RAMP1) within their receptor structure [131], and both are thought to exist in the trigeminal ganglion and surrounding vasculature, although amylin to a much lesser degree than CGRP [132, 133]. Amylin and CGRP may have roles in feeding and satiety regulation, as well as nociception [134], and amylin is believed to be involved in blood glucose regulation. Both CGRP and amylin can cause vasodilatation that is reversed with a CGRP antagonist [132]. In humans, interictal blood levels of amylin are higher in chronic migraine compared with episodic migraine and healthy controls and are better at distinguishing chronic migraine from episodic migraine compared with CGRP [135].

An analogue of amylin, pramlintide, is used clinically for diabetes mellitus for its hypoglycaemic effect [136], and intravenous infusion can provoke migraine [137]. Blocking amylin may therefore have theoretical untoward effects including hyperglycaemia and hypertension, but this may be a concept that warrants further investigation in migraine treatment going forwards.

### **3.6 Cannabinoids: Acute Treatment**

There are cannabinoid receptors within the nervous system, and these are known to interact with the pathways involved in central pain modulation at various brain sites, including regulating noradrenergic and serotonergic neuronal activity in the locus coeruleus and dorsal raphe nucleus, respectively [138]. Multiple molecules related to the endocannabinoid system have emerged as potential therapeutic targets for migraine [139]. The complexities of these pathways and their interactions, particularly with the opioid pathway [140], make the ascertaining of a useful response to migraine difficult to clarify, despite the known analgesic effect of cannabinoids in chronic pain conditions [141]. There is some evidence that use of peripherally restricted cannabinoids, that is, those that do not enter the central nervous system, hence do not have central adverse effects, or contribute to medication overuse, may still be useful in treating allodynia as a surrogate of central sensitisation in a mouse model [142]. The increasing availability of over-the-counter synthetic cannabinoids is leading to increased numbers of patients using these agents for headache control or asking about them. Whilst there is currently no evidence

to support their use, cautious trials using compounds formulated through biochemical and pharmacological studies may in the future help shed light on whether these are agents that may be useful for migraine management.

### 3.7 Non- $\mu$ -Opioid Receptors: Acute and Preventive Treatment

Whilst the use of opioids in migraine has been historically avoided by headache physicians (although they continue to be used widely by emergency and acute medicine physicians) because of the side effect profile, risk of dependence and tolerance and the risks of medication overuse, preclinical studies suggest that targeting non- $\mu$  receptors ( $\mu$  receptors are targeted by commonly used opioid analgesics such as morphine and oxycodone) may be an effective alternative approach [143]; the two proposed targets being the  $\delta$  [144, 145] and  $\kappa$  opioid receptors [146].  $\delta$  Agonists have good preclinical evidence in migraine for chronic rather than acute use, and also have evidence in models of MOH and post-traumatic headache, and there is suggestion that they can reduce rather than drive central sensitisation [145, 147]. There has also been a demonstrated effect on CSD [148]. Pharmacological  $\delta$  agonist compounds have been developed and a clinical trial has been published in anxiety and depression, but there have been no published efficacy trials in migraine as yet [149]. Peripherally restricted  $\kappa$  agonists, similarly to the peripherally restricted compounds preclinically in the cannabinoid studies (as a means of avoiding central side effects and medication overuse), have been developed and used in other pain conditions in studies [150], but to date none have been conducted in migraine.

Investigating these receptors further in migraine may yield interesting results in the future, which could impact migraine treatment.

## 4 The Future of Migraine Therapeutics

We are currently witnessing a unique and exciting time in migraine therapeutics, where we are directly observing the bench to bedside translation of years of basic science, animal model research and human experimental medicine into our clinical practice, with the emergence of novel targeted acute and preventive migraine treatments. For the first time, we are able to offer our patients options of specific acute and preventive treatments tailored to their condition, which are efficacious and well tolerated. The understanding of concepts such as vasoconstriction not being necessary for therapeutic effect, the central mechanisms of medication overuse and sensitisation and how to avoid drug central effects that may drive this, as well as the quantum between acute and

preventive migraine treatment, are paving the way for further innovative research in this area.

The future needs to involve the development of acute treatments that do not cause medication overuse nor vasoconstriction and are safe with long-term use, with sustained response with time. The ability to use different agents, such as a triptan and a gepant, and a gepant and a monoclonal antibody, together safely are important concepts that will increase treatment options for patients. Some patients develop a plateau or weaning of response to currently used oral migraine preventives, and there is a need to address this with novel therapies, if possible, to avoid periods of treatment failure, switching treatments and patient and physician dissatisfaction. Ideally, acute and preventive strategies should be migraine-specific, but increasing understanding of migraine neurobiology may continue to produce ideas of how other non-specific drugs used for other conditions may provide benefit in migraine, and these can only increase the treatment options we have for our patients.

Taking advantage of the quantum between acute and preventive treatment is likely to be attractive to patients, where their daily preventive treatment could also have an acute effect on headache. Moreover, an active question in research is perhaps the apogee of treatment during the premonitory phase: the tantalizing concept of eliminating pain altogether may not be Panglossian.

For the foreseeable future, there will be a need for more treatments, particularly for specific underserved groups of patients such as pregnant women, children and adolescents and the elderly. The ongoing trials of oral lasmiditan and rimegepant in children may provide a useful therapeutic avenue for our younger patients in the future. For many patients, migraine affects them for decades during the prime of their working lives, and there is a constant need for therapies that can be used long term without significant drug interactions and with sustained response. Migraine spares no gender, age group or demographic, and the availability of several acute and preventive options, with different modes of administration, is important in tailoring treatment to our individual patients.

## 5 Conclusions

Much has been achieved in migraine therapeutics of late, and translational research and pharmaceutical collaboration has led to a hopeful and promising time for headache physicians and their patients. Well tolerated specific drugs with good long-term safety profiles have proven to be an attractive therapeutic strategy with the now widely used CGRP antibodies. Real-world use of the oral ditans and gepants will reveal whether these drugs follow suit and change the landscape of acute treatment for many sufferers, by providing

an even more logistically simple means of administering such treatments. The once-daily dosing of even preventive doses of the gepants is attractive in terms of feasibility and compliance. Ongoing clinical use of non-migraine-specific available drugs used in other disorders, such as melatonin and memantine, will continue to provide treatment options for some of our patients.

Further understanding of novel therapeutic targets, the interaction of different brain pathways, the mechanisms of central sensitisation, pain chronification and medication overuse and the site of action of emerging treatments will allow further exploration of potential treatment options in the future. The potential for the gepants to avoid medication overuse issues, and the possibility of this also being avoided using peripherally restricted opioid and endocannabinoid drugs, as well as the demonstrated cardiovascular safety profile of the gepants and ditans holds promise for the future of migraine sufferers. Exploration of untargeted drugs that may have a beneficial effect in migraine has been the mainstay of migraine prevention until the development of the CGRP antibodies. Whilst broad effects and therefore limited efficacy and adverse effects can be problematic, understanding the biology of migraine has led to the use of available drugs that are used in other disorders that we are using with effect in clinical practice, such as memantine and melatonin. These continue to offer options for our most disabled patients who may have failed other available therapies. Hopefully, ongoing translational research will continue to produce compounds of therapeutic interest in migraine, for the benefit of sufferers.

Ideally in the future, we can reach a point where we can personalise migraine treatment to the patient in front of us; be that offering a ditan to an elderly patient with a previous stroke for their high frequency episodic migraine or allowing a teenager to use daily atogepant long-term for problematic migraine prevention, or alternatively being able to offer a specific ASIC1a inhibitor to a patient with prolonged severe aura. Whilst an ambitious aim, understanding the biological and treatment-related heterogeneity of migraine and being able to develop models of prediction of treatment response are the most favourable ways forward for patients and their treating clinicians. Each small step in understanding this fascinating disorder takes us closer to this goal, and several of these steps have led to suggestions of promising new therapeutic targets for migraine, such as the ASICs, mGluR5 antagonists and nNOS inhibitors, further research into which is likely to emerge in the future. The migraine future is bright and holds hope for our patients.

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