General

Rimegepant for the treatment of migraine

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Migraine is a common form of primary headache, affecting up to 1 in every 6 Americans. The pathophysiology is an intricate interplay of genetic factors and environmental influence and is still being elucidated in ongoing studies. The trigeminovascular system is now known to have a significant role in the initiation of migraines, including the release of pain mediators such as CGRP and substance P. Traditional treatment of migraine is usually divided into acute and preventive treatment. Acute therapy includes non-specific therapy, such as NSAIDs and other analgesics, which may provide relief in mild to moderate migraines. 5-HT1 agonists may provide relief in severe migraine, but are not universally effective and carry a significant side-effect profile with frequent redosing requirement. Prophylactic therapy may reduce the occurrence of acute migraine attacks in selected patients, but does not completely eliminate it. More recently, CGRP antagonism has been studied and shown to be effective in both abortion and prevention of migraine. Novel medications, targeting CGRP, divide into CGRP antibodies and receptor antagonists (gepants). Rimegepant, a second-generation gepant, has shown efficacy in several clinical trials in treating acute migraine. Ongoing trials are also evaluating its role in migraine prophylaxis, and results are promising. It is also generally safer for use than existing options, does not appear to increase the chance of developing chronic migraines, and carries a very tolerable side effects profile. It is a part of a growing arsenal in migraine treatment, and may present the silver bullet for treatment of this disease.

INTRODUCTION

Migraines present as 4-72 hours of unilateral, throbbing head pain with accompanying symptoms such as aversion to light, sound, or other generally non-noxious stimuli along with potential nausea and vomiting.[1,2] Migraines can be classified into two types: episodic migraines (EM) with or without aura and chronic migraines (CM). EMs occur on less than 15 days per month, while CMs occur on more than 15 days per month for at least three months. Over time, a small percentage of patients develop increasingly frequent migraines that represent a "transformation" from the EM subtype to the CM subtype. While this percentage of patients is small, individuals with CMs typically represent 1-2% of the general population and experience significantly increased disability and reduced quality of life.[3] Aura can be described as short and reversible visual, sensory, speech/language, motor, brainstem, or retinal symptoms that occur along with migraine in up to 30% of patients.[4] In the United States, the burden of migraine is enormous. In certain populations, up to 21% of individuals report experiencing migraines, with women aged 15-49 most severely affected.[5] This ultimately leads to billions of dollars in both direct and indirect costs, missed work days and reduced productivity.[6,7] Although migraines have been treated largely by primary care providers for decades, recent advances have led to rapid improvements in the treatment of migraines. Calcitonin-gene related peptide (CGRP), a neurotransmitter that is released in large quantities during migraines, is one such target that has been shown to be protective against migraines when blocked or antagonized.[8–10] Rimegepant, a CGRP antagonist, received FDA approval in February 2020.[11] Here we review the background and evidence regarding its use for migraine treatment.

MIGRAINES

Headache can be defined as any pain occurring in the head region and has an extremely high lifelong prevalence at 96% with a cost burden of up to $20 billion in the US and €27 billion in Europe.[12–15] Though there are numerous subsets of headache, in 2013, the third edition of the International

Classification of Headache Disorders (ICHD-3) was released.[16] This system classifies headaches as primary or having no underlying cause, or secondary due to an identifiable etiology such as trauma, infection, or tumors. Within the primary classification, migraine headaches remain one of the most common subtypes accounting for up to 10% of headaches.[15] As previously described, the ICHD-3 classifies migraines as being of the EM subtype with or without aura, and the CM subtype that occurs on 15 or more days a month for at least 3 months.

EPIDEMIOLOGY OF MIGRAINES

Migraine is an extremely common condition that has been shown to affect 1 in 6 Americans, with studies demonstrating migraines in up to 20.7% of women and 9.7% of men.[6,17] According to data from the 2015 Global Burden of Disease (GBD) study, it was also found to be the third-highest cause of disability worldwide in men and women under 50 years old, with the highest predilection for women 15–49 years old.[5] One large study of 120,000 US households demonstrated that 17.4% of women and 5.7% of men experience EMs, while 1.29% of women and 0.48% of men experience CMs, which typically begin with EM slowly transforming into CM over time.[12] Unfortunately, those with CM experience significantly higher rates of disability and lower incomes than those with EM.[18] Ultimately, migraines result in a massive economic cost to the US in both direct and indirect costs. Unadjusted total expenditures result in a burden of $56.31 billion per year, with an adjusted expenditure of $9.20 billion per year. On an individual level, the average annual burden for those with migraines is $8,033 per affected person resulting in systemic and individual financial strain.[7]

PATHOPHYSIOLOGY OF MIGRAINES

It is now well understood that migraines are generated via complex interactions between genes, environmental factors, and multiple brain regions, including the trigeminovascular system, brainstem nuclei, hypothalamus, cortex, and others.[19,20] As described by Charles et al., there are more than 38 gene polymorphisms that have been associated with migraines.[21] One of the most widely implicated brain regions is the trigeminovascular system, which consists of the trigeminal nerve as well as its peripheral axons and their targets. These axons project to the dura mater, leptomeninges, and cerebral vasculature and release vasoactive neurotransmitters that have been implicated in migraines such as CGRP and substance P.[22,23] When administered, CGRP has been shown to cause mast cell degranulation and cerebral vasculature vasodilation leading directly to the development of migraine.[24–26] Another commonly implicated brain region in migraines is the hypothalamus, which has been connected to the premonitory phase of migraines, which tends to occur several hours before the attack. This finding has been corroborated on radiologic imaging and is potentially responsible for typical premonitory symptoms such as irritability, sensitivity to light, and/or discomfort that proceed migraines.[8,27–29] Finally, evidence has demonstrated that brainstem nuclei also play a role in migraine pathophysiology with one study showing that sumatriptan decreased blood flow to numerous cortex areas but failed to decrease flow to brainstem regions leading to persistent migraine symptomology.[8,20] Even though these cortical and subcortical structures are current targets for treatment and research, it should be noted that migraines are complex, network disorders with multiple etiologies, and pain generators.[30]

RISK FACTORS FOR MIGRAINES

Risk factors for the development of EM and the slow transformation of EM into CM often overlap in the literature. One longitudinal study of 5,323 individuals found that a family history of migraines (p=0.016) and a history of depression (p=0.01) were statistically significant risk factors for migraine.[31] Others have described that pregnancy, barometric pressure, drugs, and other environmental factors such as diet determine migraine risk.[21] Several other studies have delineated risk factors for the transformation of EM into CM, which includes medication overuse, obesity, caffeine overuse, stress, snoring, female sex, cutaneous allodynia, sleep disorders, psychiatric disorders, and lower socioeconomic status among others.[12,15,32–36] Further, one systematic review investigated factors thought to precipitate migraine attacks. Stress was found to be the most common precipitating event occurring in up to 58% of migraineurs followed by auditory triggers, fatigue, fasting, hormonal changes in females, sleep disturbance, weather changes, visual and olfactory changes, and alcohol consumption.[37,38]

DIAGNOSIS AND CLINICAL PRESENTATION

The diagnosis of migraines requires a detailed physical examination and thorough history as studies have found that MRI and radiologic imaging techniques are not capable of diagnosing the condition.[15,39,40] Generally, migraines present in four stages, including the premonitory phase that occurs several hours before the attack, the aura phase, the headache phase, and the postdrome or recovery phase.[41,42] However, not all individuals go through the sequential experience, and stages may overlap. As previously described, the premonitory phase typically presents with tiredness, mood changes, discomfort, and even changes in urine output, while aura presents as a short, reversible central nervous system deficit.[2,16] The postdrome phase can last up to 1-2 days after the attack and can cause discomfort, difficulty concentrating, sleep disturbances, weakness, gastrointestinal symptoms, and even disability; a postdrome has been demonstrated in 68% of migraine patients.[42–44]

Clinicians will often refer to a symptom diary that may also list triggers, such as alcohol use, as well as successful and failed headache treatmens. In order to address migraines and avoid medication overuse that leads to further migraine burden, physicians must take precise histories to determine the frequency and stages of migraine that their patient experience.

TRADITIONAL MIGRAINE TREATMENT

Migraine treatment has traditionally been separated into acute therapy, aimed at aborting migraine attacks, and preventive therapy, aimed at reducing both migraine attack frequency and severity.[36,45] Although migraine treatment has been designated as either abortive or preventive; some novel therapies, such as CGRP antagonists, have shown efficacy as both acute and preventive agents, and will be discussed at the end of this section.[46,47]

ACUTE MIGRAINE THERAPY

Acute (abortive) migraine therapy aims to provide prompt relief from a migraine attack with little to no side effects, thereby returning the patient's ability to function. These agents are started at a low dose and titrated slowly up to a therapeutic dose and administered as early as possible within a migraine episode in order to maximize drug efficacy.[21,48]

NON-SPECIFIC DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are among the most commonly used pharmacologic options for acute migraine therapy, with up to forty-nine percent of patients with acute migraine using only OTC medications, and twenty-nine percent using non-specific drugs in conjunction with prescription medication.[36] NSAIDs have consistently shown good efficacy for mild to moderate migraine attacks, and remain the first-line drugs of choice.[36,49] Analgesics such as acetaminophen are not indicated for moderate to severe migraine episodes but are effective in the treatment of mild migraine attacks. Barbituates, often combines with acetaminophen, codeine and caffeine, may serve as a second, non-specific line of treatment.[36]

5HT AGONISTS

Triptans are a class of 5-HT1 agonists that were historically developed for the treatment of symptomatic migraine and have been associated with increased headache relief at 24-hours and long-term freedom from pain.[49–52] This class has also shown comparatively higher efficacy than ergots, equal or better outcomes than aspirin (ASA), acetaminophen, and NSAIDs, and equal or slightly lower efficacy than combination therapy, such as sumatriptan with naproxen.[53] Newer formulations and delivery systems, such as DFN-02 (sumatriptan 10mg with a permeation enhancer), AVP-825, and iontophoretic transdermal delivery, have shown promising efficacy as well.[54–57]

Ditans are selective 5-HT1F agonists that have also shown good efficacy as agents in acute migraine.[36,58] These drugs differ from triptans in that they are able to penetrate the blood-brain barrier (BBB), and that their target is not expressed on vasculature; thus, ditans act without cardiovascular or cerebrovascular effects, making them useful in patients with existing cardiovascular risk factors; though some recent evidence suggests that sumatriptan can cross the BBB, albeit to an unknown clinical significance.[19,36,58–61]

SPHENOPALATINE GANGLION BLOCK

Certain patients experience acute migraine attacks known as status migrainosus, which is defined as a debilitating migraine attack lasting over 72 hours and fail to respond to standard abortive therapy.

Regional sphenopalatine ganglion blocks have been shown to provide immediate relief of status migrainosus with minimal side effects.[62]

TIMING, LIMITATIONS, CONTRA-INDICATIONS FOR ACUTE THERAPY

Studies estimate up to ninety-eight percent of migraine patients using pharmacological intervention for acute migraine therapy.[63] However, medication overuse in acute migraine treatment is believed to be a causative factor in progression from episodic migraine to chronic migraine; thus, patients must be discouraged from drug overuse.[48] Studies have established barbiturate and opiate use with the risk of developing chronic migraines, as well as mixed results regarding the relative risk of triptans.[17,64] Interestingly, NSAIDs were shown to be protective against chronic migraine progression in patients with low monthly headache days, but were a risk factor in patients with high levels of monthly headache days.[17,64]

Triptans have been associated with the risk of general adverse events, such as somnolence, fatigue, and chest discomfort.[52,65] Additionally, triptans have been associated with severe adverse cardiovascular events and are contraindicated in patients with cardiovascular risk factors. The incidence of these events is unclear, and some studies show it may be lower than previously believed.[51,60,66,67]

Non-triptan abortive therapy is generally well tolerated, although acetaminophen has also been shown to be correlated with increased risk of general adverse events.[65] Combination therapy, such as sumatriptan with naproxen, increases the risk of adverse events, such as gastrointestinal discomfort or bleeding.[53,65]

Ditans have been commonly associated with dizziness in up to 38% of patients.[36] As 5-HT1F receptors are not expressed on vascular tissue, ditans have improved cardiovascular safety compared to triptans.[59,67] Ditans such as lasmiditan are able to penetrate the blood-brain barrier, and central side effects mediated by 5-HT1F receptor activation are not currently well understood.[59]

ADHERENCE ISSUES WITH ACUTE AND CHRONIC PREVENTATIVE THERAPY

Unfortunately, many existing migraine pharmacologic options provide different levels of efficacy and tolerability, often resulting in poor patient compliance; up to one in five patients discontinue treatment due to adverse effects, and over three out of four patients with chronic migraine choose to discontinue treatment within one year of commencement.[68] Providers must establish appropriate therapeutic expectations with patients in order to maximize treatment adherence and efficacy.[48]

PREVENTIVE MIGRAINE THERAPY

Preventive migraine therapy aims to reduce both the frequency and intensity of acute migraine attacks, and are indicated in over one-third of episodic migraine patients, especially in those who do not respond well to acute migraine therapy.[19] Preventative treatment does not aim to completely prevent migraine episodes, as up to two-thirds of patients can be expected to experience a 50% reduction in migraine frequency.[36] Therefore, preventive therapy is designed for use in conjunction with abortive therapy.

ONABOTULINUMTOXIN A (OBT-A) INJECTION THERAPY

OBT-A injections were first approved for preventive migraine therapy in 2010 and have been shown to be effective in reducing the overall number of migraine days per month.[69–71] The therapy acts by inhibiting peripheral pain neurotransmitter release, thereby reducing central neuron sensitization and over-activity associated with chronic pain.[69,72,73] OBT-A injections are particularly effective in patients with pericranial muscle tenderness, as well as those suffering medication-overuse headache.[69,72,73] OBT-A injections possess a long duration of action (3 months), as shown in the PREEMPT study, making it an attractive alternative for patients who are not compliant with daily medications.[71] Side effects are mild and most common being injection site pain and neck pain.[60,72] Of note, OBT-A has not been shown to be effective in abortive migraine treatment.[60,74]

TOPIRAMATE

Topiramate is an antiepileptic medication with a complex mechanism of action that has shown effectiveness in treating both episodic and chronic migraine.[69,75] Topiramate functions by increasing neural thresholds via both blocking voltage-gated Ca^{2+} channels and enhancing GABA-mediated inhibition.[76,77] It is associated with minor side effects such as weight loss, paresthesia, fatigue, and nausea, though increased doses may be associated with more significant cognitive decline.[75]

CALCITONIN GENE-RELATED PEPTIDE (CGRP) MODULATION

Recent studies have shown CGRP's importance in migraine pathophysiology, which has resulted in the development of numerous CGRP-related therapies.[76,78,79] Thus far, two main classes of CGRP modulators have been developed: CGRP receptor antagonists (gepants) and CGRP monoclonal antibodies. Both gepants and CGRP monoclonal antibodies are believed to target peripheral CGRP receptors.[59,80] First-generation gepants showed high efficacy in treating acute migraine attacks, although formulation challenges and off-target hepatotoxicity hindered clinical use.[46,58,59,69,81,82] Second generation gepants show similar efficacy in abortive migraine treatment, as well as improved safety profiles.[9,59,67,68]

Existing CGRP monoclonal antibodies have demonstrated excellent abortive and preventive efficacy profiles, with up to 32% of patients experiencing complete migraine relief after therapy.[78,83–85] Monoclonal antibodies have not been associated with emergent safety concerns, hepatotoxicity, or cardiotoxicity, despite CGRP's role as a vasodilator.[59,78,83,86–88] Interestingly, CGRP monoclonal antibodies have been linked to exacerbation of Raynaud's phenomenon.[89] These agents have long half-lives and do not seem to carry any risk of medication overuse, thus showing promising efficacy for the treatment of both abortive and preventive migraine therapies.[46,58,79,81,82,84,85,87,90]

RIMEGEPANT

Rimegepant (Nurtec™ ODT) is a second-generation gepant that was first introduced in 2012 and developed by Biohaven Pharmaceutical for abortive migraine therapy, with or without aura.[91,92] A 75mg once-daily dose in orally disintegrating tablet (ODT) formulation was approved by the FDA in February 2020, with a maximum dose of 75mg per 24 hours.[86,91–95] A 75mg conventional tablet formulation is currently also being reviewed for migraine prevention and refractory trigeminal neuralgia.[91]

The ODT formulation is ingested by placement under the patient's tongue and will dissolve in saliva, allowing for ingestion without additional fluid, making administration comfortable even during a severe migraine attack.[91]

MECHANISM OF ACTION

Although migraine has a complex pathophysiology that is not completely understood, CGRP and its role in migraine has been extensively studied.[96] CGRP is a 37-amino acid neuromodulating vasodilator that was first discovered in the trigeminovascular system in 1985.[97] CGRP is produced in both peripheral and central neurons and is released during severe migraine episodes.[47,58,82,86,87,98–101] CGRP receptors are located in neuronal sites involved in migraine pathophysiology, including the cortex, thalamic nuclei, amygdalostriate area, the nucleus of the solitarius tract, vagus nerve, trigeminal nerve, and dorsal root ganglia.[102]

Notably, CGRP is abundantly released in trigeminal nerve unmyelinated C fibers and A-delta fibers.[58,60,79,81,94,97,103–105] CGRP infusion also precipitates migraine attacks in migraine patients.[102,106] Additionally, increased levels of CGRP outside of acute migraine attacks are a potential biomarker of chronic migraine.[99] CGRP has also been associated with somatic pain and may play a neuromodulatory role in general non-migraine pain.[97]

CGRP receptor activation results in cortical spreading depression (CSD) via increasing levels of cyclic AMP (cAMP), protein kinase A (PKA), and phosphorylation of the glutamate N-methyl-D-aspartate (NMDA) receptor.[102] In the meninges, CGRP receptor activation causes potent vasodilation within vascular beds via direct activation of smooth muscle cells and mast cells, resulting in inflammation and peripheral sensitization of nociceptive neurons.[81,86,98,107]

The pro-migraine effects of CGRP receptors can be blocked by CGRP receptor blockade.[102,108] Rimegepant is a second-generation gepant with potent, selective, competitive human CGRP receptor antagonistic properties, thus attenuating neurogenic inflammation.[47,58,94,103,109] Rimegepant primarily acts in the peripheral nervous system and has shown a significantly higher affinity to peripheral CGRP receptors than central receptors.[110] Rimegepant is thus able to antagonistically bind CGRP receptors located on the trigeminovascular system, which is localized outside of the blood-brain barrier.[111,112]

PHARMACOLOGY

The ODT formulation of rimegepant is ingested sublingually with a bioavailability of 0.64 and tmax of 1.5 hours, although this is delayed when taken with food.[67,93,103,113] The impact of food on efficacy of rimegepant is not well understood.[91] The ODT formulation was absorbed significantly faster than standard tablet formulation.[91] The volume of distribution was measured to be 120 L, with a plasma protein binding of 96%.[93] Rimegepant is metabolized by CYP3A4 and CYP2C9 and is largely excreted unchanged in the feces (78%) and urine (24%) without significant metabolite generation.[91,93] Rimegepant has a half-life of 11 hours in healthy patients.[91,93]

The pharmacokinetic properties of rimegepant were not influenced by patient age, sex, race, weight, or CYP2C9 genotype.[91] Pharmacokinetic properties were also not influenced by mild or moderate kidney and liver disease, although ODT rimegepant has not been studied in patients with end-stage renal disease (ESRD) or patients on dialysis, and is contraindicated in these patients.[91] ODT rimegepant exposure in patients with severe liver disease was significantly higher, and thus rimegepant is also contraindicated in these patients.[91]

Since rimegepant is metabolized mainly through CYP3A4 and CYP2C9, concurrent administration with CYP450 inducers and inhibitors result in altered levels of rimegepant efficacy and risk, and is therefore contraindicated.[91] Rimegepant is also a weak OAT1B1 and OAT3 inhibitor, although no clinical consequences are expected at recommended dosage levels.[91]

CLINICAL EVIDENCE FOR THE USE OF RIMEGEPANT IN MIGRAINE

Overexpression of CGRP receptors is central to migraine pathogenesis. Recently, rimegepant, a CGRP receptor antagonist, has shown promise as potential acute treatment for migraines. The relative success of CGRP-related antibodies in treating migraines has sparked the additional interest in CGRP receptor antagonists as potential treatments.[114] Overall, rimegepant has demonstrated efficacy and safety in alleviating migraine pain and patients' most bothersome migraine-associated symptoms with minimal adverse effects.

The Phase IIb: Double-Blind, Randomized, Placebo-Controlled, Dose-ranging Trial of BMS-927711 for the Acute Treatment of Migraine sought to identify the effective and safe dose of BMS-927711 (rimegepant), a CGRP receptor antagonist for migraine treatment. Of the 1,026 patients enrolled in the study, 885 (86.3%) were randomized to the following treatment groups: placebo (n=210), sumatriptan 100mg (n=100), or different doses of rimegepant, including 10 mg (n=72), 25 mg (n=62), 75 mg (n=86), 150 mg (n=86), 300 mg (n=112), 600 mg (n=84). Notably, this study included comparison groups of both sumatriptan 100 mg and placebo, making it an important comparative trial. The total study duration was approximately 11 weeks. Patients included in this study were males and females between 18 and 65 years old with at least a one-year history of migraines. The main outcome of interest was pain freedom from a single migraine occurrence two hours following medication dose. It was found that patients taking 75, 150, and 300mg of rimegepant had superior pain alleviation without significant adverse effects compared to placebo. Additional freedom from photophobia and phonophobia was noted with rimegepant and sumatriptan versus placebo. On the other hand, only rimegepant 75mg and 300mg gave an increased percentage of patients relief from nausea compared with placebo, and this effect was not found with sumatriptan compared with placebo.[115] It was also noted that the therapeutic gain (TG), or symptomatic improvement with the drug minus symptomatic improvement with a placebo, of other CGRP receptor antagonists, such as olcegepant and telcagepant, was not as large as that of triptans, and therefore suggests the limited efficacy of CGRP receptor antagonists relative to the current standard of care, triptans.[116] Rimegepant did demonstrate these beneficial effects, and thus further research on rimegepant use ensued. With regards to safety, during this trial no deaths or serious adverse events were reported secondary to treatment.[115] There were comparable rates of adverse events, including nausea, dizziness, vomiting, diarrhea, paresthesia, dysgeusia, chest discomfort, and myalgia across all treatment groups. Interestingly, nausea was the most common adverse event in the rimegepant groups which showed dose-dependence: 1.4% in the 10 mg group; 0 in the 25mg group; 3% in the 75mg group; 3% in the 150mg group; 4% in the

300 mg group; and 8% in the 600 mg group. Two patients experienced increased hepatic enzymes, one patient was in the rimegepant 75mg group, and one was in the placebo group. This study provided important knowledge about the effective doses of rimegepant in addition to a comparison with sumatriptan 100mg, a typical abortive migraine treatment. Due in part to the informative results of this study, 75mg rimegepant became the dose most often used in future clinical trials.

The BHV3000-303: Phase III, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (Rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine also investigated the safety and efficacy of rimegepant in the treatment of adult migraines. Patients were randomly assigned to receive either 75mg ODT of rimegepant or placebo to treat a single moderate to severe migraine. Of the total 1,466 patients initially included in the study and assigned to rimegepant (n=732) or placebo (n=734), 1,351 were included in the modified intention-to-treat analysis for drug efficacy (rimegepant n=669, placebo n=682). Though adverse events were rare, the most common side effects observed were nausea (rimegepant n=11; placebo n=3) and urinary tract infection (rimegepant n=10; placebo n=4). Results showed that rimegepant provided increased freedom from pain and freedom from patients' most bothersome symptoms, including photophobia and nausea, within two hours of treatment compared with controls (35% vs. 27%, p=0·0009; risk difference 8, 95% CI 3–13).

Importantly, in this trial, rimegepant was given via ODT, which offers improved drug absorption and bypasses liquid administration, which can otherwise be problematic for patients who experience nausea and vomiting with migraines.[117] Criticism was voiced about the significantly higher rate of women participating(85% of the patients in this study); however, the authors note that this reflects the female-predominance of migraines in the United States.[117–119] This study did not compare rimegepant with an alternative migraine treatment, like sumatriptan, and only used a placebo for control. Critics suggest that a comparison of rimegepant versus the first line abortive treatments, such as antidopaminergics, triptans, and non-steroidal anti-inflammatory drugs, may provide more clinically-relevant evidence to guide treatment decisions.[120] Alternatively, others noted that rimegepant did not increase the risk of adverse events in this phase 3 trial, whereas sumatriptan did increase adverse event risk in previous studies.[121] This argument serves to support the use of placebo rather than other comparative agents. However, most argue that future studies aimed at comparing the safety and efficacy of remigepant versus other treatment agents are warranted.

Similarly, findings from the BHV3000-302: Phase III: Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine of 1,186 participants with a 1-year history of migraines showed consistent results with the study by Croop et al. for treatment of an acute attack.[117] 537 patients were assigned to the 75mg rimegepant group, and 535 were assigned to placebo. Overall, more patients taking rimegepant had freedom from pain and most bothersome symptoms at two-hours post-dose than controls. Again, nausea and urinary tract infection were the most common adverse events.[122] Consistency amongst these two large RCTs strongly points to the clinical utility of rimegepant for migraine treatment.

A 2020 meta-analysis was performed investigating the efficacy and safety of rimegepant for migraine treatment. Pooled data from four RCTs, including 3,827 patients, showed that 75mg rimegepant gave patients significant freedom from pain, pain relief, and freedom from the most bothersome symptom at two hours after medication dose.[123] The most common adverse events associated with rimepegant included nausea, urinary tract infection, dizziness, and increases in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT). While these side effects are undesirable, it was found in a recent study that instances of the aforementioned adverse events occur at comparable rates among patients treated with rimegepant as with placebo.[123]

Tfelt-Hansen and Loder brought into question the clinical significance of the aforementioned RCTs' data supporting CGRP antagonist use for migraines due to concerns about small effect sizes and possible low efficacy.[124] The authors argue that the large sample sizes of some of the clinical trials may have allowed for the achievement of statistical significance even when the outcomes were not clinically meaningful. They note that telcagepant, a different CGRP receptor antagonist, was used in a clinical trial and was effective in the acute treatment of migraines; however, unfortunately, the trial was halted due to associated liver toxicity. Subsequently, rimegepant became the focus of additional clinical trials with hopes of achieving similar efficacy without adverse side effects. The authors criticize that the preliminary therapeutic gain (TG) of telcagepant was much higher than that of rimegepant; this warrants further investigation as it appears that this difference in TG was not due to dosing or absorption differences between medications.[124]

Despite the concerns mentioned, additional case reports of rimegepant use in two female patients treated with rimegepant further support the larger RCT findings demonstrating the clinical success of rimegepant treatment.[124] Rimegepant use caused the successful cessation of migraines for the two patients when used concomitantly with preventative erenumab treatment, an anti-CGRP receptor antibody.[125] The female patients were 44 and 36 years old, each with greater than a 20-year history of migraines without adequate medication relief. One patient used rimegepant for six months for acute treatment then began 70mg erenumab monthly. This patient achieved pain relief for 7 of 7 acute migraines and noted that she was able to eliminate both ibuprofen and caffeinated analgesic use. During treatment, she experienced an adverse event of streptococcal pharyngitis that was determined to be unrelated to rimegepant use, and no adverse events were related to erenumab. The other patient was treated with rimegepant for two months for acute relief and then began

erenumab 140mg monthly. With concomitant erenumab use, she experienced pain relief from 9 of 9 acute migraine attacks and was able to stop nearly all additional use of ketorolac and diphenhydramine. She experienced no adverse events during treatment. The results of these two case reports indicate that rimegepant when combined with erenumab, can help provide relief from migraines with the additional benefit of ceasing the use of additional treatment medications.

More robust literature demonstrating the clinical safety and efficacy of rimegepant is needed, and there are several ongoing studies that may soon help answer these questions. The BHV3000-301: Phase III: Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (Rimegepant) for the Acute Treatment of Migraine of 1,485 participants is investigating rates of pain improvement and relapse rates amongst patients taking rimegepant versus controls throughout a 2- to 24-hour interval after drug dosage. Pain measures are recorded using a 4 point Likert scale. Additional characteristics of migraines, such as photophobia, phonophobia, nausea, and pain-free intervals, will also be assessed.[126] Several other outcomes are being assessed and compared between rimegepant and placebo groups in this trial, including the following: number of subjects that do not experience any headache within 2 to 24 hours post-dose, the requirement for additional rescue medication, sustained freedom from pain, pain relief and relapse rates, and number of participants able to return to normal function two hours after medication dose. Information from this trial can help expand our current knowledge of medication efficacy and direct future treatment guidelines.

A Phase II/III, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention of 1,629 patients is currently assessing changes in migraine occurrences and treatment needs with 75mg rimegepant versus placebo.[127] The primary outcome of interest is a change in migraine frequency, as measured by a change in the mean number of days per month with migraines. Additionally, the investigators will evaluate the following between both treatment groups: achievement of at least 50% reduction in the mean number of monthly migraines, number of days with migraine per month, adverse events, frequency of transaminase elevations and hepatic-related adverse events, changes in Migraine Specific Quality of Life Questionnaire (MSQ) scores, and improvements in Migraine Disability Assessment (MIDAS) score. Knowledge of these outcomes can help strengthen our understanding of the efficacy of rimegepant in the setting of acute migraine treatment.

In addition to its potential as a migraine treatment, studies have been investigating its use in the management of treatment-refractory trigeminal neuralgia. One such trial has been investigating outcomes including pain relief, safety, and tolerability of the medication, and improvements in physical and global functioning.[128] Outcomes from this trial may help expand the utility of rimegepant as a treatment for other conditions, like trigeminal neuralgia.

CONCLUSION

Migraines are prevalent and disabling, affecting 1 in 6 Americans. They are one of the leading causes of disability in young men and women in the Western World and carry a significant price tag. Traditional treatment is effective for mild and moderate disease but falls short in the prevention and treatment of severe attacks and carries a significant adverse effects profile.

Years of research have helped develop a better understanding of the pathophysiology and mechanisms that underlie migraines, with the isolation of key players, such as CGRP and substance P. Targeted therapy concentrating on antagonizing and modulating CGRP, and its receptors has proven to be effective for both treatment and prevention of migraines. Here we reviewed the specific data that is available to support the use of rimegepant, a second-generation gepant that has been recently (February 2020) approved for the treatment of acute migraine in a sublingual ODT formulation.

Rimegepant has undergone a number of double-blind, dose-ranging RCTs, which have shown that rimegepant is generally well-tolerated, with comparable to slightly elevated rates of adverse events compared to placebo.[58,86,90,94,96,103,109] Importantly, unlike first-generation gepants, rimegepant carries no risk of hepatotoxicity.[79,107,129] Serious adverse events in rimegepant patients were exceedingly rare and not statistically significant in comparison to control arms.[91]

Based on the currently existing evidence, rimegepant appears to be an effective and safe acute migraine treatment with few adverse effects. The most common and promising effects include freedom from pain and freedom of most bothersome migraine-related symptoms when used as an acute treatment.

Importantly, Gepants have shown comparable efficacy to triptans in abortive migraine therapy.[130] Therefore, gepants are well-positioned to replace triptans as standard therapy for acute migraine attacks, though cost considerations may curtail their position as first line treatment.

Ongoing and future clinical trials can bolster and expand upon the current knowledge base by providing further information about the specific outcomes that may be achieved with rimegepant use. Though the results of several large clinical trials are pending, rimegepant holds promise as a potential mainstay treatment for acute migraines. Additionally, CGRP modulation does not seem to carry any risk of progression to chronic migraine due to medication overuse and remains a promising agent in the field of migraine abortion and prevention.[83,90]

As with every newly approved medication, it is important to remember that rare side effects, as well as the magnitude of side-effects already known, are more likely to be identified from post-marketing analysis. Importantly, CGRP and its receptor are active in many biological processes, and further studies must be conducted to evaluate long-term therapeutic risk, especially in patients with cardiovascular disease.[60,82]

Table 1. Clinical Efficacy and Safety

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Croop et al. (2019)[117]	1,466 participants aged 18 or older with a history of migraines for at least 1 year were randomly assigned to the 75 mg rimegepant or placebo groups. A total of 682 participants received rimegepant and 693 received placebo. Rimegepant was delivered in the form of an orally disintegrating tablet (ODT).	Rimegepant ODT provided patients with superior freedom from pain (21% vs 11%, p<0.0001; risk difference 10, 95% CI 6-14) and freedom from most bothersome symptom (35% vs 27%, p=0.0009, risk difference 8, 95% CI 3-13) at 2 hours post dose compared with placebo. The following were the most common adverse events: nausea (rimegepant n=11 [2%]; placebo n=3 [<1%]), urinary tract infection (rimegepant n=10 [1%]; placebo n=4 [1%]). In both the rimegepant and placebo groups, one participant in each group had a transaminase level that was more than 3x the upper limit of normal; however neither was found to be related to the medications given in the study.	A single dose of 75 mg rimegepant ODT provided superior symptom control than placebo with similar safety.
Lipton et al. (2019)[122]	1,186 patients with at least a 1 year history of migraines were randomly assigned to receive 75 mg rimegepant or placebo. Overall 537 patients receiving rimegepant and 535 patients receiving placebo were evaluated. The primary outcome was freedom from pain, defined as absence of pain in a person who had previous moderate or severe pain before dose administration. The secondary outcome was freedom from most bothersome associated migraine symptom, including photophobia, phonophobia, or nausea.	A modified intention-to-treat analysis found that 19.6% of patients who received rimegepant were pain- free after 2 hours of the dose versus 12.0% of those who received the placebo (95% CI, 3.3 to 11.9; P<0.001). 37.6% of patients in the rimegepant group were free of their most bothersome symptom 2 hours after the dose and 25.3% of patients in the placebo group (95% CI, 6.9 to 17.9; P<0.001). Nausea and urinary tract infection were the most common adverse effects.	Treatment with rimegepant provided patients with increased freedom from pain and their most bothersome symptom than did placebo.
Gao et al. (2019)[123]	A systematic review of Pubmed, Embase, and Cochrane between January 2001 and August 2019 using keywords “rimegepant; migraine; BMS-927711; BHV-3000” was conducted. A meta-analysis of four RCTs identified in the review was performed including 3,827 patients total, was performed. Each RCT involved randomization of patients to either 75 mg rimegepant or placebo.	Across all four RCTs, 75 mg rimegepant provided significantly greater freedom from pain (P <0.001), pain relief (P <0.001), and freedom from most bothersome symptom (P <0.001) at 2 hours post dose versus placebo. Instances of adverse events were comparable in both groups.	75 mg rimegepant is safe and effective for acute treatment of migraines.
(2022)[128]	Sixty patients diagnosed with treatment- refractory trigeminal neuralgia were randomly assigned to receive 75 mg rimegepant then placebo or vice versa in this crossover study. The outcomes were measured using the Numeric Pain Rating Scale, a four-point likert scale from 0=none to 3=severe. Changes in symptomatic pain relief were measured as a daily rating of their worst pain episode based on an 11 point numeric rating scale.	The outcomes being studied are safety and tolerability of rimegepant, efficacy for improving physical function and global functioning, improving functional disability, and providing symptomatic pain relief based on daily worst episode of pain.	N/A
(2021)[127]	1629 patients with at least a 1 year history of migraine were randomly assigned to receive 75 mg rimegepant or 75 mg matching placebo.	The main outcome of interest is change from baseline in the mean number of days per month in the last four weeks with migraine. Additional outcomes being evaluated include achievement of at least 50% reduction in mean number of monthly moderate to severe migraines and migraine days per month during the treatment phase of the trial. The	N/A

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
		following are also outcomes of interest: change in number of migraine days per month for first month of treatment phase, adverse events, frequency of AST or ALT elevations and hepatic-related adverse events, and mean change in Migraine-Specific Quality of Life Questionnaire (MSQ) role function and Migraine Disability Assessment (MIDAS) total score.	
(2021)[126]	1485 participants with at least 1 year history of migraines were assigned to receive either 75 mg rimegepant or placebo. Outcomes were measured by presence or absence of most bothersome symptom (MBS), a 4 point Likert scale of pain, functional disability score and a 4 point numeric rating scale (none, mild, moderate, severe) for sustained pain relief and/or pain relapse.	Primary outcome measures include pain freedom and freedom from MBS at 2 hours post dose with rimegepant versus placebo. Secondary outcomes assess the following measures in rimegepant versus placebo groups: number of subjects in each group that do not experience any headache pain from 2 to 24 hours post dose, differences in presence of photophobia and phonophobia, pain relief, freedom from nausea, requirement for rescue medication, sustained pain freedom and relief, proportion of patients able to return to normal function at 2 hours post dose, and pain relapse scores.	N/A

Table 2. Comparative Studies

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Marcus et al. (2013)[115]	This dose-ranging study randomized 885 patients to one of the following dose groups: rimegepant, (10, 25, 75, 150, 300, or 600 mg); sumatriptan 100 mg; and placebo. Main outcome was the ability to treat a single migraine attack	Significantly more patients who took rimegepant 75 mg (31.4%, p=0.002), 150 mg (32.9%, p<0.001), and 300 mg (29.7%, p=0.002) and sumatriptan 100 mg (35%, p<0.001) achieved pain freedom 2 hours post dose compared with placebo. Patients who took rimegepant doses 25-600 mg had significantly more patients who had sustained freedom from pain between 2 to 24 hours post dose compared with placebo. No adverse events related to treatments were reported.	rimegepant doses of 75mg, 150 mg, and 300 mg are superior to placebo for acute treatment of migraine, and may provide additional advantage alleviating nausea, phonophobie and photophobia. These treatments are safe and well-tolerated.

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ETHICAL CONSIDERATIONS

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued study exemption # 2022-740.

CONFLICTS OF INTEREST

None of the authors report any conflicts of interest.

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REFERENCES

1. Munjal S, Singh P, Reed ML, et al. Most Bothersome Symptom in Persons With Migraine: Results From the Migraine in America Symptoms and Treatment (MAST) Study. *Headache*. 2020;60(2):416-429. doi:10.1111/head.13708

2. Goadsby PJ. Pathophysiology of migraine. *Ann Indian Acad Neurol*. 2012;15(SUPPL.):15-22.

3. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: A systematic review. *Cephalalgia*. 2010;30(5):599-609. doi:10.1111/j.1468-2982.2009.01941.x

4. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: An epidemiological study. *Cephalalgia*. 1992;12(4):221-228. doi:10.1046/j.1468-2982.1992.1204221.x

5. Steiner TJ, Stovner LJ, Vos T. GBD 2015: migraine is the third cause of disability in under 50s. *J Headache Pain*. 2016;17(1):0-3. doi:10.1186/s10194-016-0699-5

6. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache*. 2018;58(4):496-505. doi:10.1111/head.13281

7. Raval AD, Shah A. National Trends in Direct Health Care Expenditures Among US Adults With Migraine: 2004 to 2013. *J Pain*. 2017;18(1):96-107. doi:10.1016/j.jpain.2016.10.005

8. Bohm PE, Stancampiano FF, Rozen TD. Migraine Headache: Updates and Future Developments. *Mayo Clinic Proceedings*. 2018;93:1648-1653.

9. Tepper SJ. Anti-Calcitonin Gene-Related Peptide (CGRP) Therapies: Update on a Previous Review After the American Headache Society 60th Scientific Meeting, San Francisco, June 2018. *Headache*. 2018;58:276-290. doi:10.1111/head.13417

10. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377(22):2113-2122. doi:10.1056/nejmoa1709038

11. Mullin K, Kudrow D, Croop R, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. *Neurology*. 2020;94(20):e2121-e2125. doi:10.1212/wnl.0000000000008944

12. Schwedt TJ. Chronic migraine. *Br Med J*. 2014;348:g1416.

13. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost Productive Time and Cost Due to Common Pain Conditions in the US Workforce. *J Am Med Assoc*. 2003;290(18):2443-2454. doi:10.1001/jama.290.18.2443

14. Stovner LJ, Andrée C. Impact of headache in Europe: A review for the Eurolight project. *J Headache Pain*. 2008;9(3):139-146. doi:10.1007/s10194-008-0038-6

15. Rizzoli P, Mullally WJ. Headache. *Am J Med*. 2018;131(1):17-24. doi:10.1016/j.amjmed.2017.09.005

16. Olesen J. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.

17. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population- based study. *Headache*. 2008;48(8):1157-1168. doi:10.1111/j.1526-4610.2008.01217.x

18. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry*. 2010;81(4):428-432. doi:10.1136/jnnp.2009.192492

19. Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. *J Neurol*. 2017;264(9):2031-2039. doi:10.1007/s00415-017-8434-y

20. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med*. 1995;1(July):658-660.

21. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol*. 2018;17(2):174-182. doi:10.1016/s1474-4422(17)30435-0

22. Moskowitz MA, Romero J, Reinhard JF Jr, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine? *Lancet*. 1979;314(8148):883-885. doi:10.1016/s0140-6736(79)92692-8

23. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system—40 years and counting. *Lancet Neurol*. 2019;18(8):795-804. doi:10.1016/s1474-4422(19)30185-1

24. Lennerz JK, Rühle V, Ceppa EP, et al. Calcitonin receptor-like receptor (CLR), receptor activity-modifying protein 1 (RAMP1), and calcitonin gene-related peptide (CGRP) immunoreactivity in the rat trigeminovascular system: Differences between peripheral and central CGRP receptor distribution. *J Comp Neurol*. 2008;507(3):1277-1299. doi:10.1002/cne.21607

25. Hansen JM, Ashina M. Calcitonin gene-related peptide and migraine with aura: A systematic review. *Cephalalgia*. 2014;34(9):695-707. doi:10.1177/0333102413520084

26. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia*. 2010;30(10):1179-1186. doi:10.1177/0333102410368444

27. Schulte LH, Jürgens TP, May A. Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? *J Headache Pain*. 2015;16(1):1-5. doi:10.1186/s10194-015-0495-7

28. Schulte LH, May A. The migraine generator revisited: Continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain*. 2016;139(7):1987-1993. doi:10.1093/brain/aww097

29. Charles A. The evolution of a migraine attack - a review of recent evidence. *Headache*. 2013;53(2):413-419. doi:10.1111/head.12026

30. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci*. 2015;35(17):6619-6629. doi:10.1523/jneurosci.0373-15.2015

31. Baykan B, Ertas M, Karlı N, et al. Migraine incidence in 5 years: a population-based prospective longitudinal study in Turkey. *J Headache Pain*. 2015;16(1):1-10. doi:10.1186/s10194-015-0589-2

32. Bigal ME, Lipton RB. Modifiable Risk Factors for Migraine Progression. *Headache*. 2006;46(9):1334-1343. doi:10.1111/j.1526-4610.2006.00577.x

33. Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. *Headache*. 2008;48(1):16-25. doi:10.1111/j.1526-4610.2007.00970.x

34. Scher AI, Stewart WF, Buse D, Krantz DS, Lipton RB. Major life changes before and after the onset of chronic daily headache: A population-based study. *Cephalalgia*. 2008;28(8):868-876. doi:10.1111/j.1468-2982.2008.01634.x

35. Louter MA, Bosker JE, Van Oosterhout WPJ, et al. Cutaneous allodynia as a predictor of migraine chronification. *Brain*. 2013;136(11):3489-3496. doi:10.1093/brain/awt251

36. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. *Springerplus*. 2016;5(1):1-14. doi:10.1186/s40064-016-2211-8

37. Peroutka SJ. What Turns on a Migraine? A Systematic Review of Migraine Precipitating Factors. *Curr Pain Headache Rep*. 2014;18(10):453-458. doi:10.1007/s11916-014-0454-z

38. Marmura MJ. Triggers, Protectors, and Predictors in Episodic Migraine. *Current Pain and Headache Reports*. 2018;22.

39. Holle D, Obermann M. The role of neuroimaging in the diagnosis of headache disorders. *Ther Adv Neurol Disord*. 2013;6(6):369-374. doi:10.1177/1756285613489765

40. Tsushima Y, Endo K. MR imaging in the evaluation of chronic or recurrent headache. *Radiology*. 2005;235(2):575-579. doi:10.1148/radiol.2352032121

41. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: An electronic diary study. *Neurology*. 2003;60(6):935-940. doi:10.1212/01.wnl.0000052998.58526.a9

42. Giffin NJ, Lipton RB, Silberstein SD, Olesen J, Goadsby PJ. GLOSSARY ICHD 5 International Classification of Headache Disorders. *Neurology*. 2016;87:309-313.

43. Quintela E, Castillo J, Muñoz P, Pascual J. Premonitory and Resolution Symptoms in Migraine: A Prospective Study in 100 Unselected Patients. *Cephalalgia*. 2006;26(9):1051-1060. doi:10.1111/j.1468-2982.2006.01157.x

44. Kelman L. The postdrome of the acute migraine attack. *Cephalalgia*. 2006;26(2):214-220. doi:10.1111/j.1468-2982.2005.01026.x

45. Gazerani P, Cairns BE. Sex-Specific Pharmacotherapy for Migraine: A Narrative Review. *Front Neurosci*. 2020;14:222. doi:10.3389/fnins.2020.00222

46. Goadsby PJ. Bench to bedside advances in the 21st century for primary headache disorders: Migraine treatments for migraine patients. *Brain*. 2016;139(10):2571-2577. doi:10.1093/brain/aww236

47. Diener HC, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. *Lancet Neurol*. 2015;14:1010-1022.

48. Society AH. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache*. 2019;59(1):1-18.

49. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The american headache society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20. doi:10.1111/head.12499

50. Hou M, Kanje M, Longmore J, Tajti J, Uddman R, Edvinsson L. 5-HT1B and 5-HT1D receptors in the human trigeminal ganglion: Co-localization with calcitonin gene-related peptide, substance P and nitric oxide synthase. *Brain Res*. 2001;909(1–2):112-120.

51. Cady RK, McAllister PJ, Spierings ELH, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). *Headache*. 2015;55(1):88-100. doi:10.1111/head.12472

52. Bird S, Derry S, Moore RA. Zolmitriptan for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2014;2017(5):CD008616. doi:10.1002/14651858.cd008616.pub2

53. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for acute migraine attacks in adults. *Cochrane database Syst Rev*. 2013;2013(10):CD008541.

54. Tepper SJ, Cady RK, Silberstein S, et al. AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. *Headache*. 2015;55(5):621-635. doi:10.1111/head.12583

55. Lipton RB, Munjal S, Brand-Schieber E, Rapoport AM. DFN-02 (Sumatriptan 10 mg With a Permeation Enhancer) Nasal Spray vs Placebo in the Acute Treatment of Migraine: A Double-Blind, Placebo-Controlled Study. *Headache*. 2018;58(5):676-687. doi:10.1111/head.13309

56. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis. *Headache*. 2015;55(S4):221-235.

57. Rapoport AM, Freitag F, Pearlman SH. Innovative delivery systems for migraine: the clinical utility of a transdermal patch for the acute treatment of migraine. *CNS Drugs*. 2010;24(11):929-940. doi:10.2165/11317540-000000000-00000

58. Ceriani CEJ, Wilhour DA, Silberstein SD. Novel Medications for the Treatment of Migraine. *Headache*. 2019;59(9):1597-1608. doi:10.1111/head.13661

59. de Vries T, Villalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. *Pharmacology and Therapeutics*. 2020;211:107528.

60. Digre KB. What's New in the Treatment of Migraine? *J Neuro-Ophthalmology*. 2019;39(3):352-359. doi:10.1097/wno.0000000000000837

61. Tfelt-Hansen PC. Does sumatriptan cross the blood-brain barrier in animals and man? *Journal of Headache and Pain*. 2010;11:5-12.

62. Mehta D, Leary MC, Yacoub HA, et al. The Effect of Regional Anesthetic Sphenopalatine Ganglion Block on Self-Reported Pain in Patients With Status Migrainosus. *Headache*. 2019;59(1):69-76. doi:10.1111/head.13390

63. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: Results from the American migraine prevalence and prevention study. *Headache*. 2007;47(3):355-363.

64. Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC, Reed ML. Impact of NSAID and Triptan Use on Developing Chronic Migraine: Results From the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2013;53(10):1548-1563. doi:10.1111/head.12201

65. Thorlund K, Toor K, Wu P, et al. Comparative tolerability of treatments for acute migraine: A network meta-analysis. *Cephalalgia*. 2017;37(10):965-978. doi:10.1177/0333102416660552

66. Dodick D, Lipton RB, Martin V, et al. Consensus statement: Cardiovascular safety profile of triptans (5-HT 1B/1D agonists) in the acute treatment of migraine. *Headache*. 2004;44(5):414-425. doi:10.1111/j.1526-4610.2004.04078.x

67. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: New drugs, new hope? *J Headache Pain*. 2019;20(1):1-13.

68. Ong JJY, Wei DYT, Goadsby PJ. Recent Advances in Pharmacotherapy for Migraine Prevention: From Pathophysiology to New Drugs. *Drugs*. 2018;78(4):411-437. doi:10.1007/s40265-018-0865-y

69. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin A. *Park Relat Disord*. 2011;17(SUPPL. 1):S28-33.

70. Mathew NT, Frishberg BM, Gawel M, et al. Botulinum toxin type a (Botox) for prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45(4):293-307. doi:10.1111/j.1526-4610.2005.05066.x

71. Proietti Cecchini A, Grazzi L. Emerging therapies for chronic migraine. *Curr Pain Headache Rep*. 2014;18(4).

72. Sandrini G, Perrotta A, Tassorelli C, et al. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: A multicenter, double-blind, randomized, placebo-controlled, parallel group study. *J Headache Pain*. 2011;12(4):427-433. doi:10.1007/s10194-011-0339-z

73. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Ann Neurol*. 2008;64(3):274-283. doi:10.1002/ana.21427

74. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. *Cochrane Database of Systematic Reviews*. 2018;2018.

75. Naegel S, Obermann M. Topiramate in the prevention and treatment of migraine: Efficacy, safety and patient preference. *Neuropsychiatr Dis Treat*. 2010;6(1):17-28.

76. Urits I, Clark G, An D, et al. An Evidence-Based Review of Fremanezumab for the Treatment of Migraine. *Pain Ther*. 2020;9(1):195-215. doi:10.1007/s40122-020-00159-3

77. White HS. Molecular pharmacology of topiramate: Managing seizures and preventing migraine. *Headache*. 2005;45(SUPPL. 1):48-56.

78. Raffaelli B, Reuter U. The Biology of Monoclonal Antibodies: Focus on Calcitonin Gene-Related Peptide for Prophylactic Migraine Therapy. *Neurotherapeutics*. 2018;15(2):324-335. doi:10.1007/s13311-018-0622-7

79. Yuan H, Spare NM, Silberstein SD. Targeting CGRP for the Prevention of Migraine and Cluster Headache: A Narrative Review. *Headache*. 2019;59(S2):20-32.

80. Paemeleire K, MaassenVanDenBrink A. Calcitonin-gene-related peptide pathway mAbs and migraine prevention. *Curr Opin Neurol*. 2018;31(3):274-280. doi:10.1097/wco.0000000000000548

81. Russo AF. Calcitonin Gene-Related Peptide (CGRP): A New Target for Migraine. *Annu Rev Pharmacol Toxicol*. 2015;55(2):533-552. doi:10.1146/annurev-pharmtox-010814-124701

82. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients – a review of pros and cons. *Journal of Headache and Pain*. 2017;18.

83. Raffaelli B, Neeb L, Reuter U. Monoclonal antibodies for the prevention of migraine. *Expert Opin Biol Ther*. Published online 2019:1-11.

84. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018;392(10161):2280-2287. doi:10.1016/s0140-6736(18)32534-0

85. Xu D, Chen D, Zhu L na, et al. Safety and tolerability of calcitonin-gene-related peptide binding monoclonal antibodies for the prevention of episodic migraine – a meta-analysis of randomized controlled trials. *Cephalalgia*. 2019;39(9):1164-1179. doi:10.1177/0333102419829007

86. Negro A, Martelletti P. Gepants for the treatment of migraine. *Expert Opin Investig Drugs*. 2019;28(6):555-567. doi:10.1080/13543784.2019.1618830

87. Bigal ME, Walter S, Rapoport AM. Therapeutic antibodies against CGRP or its receptor. *Br J Clin Pharmacol*. 2015;79(6):886-895. doi:10.1111/bcp.12591

88. Favoni V, Giani L, Al-Hassany L, et al. CGRP and migraine from a cardiovascular point of view: what do we expect from blocking CGRP? *J Headache Pain*. 2019;20(1):27. doi:10.1186/s10194-019-0979-y

89. Evans RW. Raynaud's Phenomenon Associated With Calcitonin Gene-Related Peptide Monoclonal Antibody Antagonists. *Headache*. 2019;59(8):1360-1364. doi:10.1111/head.13596

90. Chan C, Goadsby PJ. Recent Advances in Pharmacotherapy for Episodic Migraine. *CNS Drugs*. 2019;33(11):1053-1071. doi:10.1007/s40263-019-00665-9

91. Scott LJ. Rimegepant: First Approval. *Drugs*. 2020;80(7):741-746. doi:10.1007/s40265-020-01301-3

92. Luo G, Chen L, Conway CM, et al. Discovery of (5*S*,6*S*,9*R*)-5-Amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (BMS-927711): An Oral Calcitonin Gene-Related Peptide (CGRP) Antagonist in Clinical Trials for Treating Migraine. *J Med Chem*. 2012;55(23):10644-10651. doi:10.1021/jm3013147

93. Nurtec ODT [prescribing information]. New Haven, CT; 2020.

94. Mallick-Searle T, Moriarty M. Unmet needs in the acute treatment of migraine attacks and the emerging role of calcitonin gene–related peptide receptor antagonists. *J Am Assoc Nurse Pract*. 2020;1.

95. Biohaven Pharmaceuticals I. Dosing and Administration | NurtecTM ODT (rimegepant) 75 mg Orally Disintegrating Tablets.

96. De Matteis E, Guglielmetti M, Ornello R, Spuntarelli V, Martelletti P, Sacco S. Targeting CGRP for migraine treatment: mechanisms, antibodies, small molecules, perspectives. *Expert Rev Neurother*. Published online 2020:1-15.

97. Maasumi K, Michael RL, Rapoport AM. CGRP and Migraine: The Role of Blocking Calcitonin Gene-Related Peptide Ligand and Receptor in the Management of Migraine. *Drugs*. 2018;78(9):913-928. doi:10.1007/s40265-018-0923-5

98. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies — successful translation from bench to clinic. *Nat Rev Neurol*. 2018;14(6):338-350. doi:10.1038/s41582-018-0003-1

99. Cernuda-Morollon E, Larrosa D, Ramon C, Vega J, Martinez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology*. 2013;81(14):1191-1196. doi:10.1212/wnl.0b013e3182a6cb72

100. Urits I, Jones MR, Gress K, et al. CGRP Antagonists for the Treatment of Chronic Migraines: a Comprehensive Review. *Current Pain and Headache Reports*. 2019;23.

101. Pascual J. Efficacy of BMS-927711 and other gepants vs triptans: there seem to be other players besides CGRP. *Cephalalgia*. 2014;34(12):1028-1029. doi:10.1177/0333102414526052

102. Tepper SJ. History and Review of anti-Calcitonin Gene-Related Peptide (CGRP) Therapies: From Translational Research to Treatment. *Headache*. 2018;58(Suppl 3):238-275.

103. de Vries T, Villalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. *Pharmacol Ther*. 2020;211.

104. Eftekhari S, Salvatore CA, Calamari A, Kane SA, Tajti J, Edvinsson L. Differential distribution of calcitonin gene-related peptide and its receptor components in the human trigeminal ganglion. *Neuroscience*. 2010;169(2):683-696. doi:10.1016/j.neuroscience.2010.05.016

105. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. *J Pain*. 2013;14(11):1289-1303. doi:10.1016/j.jpain.2013.03.010

106. Edvinsson L, Ekman R, Goadsby PJ. Measurement of vasoactive neuropeptides in biological materials: problems and pitfalls from 30 years of experience and novel future approaches. *Cephalalgia*. 2010;30(6):761-766. doi:10.1177/0333102409351807

107. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. *Expert Opin Ther Targets*. 2020;24(2):91-100. doi:10.1080/14728222.2020.1724285

108. Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene–related peptide in peripheral and central pain mechanisms including migraine. *Pain*. 2017;158(4):543-559. doi:10.1097/j.pain.0000000000000831

109. Hong P, Tan T, Liu Y, Xiao J. Gepants for abortive treatment of migraine: A network meta-analysis. *Brain Behav*. Published online 2020.

110. Sheykhzade M, Amandi N, Pla MV, et al. Binding and functional pharmacological characteristics of gepant-type antagonists in rat brain and mesenteric arteries. *Vascul Pharmacol*. 2017;90:36-43. doi:10.1016/j.vph.2017.02.001

111. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. *Cephalalgia*. 2019;39(3):366-373. doi:10.1177/0333102417736900

112. Eftekhari S, Salvatore CA, Johansson S, Chen TB, Zeng Z, Edvinsson L. Localization of CGRP, CGRP receptor, PACAP and glutamate in trigeminal ganglion. Relation to the blood–brain barrier. *Brain Res*. 2015;1600:93-109. doi:10.1016/j.brainres.2014.11.031

113. Dubowchik GM, Conway CM, Xin AW. Blocking the CGRP Pathway for Acute and Preventive Treatment of Migraine: The Evolution of Success. *Journal of Medicinal Chemistry*. Published online 2020.

114. Edvinsson L. Rimegepant oral disintegrating tablet for migraine. *Lancet*. 2019;394(10200):711-712. doi:10.1016/s0140-6736(19)31611-3

115. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: A double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*. 2014;34(2):114-125. doi:10.1177/0333102413500727

116. Pascual J. Efficacy of BMS-927711 and other gepants vs triptans: there seem to be other players besides CGRP. *Cephalalgia*. 2014;34(12):1028-1029. doi:10.1177/0333102414526052

117. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10200):737-745. doi:10.1016/s0140-6736(19)31606-x

118. Croop R, Goadsby PJ, Stock DA, Lipton RB. Testing rimegepant for migraine—time to revise the trial design? – Authors' reply. *Lancet*. 2020;395:1901-1902.

119. Gasparini S, Torino C, Branca D, Ferlazzo E, Aguglia U. Testing rimegepant for migraine—time to revise the trial design? *Lancet*. 2020;395(10241):1901. doi:10.1016/s0140-6736(20)30241-5

120. Ju C, Spiegel R, Radecki R, Swaminathan AK. Rimegepant in the Treatment of Migraine Headache: The Importance of Comparator Treatments: November 2019 Annals of Emergency Medicine Journal Club. *Ann Emerg Med*. 2019;74(5):721-723. doi:10.1016/j.annemergmed.2019.09.014

121. McCarthy L. Commentary. *Annals of Internal Medicine*. 2019;171:JC58-59.

122. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019;381(2):142-149. doi:10.1056/nejmoa1811090

123. Gao B, Yang Y, Wang Z, et al. Efficacy and Safety of Rimegepant for the Acute Treatment of Migraine: Evidence From Randomized Controlled Trials. *Front Pharmacol*. 2019;10:1577. doi:10.3389/fphar.2019.01577

124. Tfelt-Hansen P, Loder E. The Emperor's New Gepants: Are the Effects of the New Oral CGRP Antagonists Clinically Meaningful? *Headache*. 2019;59(1):113-117. doi:10.1111/head.13444

125. Mullin K, Kudrow D, Croop R, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. *Neurology*. 2020;94(20):e2121-e2125. doi:10.1212/wnl.0000000000008944

126. Safety and Efficacy Study in Adult Subjects With Acute Migraines - Full Text View - ClinicalTrials.gov.

127. Efficacy and Safety Trial of Rimegepant for Migraine Prevention in Adults - Full Text View - ClinicalTrials.gov.

128. Trial for Treatment Refractory Trigeminal Neuralgia - Full Text View - ClinicalTrials.gov.

129. Edvinsson L. The Trigeminovascular Pathway: Role of CGRP and CGRP Receptors in Migraine. *Headache*. 2017;57(Suppl 2):47-55.

130. Edvinsson L. The CGRP Pathway in Migraine as a Viable Target for Therapies. *Headache*. 2018;58:33-47. doi:10.1111/head.13305