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General

A Comprehensive Review of Zavegepant as Abortive Treatment for Migraine

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Migraine headache is a widespread and complex neurobiological disorder that is characterized by unilateral headaches that are often accompanied by photophobia and phonophobia. Migraine is one of the leading chief complaints in the emergency department with negative impacts on quality of life and activities of daily living. The high number of emergency presentations also results in a significant economic burden. Its risk factors include family history, genetics, sex, race, socioeconomics, the existence of comorbid conditions, and level of education. Triggers include stress, light, noise, menstruation, weather, changes in sleep pattern, hunger, dehydration, dietary factors, odors, and alcohol. The International Headache Society has defined criteria for the diagnosis of migraine with and without aura. The pathophysiology of migraine headaches is multifactorial so there are a variety of treatment approaches. The current treatment approach includes abortive medications and prophylactic medications. Abortive medications include the first-line treatment of triptans, followed by ergot alkaloids, and calcitonin gene-related peptide (CGRP) receptor antagonists along with supplemental caffeine and antiemetics. Trigeminal afferents from the trigeminal ganglion innervate most cranial tissues and many areas of the head and face. These trigeminal afferents express certain biomarkers such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A, and pituitary adenylate cyclase-activating polypeptide that are important to the pain and sensory aspect of migraines. In this comprehensive review, we discuss Zavegepant, a calcitonin gene-related peptide receptor antagonist, as a new abortive medication for migraine headaches.

INTRODUCTION

Migraine headache is a widespread and complex neurobiological disorder. This condition is characterized by recurring unilateral headaches and is commonly associated with increased sensitivities to visual and auditory stimulation, nausea, and possible transient focal neurological effects or aura. Episodes may last hours to several days leading to impairment in everyday functioning. Identified as the second-leading cause of disability throughout the world, migraine headaches have widespread personal and socioeconomic implications.[1]

With the emerging understanding of the complexity behind migraine pathogenesis and its many associated symptoms, the previously recognized vascular theory of migraine pathogenesis has shown insufficient to explain the pain and many associated symptoms associated with migraine headaches.[1,2] Further research has demonstrated that the pathogenesis of this disorder is attributed to a complex interaction of many neuronal networks.[1] Current understanding is that migraine arises from central and peripheral nervous system processes that include the cerebral cortex, meninges, and brainstem. These processes elicit an inflammatory response leading to aura due to cortical depression and activation of trigeminal afferent nerves resulting in the primary headache of migraine.[3]

Established pharmacological management options include beta-blockers, tricyclic antidepressants, calcium channel blockers, and anticonvulsants.[4,5] Although successful management is achieved for some of these medications, marked variability in effectiveness and tolerance has been exhibited with these existing treatments and thus compliance to these medical therapies.[5-7]

Many triggers are known to prompt the onset of migraines. Both physiological and or emotional have been shown to disrupt central nervous system (CNS) structures leading to stimulation of the Trigeminovascular system and other CNS structures.[1,2,4,8] This stimulation leads to the release of vasoactive molecules including calcitonin gene-related peptide (CGRP), neurokinin A, and pituitary cy-

clase-activating peptide (PACAP), thus leading to the characteristic pulsatile headache of migraine and other associated symptoms.[9,10]

Calcitonin gene-related peptide (CGRP) has been found to be greatly associated with migraine pathophysiology.[10] Following stimulation of the Trigeminovascular system, CGRP has shown to be released and found at high levels in the cerebrovascular circulation and Trigeminovascular system.[11] CGRP receptors are found to be localized at vascular smooth muscle cells of the dura meninges as well as neurons and glial cells involved in the trigeminal system.[12] Acting on smooth muscle cell receptors, neurovascular structures, and spinothalamic pathways the release of CGRP results in vasodilation, possible central nervous system sensitization, and transmission of pain characteristic of acute migraine episodes.[4,12]

As a major component in migraine pathogenesis, CGRP has been a focus of migraine research since the 1980s.[13] The advancement in the understanding of migraine pathophysiology and involvement of specific molecular targets has been encouraging for further target-based treatments with the aim of improving effectiveness in migraine management. As a promising target-specific treatment for migraines, we aim to review intranasal third-generation CGRP antagonists as a novel treatment in the setting of acute migraine management.

EPIDEMIOLOGY

PREVALENCE

Globally, among the top three most prevalent illnesses and the sixth leading cause of years lived with disability, migraine is a common disorder worldwide.[14-16] Migraine affects up to 18% of people each year.[4,17,18] The peak prevalence of migraine has been identified in middle life, typically in the thirties and forties, with a midlife prevalence of 25% and 8% in females and males, respectively. A nonlinear decrease in prevalence is appreciated in adults greater than 60 years of age with approximately 5% of females and 1.6% of males affected.[17,19] Despite the availability of both acute and chronic treatment options, the prevalence of migraine has remained relatively stable in the United States over the years.[14,19]

Worldwide, the highest prevalence of migraine has been identified in North America and South America, with a decreased prevalence in Europe, and the lowest prevalence in Asian countries.[20] Within the United States, the prevalence of migraine has shown to be highest among Caucasian populations compared to African American populations and the lowest prevalence amongst Asian Americans.[19]

As with many clinical pain disorders, migraine occurrence is higher in females compared to males with an approximately two-fold increase in migraine prevalence in females compared to males.[17,21,22] In midlife, when migraine prevalence is greatest, there is a roughly 3:1 female-to-male ratio.[18] This difference is made evident through a study by Stewart *et al.* demonstrating a lifetime incidence of 43% in females compared to an 18% lifetime incidence in males.[23] However, prior to the onset of puberty, the occurrence of migraine is found to be higher in males than females. Following puberty, the prevalence of migraine continues to increase in females until about the age of 40. This pattern is not observed in males.[20] Despite geographic differences in migraine prevalence, the pattern of female predominance in migraine prevalence remains consistent.[20]

SOCIOECONOMIC BURDEN

Of those affected by migraine, up to ninety-one percent report decreased functionality as a result of migraine episodes with over half with severe functional impairment requiring bed rest for up to two days.[17,19] Lipton et al. reports one or more days of missed work or school in patients experiencing migraine and 51% with decreased productivity by 50% or more while at work or school.[19] This impact on functionality leads to not only personal but also financial and economic burdens. Those who experience migraine are at a higher risk for greater indirect costs related to increased work loss, and short- and long-term disability compared to those without migraine.[24]

Headache, commonly migraine, is a leading cause of emergency department (ED) visits and among the front 20 causes of outpatient appointments.[14,18] In the United States alone, there is an estimated $36 billion spent from direct costs of healthcare resources and indirect costs of loss of productivity.[15] A study published by the American Headache Society showed that those who experience migraines had an annual cost of $8924 greater from both direct healthcare costs and indirect costs compared to a matched group of patients without migraine.[24]

QUALITY OF LIFE

In addition to economic costs, migraines have been associated with another great cost – a lower quality of life. Along with physical pain, migraine is found to be significantly related to impaired social functioning.[25] Not only is migraine a prominent disorder worldwide but has been found associated with medical and psychiatric comorbidities.[18] Such comorbid disorders include stress, depression, anxiety, and suicide intent.[25,26] Additionally, according to Buse et al. using the Chronic Migraine Epidemiology and Outcomes (CaMEO) study, roughly half of migraineurs report decreased participation in family activities associated with an increasing frequency of headache episodes.[27]

RISK FACTORS FOR MIGRAINE

As a complex disorder, many risk factors associated with the onset and progression of migraine have been identified and continue to be an area of ongoing research. Currently, many risk factors for the onset of migraine have been identified including family history, genetics, sex, race, socioeconomics, the existence of comorbid conditions, and level of education. Additionally, numerous triggers have also been identified. Both risk factors and triggers of migraine are described in this section of our review.

Table 1. Gene association with migraine subtypes.

Migraine subtype	Gene(s) involvement
Primary Migraine with Aura	*MTDH*
Primary Migraine Without Aura	*MEF2D*, *TGFBR2*
Pure familial migraine	*KCNK18*
FHM	*CACNA1A*, *ATPA2*, *SCN1A*, *PRRT2*
CADASIL	*NOTCH3*
HIHRATL with migraine	*COL4A1*
RVCL	*TREX1*
FASPS	*CSNK1D*

(FHM) Familial Hemiplegic Migraine; (CADASIL) Cerebral Autosomal Dominant Arteriopathy with subcortical infarcts and leukoencephalopathy; (HIHRATL) Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy; (RVCL) Retinal Vasculopathy with cerebral leukodystrophy; (FASPS) Familial advanced sleep phase syndrome.[28]

As with many disorders, family history is a major factor in the development of migraine. Approximately 90% of migraineurs have a family history of this disorder.[15] It has been shown that the risk of developing migraine headaches is increased in those with a first-degree relative that suffers from migraine accounting for an estimated 50% heritability.[28,29] Russell et al. estimate 1 to 9 times increased risk in the development of migraine without aura in those with first-degree relatives with migraine and 1 to 4 times increased risk of migraine with aura, compared to the general population.[29]

Reflecting on the prevalence of migraine, females are at an increased risk to develop migraine compared to their male counterparts (see Prevalence).[20,22,30] Furthermore, with increased acute attack frequency and progression of migraine disorder, women are at increased risk for the development of deep white matter lesions in those who suffer from either migraine with or without aura.[31] Education level is also associated with the risk of migraine development. Completion of less than high school level education is associated with a three-fold increase in chronic headache risk. Additionally, divorce, separation, or widowhood have been attributed to an increased risk.[32] Other associations with migraine are the self-reported concurrent presence of arthritis, diabetes, previous head trauma, and medication overuse.[32-34]

Genetics play a significant role in migraine and many forms of migraine are considered to be polygenic in nature.[28] Over the past decade, an increasing number of genetic associations with migraine and migraine subtypes have been identified. Through genome-wide association studies (GWAS), genes affecting both neuronal and vascular pathways as well as the encoding for metalloproteinases have been identified as associated with polygenic migraine both with and without migraine. Each of these genes produces are associated with various degrees of vascular dysfunction which may contribute to migraine involvement.[28] Genes associated with migraine and migraine subtypes are listed in Table 1.

MIGRAINE PROGRESSION

Progression of migraine episodes has been associated with the central-sensitization-allodynia theory.[20] A study by Burstein et al. estimated that about 79% of patients experiencing an acute attack develop central sensitization (CS), or sensitization of the second-order trigeminal afferent neurons, by parasympathetic activation and or sensitization of intracranial nociceptors, leading to cutaneous allodynia.[35,36] Thus, recurrent acute attacks with repeated CS are hypothesized to place the patient at increased risk of migraine disorder progression.

TRIGGERS

Stress, noise, hormonal changes in females such as those experienced during menstruation or exogenous hormone usage, changes in weather, bright lighting, changes in the duration of sleep, hunger, dehydration, dietary factors, odors, and alcohol are among some of the many common triggers identified by Kelman and other collective studies with stress noted as the most common trigger of migraine headaches.[37-39]

In their review of migraine triggers, Borkum describes oxidative stress as a commonality between the many migraine triggers. The mechanism behind this oxidative stress has been linked to mitochondrial energy production rate or toxicity of the mitochondria, excitotoxicity, neuroinflammation, and activation of neuronal enzymes such as neuronal nicotinamide adenine dinucleotide phosphate oxidase, monoamine oxidase, cytochrome P450, or nitric oxide synthase.[40]

DIAGNOSIS AND CLINICAL PRESENTATION OF MIGRAINE

Following years of research, migraine has been identified as a neurobiological disorder with a complex clinical presentation, consistent with the complexity of migraine pathophysiology. According to the International Headache Society, migraines may be classified into migraine with or without aura and further by chronicity of headaches.[41]

Previously known as common migraine or hemicrania simplex, migraine without aura is a primary headache disorder typically characterized by recurrent headaches that persist between 4 to 72 hours. These headaches are most often having a pulsating quality and may be exacerbated

by activities of daily living such as physical activity, light, or sound and may have associated nausea. Although these headaches are most commonly unilateral frontotemporal in adults, children under the age of 18 years more often experience bilateral pain.[41]

Migraine with aura is characterized by focal neurological deficits (FND) that precede or may coincide with acute migraine episodes. Occurring in approximately 90% of migraineurs, the visual aura is the most common FND of aura. Other forms of aura manifest as paresthesia of the body, typically unilaterally, or of the face or tongue. Rarely, the aura may present with speech disturbances or aphasic aura. Importantly, an aura is transient and reversible in nature. Additionally, migraine with aura can be further classified as hemiplegic migraine which consists of motor symptoms. This classification includes familial hemiplegic migraine types 1 through 3, sporadic hemiplegic migraine, and retinal migraine.[41] However, the in-depth discussion of these subgroups extends beyond the scope of this review.

Migraineurs, with and without aura, often experience prodromal phase symptoms and or postdromal phase symptoms. Occurring anywhere from hours to days prior to headache onset, the median duration of premonitory symptoms is 2 hours with a median duration of 6.8 hours.[37] Among the most prevalent prodromal symptoms include fatigue, mood changes such as depression, gastrointestinal symptoms, phonophobia, difficulty concentrating, hyper- or hypo-activity, dietary cravings, yawning, and neck pain or discomfort.[41-45] Of note, Giffen et al. found that patient with poor functioning during the premonitory phase of migraine had a greater ability to predict onset of acute migraine headache episodes.[43] Despite occurring at different phases in relation to the headache associated with migraine, prodromal and postdromal symptoms are often similar.

In a large retrospective cohort study, trigger factors and prodromal symptoms demonstrated sizeable overlap suggesting that many of the common trigger factors for patients with migraine may, in fact, be due increased attentiveness of the migraineur secondary to prodromal migraine symptoms rather than independent instigator of acute migraine episode.[42] In fact, symptomatic changes are not only seen in the premonitory phase of migraine.

During this premonitory phase, functional neuroimaging changes have been identified involving primarily subcortical structures of the hypothalamus, thalamus, midbrain, basal ganglia, and limbic regions.[46,47] Involvement of these regions of the brain has been supported by perfusion imaging (i.e., positive emission topography (PET) scan and perfusion MRI with arterial spin labeling) whereby increased perfusion relates with increased neuronal activity and perfusion MRI. Using MRI, Manivar et al. demonstrated increased blood flow to the aforementioned subcortical areas during the prodromal phase of migraine, suggesting an increase in neuronal activity during this phase. In conjunction with prodromal phase symptoms, these imaging findings support the notion of subcortical dysfunction involvement in migraine episode onset rather than cortical

DIAGNOSIS

The diagnosis of migraine is clinical and can be most often achieved by analysis of a patient's history and physical examination.[48] Clinical diagnostic criteria for migraine with and without aura are summarized in Table 2. Testing outside of the scope of history and physical such as blood work, neuroimaging, lumbar puncture, or electroencephalography are not typically required for the diagnosis of migraine. However, these additional diagnostic tests may be required to distinguish between migraine as a primary headache or a secondary headache with migraine-like presentation or when the diagnosis unclear.[48]

The clinical diagnosis of migraine is important for the proper management of this disorder. A study by Diamond et al. showed that of all the participants with migraine, 56.2% had ever had an established medical diagnosis of migraine.[49] As seen in a study by Viana et al., the diagnostic delay may lead to prolonged suffering and inadequate treatment when symptoms are attributed to an incorrect diagnosis. Delay in the proper diagnosis of migraine may be due to either by improper self- or physician diagnosis.[50]

PATHOPHYSIOLOGY

The pathophysiology of migraines characterizes the disability as a neurological disorder. It involves multifactorial contributions (environmental and genetic) disrupting the control of sensory inputs in the brain.[1] Migraine affects over one billion people a year and is ranked the sixth most common cause of disability in the world. The outline of the disorder follows a somewhat predictable pattern: prodrome, aura, migraine headache, and postdrome. All of the phases vary from person and incident. The severity of the phases can wax and wane and are sometimes not present at all. Forty to sixty percent of migraine patients experience a prodromal phase initially. This first phase is characterized by subtle changes one to two days preceding the headache. The prodrome has been described in research as the "pre-headache" and marks the beginning of the migraine process. This phase can cause a wide range of symptoms including problems concentrating, irritability, depression, difficulty speaking and reading, trouble sleeping, yawning, nausea, fatigue, photosensitivity, phonophobia, food cravings, increased urination, or muscle stiffness. The phase following the prodrome is called the aura phase. Fewer migraine patients experience an aura phase with the rate being only about 20%. The 20% of patients that do experience this phase describe it as being a more distinct warning sign than the prodrome. Auras can be sensory, motor or verbal disturbances, but are most commonly visual. The aura can be noticed by migraine patients up to an hour before the pain begins. The aura can include seeing bright flashing dots, sparkles, or lights; blind spots in vision; numbness or tingling of skin; speech changes; tinnitus; temporary vision loss or alterations; and changes in taste and smell. The following phase is the migraine headache. This phase is characterized by pain. This pain can vary in both person and incident and can last from hours to days. The lo-

Table 2. Diagnostic criteria for migraine with and without aura.[41]

Migraine with aura	Migraine without aura
A. Two (2) or more episodes satisfying criteria B and C	A. Five (5) or more episodes satisfying criteria B–D
B. One (1) or more of the following aura symptoms: • Visual • Sensory • Speech or language • Motor • Brainstem • Retinal	B. Untreated or insufficiently treated headache lasting 4 to 72 hours
C. Three (3) or more of the following episode characteristics: • One (1) or more of criteria B aura symptoms that spreads over 5 minutes • Two (2) or more of criteria B aura symptoms occurring in series • Each criteria B aura symptom lasting five (5) to sixty (60) minutes • One or more criteria B aura symptom is unilateral • One or more criteria B aura symptom is positive • Aura is followed or accompanied by headache within sixty (60) minutes	C. Two (2) or more of the following episode characteristics: • Unilateral • Pulsating • Headache pain of moderate to severe intensity • Routine physical activities aggravate or cause avoidance
D. Not due to another International Classification of Headache Disorders (ICHD-3) diagnosis	D. One (1) or more symptoms during headache: • Nausea and/or vomiting • Photophobia • Phonophobia
	E. Not due to another International Classification of Headache Disorders (ICHD-3) diagnosis

Adopted from the International Headache Society.

cation of the pain also varies and most commonly radiates as the headache progresses. Aside from the pain, patients can also experience symptoms of photophobia, phonophobia, sensitivity to smell, nausea, vomiting, abdominal pain, loss of appetite, sweating, chills, pallor, fatigue, dizziness, diplopia, speech changes, diarrhea, scalp tenderness, and fever. The final phase of the migraine process is the postdrome. The postdrome can last for up to 2 days following the headache phase and like the other phases varies from person to person. The postdrome can have symptoms such as: inability to concentrate, depressed mood, fatigue, confusion, or euphoria.[51]

Migraines are able to penetrate through the afferent pathways of the trigeminal vasculature.[1] The afferents largely consist of thinly myelinated and unmyelinated Aδ- and C-fibers synapsing centrally on second-order trigeminopthalamic relay neurons in the dorsal horn of the trigeminal nucleus caudalis.[51] Trigeminal afferents from the trigeminal ganglion innervate most cranial tissues and many areas of the head and face. The innervation from all three divisions– ophthalmic, maxillary, and mandibular, is important in the pathophysiology of migraines, however, the ophthalmic division is considered the most relevant, as pain is often initially localized to the periorbital region. These trigeminal afferents express certain biomarkers such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A, and pituitary adenylate cyclase-activating polypeptide that are important to the pain and sensory aspect of migraines.[51] Studies have indicated that substances such as CGRP are also elevated extracranially during a migraine headache, especially in classic migraine cases.[52] It has also been found extracranially in the CSF of chronic migraine patients, that glutamate and nerve growth factor (NGF) is increased, and β-endorphin (β-EP) is decreased.[53] The brainstem has been linked to the induction and termination of migraine headaches. There are significant activations in the midbrain, pons, and hypothalamus. Studies have shown that there is the involvement of the hypothalamus in the prodrome and aura phases.[54]

As previously mentioned, migraines are shown to be multifactorial in origin. There has been data shown that links migraines to certain genetic predispositions. Through twin studies, it was able to be determined that one of the biggest links has been to a methylenetetrahydrofolate reductase gene mutation, C677T, which has shown in migraines with auras. Another genetic anomaly is the *CACNA1A* gene on chromosome 19p13 in association with familial hemiplegic migraines.[51] The environmental aspects of migraines are not supported with as much concrete data, but the main factor to consider is diet. Several dietary triggers for migraine have been identified, thus leading to strategies such as elimination diets to help in migraine prophylaxis. In some circumstances, there seems to be some benefit from dietary interventions in attempts to manipulate the gut-brain axis.[55]

TRADITIONAL TREATMENT OPTIONS

Traditional treatment of migraines depends on the severity and frequency of the migraine headaches. Migraine therapy is aiming to target the central and peripheral nervous system. Treatment is often divided into prophylactic and abortive therapies based on the frequency and severity of migraine headaches.

Acute treatment aims to manage the symptoms of a current migraine. The goal of these treatments is to treat the attacks rapidly so there is no recurrence of headache; the patient is able to restore function as quickly as possible and to minimize the use of backup/rescue medications. Abortive treatments can be migraine-specific or non-specific. Non-specific abortive treatments include analgesics such as NSAIDs or acetaminophen +/- caffeine supplementations. This is often used in patients with infrequent, mild to moderate migraine headaches. For moderate to severe migraine patients, abortive therapies include triptans, ergot alkaloids, and calcitonin gene-related peptide (CGRP) receptor antagonists along with supplemental caffeine and antiemetics. Triptans are the first-line treatment for acute migraines, they act by targeting 5-HT_{1B} and 5-HT_{1D} serotonin receptors.[51] They are often very effective in many patients, but they have limitations due to their adverse effects such as dizziness, dry mouth, sedation, flushing, nausea, muscle weakness, and numbness in the throat and skin.[56] Ergot alkaloids are particularly helpful in treating throbbing headache pain, but side effects include gangrene, vision problems, and confusion. Because of these side effects, new medications have become more popular for the treatment of acute migraines. These novel medications include CGRP receptor antagonists, CGRP monoclonal antibodies, and titans. CGRP receptors are expressed centrally and peripherally throughout the nervous system and act as cerebral vasodilators. Antagonists to these receptors increase inhibitory mechanisms to desensitize neuronal circuits.[56] Ditans are used to target serotonin receptors without vasoconstrictive effects.[57] These new medications can be used in patients with co-morbities of hypertension and heart disease.

Prophylactic treatments aim to prevent migraines from beginning at all. These treatments are often given in concordance with abortive therapies and aim to reduce the frequency and severity of headaches, reduce disability, and improve the quality of life of the patient. Preventative treatments should be considered if headaches are more frequent than twice weekly. Preventative treatments include Amitriptyline, Valproic acid, Propranolol/Timolol, and Topiramate often in combination with antiemetics. Amitriptyline is a TCA and is often used in migraine patients that also experience fragmented sleep. Propranolol and Timolol are beta-blockers and can also be used in patients with hypertension.[58] These beta-blockers often have to be discontinued because of their side effects of nausea and diarrhea.[59] Topiramate is an anti-convulsant and aids in preventing the progression from high-frequency episodic migraines into chronic migraines.

Topiramate is the most controversial because of the adverse effects of bothersome taste perversion, paresthesia, and fatigue leading to withdrawal.[60] Valproic acid is also an anticonvulsant and has shown great relief of symptoms in the ED for many patients, side effects included nausea, vomiting, diarrhea, and teratogenicity.[61] All approved drugs were better than placebo in reducing monthly migraine frequency by more than 50% in individual patients.[59] Antiemetics are used to diminish signals to the chemoreceptor trigger zone in the brain that is often activated during migraine headaches and causes nausea and vomiting.

INTRODUCTION TO AB TREATMENT FOR MIGRAINES

Antibiotics are not considered a traditional treatment for migraine headaches currently. There have been reports linking migraines secondary to H. pylori infections. Like migraines, *H. pylori* infections are believed to cause chronic inflammation and are associated with vasoconstriction of vasculature throughout the body. In these specific journals, it is reported that patients infected with *H. pylori* commonly have migraine headaches as a symptom of the infection. When these patients were treated with the appropriate antibiotics for the *H.pylori* infection, the infection and subsequent migraine dissipated and eventually resolved. This journal shows evidence that migraine headaches are multifactorial in nature and that bacteria such as H. pylori can be a cause of this neurological disorder and therefore treated with antibiotics.[62]

ZAVEGEPANT

Zavegepant (BHV-3500) is a novel pharmaceutical being studied for the purpose of treating migraine headaches. It works through its mechanism as a calcitonin gene-related peptide (CGRP) receptor antagonist.

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide that has two forms (α and β). It acts on receptors that contain a calcitonin receptor-like receptor (CLR) linked to an activity modifying protein (RAMP). CGRP is released from sensory nerves and naturally acts as a strong vasodilator. This neuropeptide is important for wound healing and cardiovascular physiology due to its vasodilatory properties. Because of these properties, CGRP is involved in pain pathways.[63] In regard to migraines, CGRP specifically innervates pain-producing meningeal blood vessels and is released by trigeminal nerve stimulation.[64] CGRP receptors are expressed centrally and peripherally throughout the nervous system.[56] Studies have shown that this peptide is unable to cross the blood-brain barrier and therefore acts peripherally on the nervous system.[64] This characteristic of CGRP indicates to researchers that some of the pain produced by a migraine headache is peripheral. Antagonist to these receptors increases inhibitory mechanisms to desensitize neuronal circuits.[56] These discoveries led to the development of a peripherally acting drug that could modulate CGRP to act abortively and prophylactically.[64]

CGRP antagonists have been used in studies with mice to show pain relief during migraine induced headaches. The trial began with dural application of capsaicin along with a mixture of inflammatory mediators (IScap). This application simulated the induction of a migraine headache episode. This application caused pain to the mice that was seen through intermittent head directed wiping and

scratching as well as the phosphorylation of c-Jun N-terminal kinase in trigeminal ganglion neurons. Dural application of CGRP(8-37), the calcitonin gene-related peptide (CGRP) receptor antagonist, was applied and proved to block the inflammatory mediators (IScap). This animal trial discovered that, "the release of endogenous CGRP in the dura is necessary for IScap-induced nociception" and correlated the behavior in mice to be related to headaches in humans.[65] This is one of the multiple studies that have linked CGRP and migraines.

Due to the mechanisms mentioned, CGRP antagonists have begun to be used in therapy for migraine headaches.[63] Compared with traditional treatment for acute migraines, CGRP antagonists have shown in trials to have better outcomes with pain. Multiple studies have shown that compared to the placebo, there has been significant improvement in patients being pain free within 2 hours of the initial attack. These same patients have remained free of pain for 24 hours following the attack. It has also been shown to eliminate the symptoms of photophobia, phonophobia, and nausea at 2 hours following CGRP antagonism dosage compared with the placebo. However, CGRP antagonists were shown to be no more superior than serotonin agonists.[66] Using serum markers such as CGRP is helpful in discovering new pathways to diagnosing and treating migraines. There are other markers that change during migraine headaches and are being used to describe and diagnose types of migraine, tension-type headache, cluster headache, trigeminal neuralgia, and medication-overuse headache. These tests are helping us uncover some of the mysteries of the pathways of headaches.[67]

As previously stated, Zavegepant is a calcitonin gene-related peptide (CGRP) receptor, antagonist. It is administered through various routes depending on the need of the patient; these routes include nasal (rapid onset of action), subcutaneous, inhalation, or oral. It is a third-generation drug that is small in size and highly soluble. It is the first CGRP receptor antagonist that can be administered intranasally. There have been no systemic toxicity or cardiovascular implications in preclinical testing. According to Biohaven (the pharmaceutical producer of Zavegepant), "it's achieved targeted therapeutic exposures with significantly earlier time to maximal concentration (T_{max}) than those observed with other small molecule CGRP receptor antagonists. The efficacy and safety of Zavegepant for the acute treatment of migraine, as compared to placebo, was demonstrated in a Phase 2/3 dose-ranging trial with a total of over 1000 patients who received Zavegepant. Zavegepant 10 and 20 mg was statistically superior to placebo on the co-primary endpoints of pain freedom and freedom from the MBS at two hours post-dose".[68] This drug was FDA approved in February 2020 for the acute treatment of migraine in adult patients and is the only drug that offers an intranasal route of administration. It was recently found as successful at the end of Phase 2 and is now advancing to Phase 3 trials. Studies have shown that Zavegepant was statistically better than the placebo at terminating migraine pain within two hours of an attack. It also relieved the symptoms of nausea, photophobia, and phonophobia.[68] Aside from it being the only drug used intranasally, it also has an improved oral bioavailability. It achieves this improved oral bioavailability through its mechanism of decreasing the number of rotatable bonds via a series of azepinones. Through this research, compound 21 was discovered which according to studies, "maintain high affinity binding and in vivo efficacy in ... facial blood flow assay, while greatly improving oral bioavailability".[69]

Another form of CGRP therapy is also being studied currently. Monoclonal antibodies (mAbs) targeting the calcitonin-gene-related peptide (CGRP) pathway have also begun to be developed for episodic and chronic migraine prevention. These therapy work either through binding the CGRP ligand (eptinezumab, fremanezumab, galcanezumab) or the CGRP receptor (erenumab).[70] This is used subcutaneously to neutralize circulating CGRP or block CGRP receptors. This type of patient-based medicine could be the way of migraine treatment in the future as they are not currently approved for clinical use. These may be given additional therapeutic options for migraine patients in the in time to come.[64]

Aside from the work with acute migraine headaches, the FDA recently approved Biohaven to initiate a Phase 2 study of Zavegepant for the treatment of COVID-19 infection-associated pulmonary complications. According to Biohaven pharmaceuticals, "the Phase 2 study, will assess the potential benefits of CGRP receptor-blockade in mitigating an excessive immune response which in some cases can be fatal in COVID-19".[68]

CGRP AS A TARGET: MECHANISM OF ACTION

Calcitonin gene-related peptide (CGRP) as previously stated is a 37 amino acid neuropeptide that has two forms, α, and β.[63] The alpha form predominates in the trigeminal ganglion. It contains both a N-terminal disulfide bond and an amidated C-terminus, both moieties are necessary for receptor-substrate interaction. The CGRP receptor is a G protein-coupled receptor. The receptor has three parts: calcitonin-like receptor, receptor activity modifying protein 1, and receptor component protein.[71] The calcitonin-like receptor is a seven-transmembrane receptor that is linked to an activity modifying protein (RAMP).[63] The receptor activity modifying protein 1 is essential for coupling the calcitonin-like receptor with CGRP and for transporting the calcitonin-like receptor to the plasma membrane. The receptor component protein is responsible for the interaction between the receptor and the G protein. Once the G protein is activated, it is able to start the secondary messenger system cascade. It works through activating adenylate cyclase causing a cAMP dependent signaling pathway. When cAMP is activated, gene expression is enabled. CGRP is expressed within the trigeminal ganglia and alters the plasma membrane receptor and ion channel activity.[71] The trigeminal ganglia are central to headache pathophysiology. Initially it was thought that migraines were strictly due to vasoconstriction, which was the reason for therapy such as triptans and ergotamines. Through extensive research, there is now evidence to support that claim that migraines are vas-

cular, but also have a component within the core circuits of the brain. The most prominent parts of the brain in migraine pathophysiology are the trigeminal ganglia, trigeminal nucleus, medulla, pons, periaqueductal gray matter, hypothalamus, and thalamus. A disturbance to any of these circuits can result in modulation to sensory activity and therefore cause a migraine headache.[10] CGRP that is released from trigeminal ganglia forms C-fibers and CGRP receptors form A-fibers. CGRP is released into cranial venous flow during headaches. This has been proven because CGRP given intravenously can cause migraine symptoms.[72] CGRP is released from sensory nerves and naturally acts as a strong vasodilator.[63] In regard to migraines, CGRP specifically innervates pain-producing meningeal blood vessels and is released by trigeminal nerve stimulation.[64] CGRP receptors are expressed centrally and peripherally throughout the nervous system.[56] CGRP levels have been shown to be increased during migraine attacks extracranially, specifically in the jugular venous blood. These levels often remain elevated through the postdrome period in episodic and chronic migraine patients.[71] In regards to how to target treatment for migraine headaches, therapy now aims at neutralizing CGRP. CGRP antagonists, "... site of action in migraine prevention is most likely peripheral due to large molecule size, which prevents the penetration through the blood-brain barrier and thereby shows that peripheral components play a pivotal role in the pathophysiology of a CNS disease".[73]

Due to these characteristics, CGRP antagonists and CGRP monoclonal antibodies have begun to be used in the treatment of acute migraines in adults. Through different trials and comparative measures, CGRP antagonists were shown to be more effective compared to placebos for reducing pain in acute migraines. They were, however, not more efficient than first line treatment, triptans. CGRP antagonists should be considered in cases when patients have failed first line treatments or when the patients have comorbities that include cardiovascular disease.[74] CGRP antagonists have improved solubility, oxidative stability, and toxicological profile compared with other migraine therapies. Recent discovery of products such as Zavegepant have opened the door for different routes of administration such as intranasally, which allows for a more rapid onset of action.[75]

The first FDA approved calcitonin gene-related peptide antagonist monoclonal antibody, used in the treatment of acute migraine headaches in adults is erenumab. Erenumab is a human monoclonal antibody that selectively binds to the CGRP receptor. It's mechanism of action is through competitive, reversible inhibition of the receptor. It targets the receptor at high affinities, not the ligand. It has shown complete inhibition of cAMP and therefore, halts gene expression at the level of the trigeminal ganglia. Continued studies have also looked at monoclonal antibodies eptinezumab, galcanezumab, and frestanezumab. These antibodies have proven to neutralize and essentially deactivate both α-CGRP and β-CGRP and the mAb anti-CGRP receptor (erenumab). Since the discovery and success of this mAb, three other monoclonal antibodies have recently undergone clinical trials for the treatment of acute migraine headaches in adults. Eptinezumab is a fully humanized IgG antibody that is used as prophylactic therapy in episodic migraines patients. It uses yeast (*Pichia pastoris*) and therefore has side effects that can include upper respiratory infections, urinary tract infections, fatigue and back pain. Galcanezumab is a fully humanized monoclonal antibody against CGRP also used in treatment for episodic migraine headaches. Galcanezumab has the added advantage of having less frequent adverse side effects. Frestanezumab is a genetically engineered humanized monoclonal antibody used in high frequency, episodic migraine headache treatment. Most of its adverse side effects include upper respiratory infections and bronchitis.[76] Monoclonal antibodies have the increased risk of hepatotoxicity and drug-drug interactions due to their elimination via proteolytic degradation, not hepatic, biliary or through renal mechanisms.[71] Another downfall of these therapies are their high cost because of the high cost of biologics.[77] According to research, these four types of monoclonal antibodies, "the mean decrease in migraine days per month was between 3.4 and 6.3 days/month after 8 to 12 weeks of treatment, and the placebo subtracted benefit ranged from 1 to 2.18 days. Notably, up to 32% of subjects experienced total migraine freedom after drug administration".[73] A 2019 study also showed that none of these antibodies had adverse impacts cardiovascularly or immunologically. Currently, migraine therapy indicates the use of monoclonal antibodies after the failure of two standard oral treatments, but the data emerging from these studies indicates the effectiveness of these treatments and believes they should be considered for first-line therapies in the future. They have not shown improved efficacy in comparison to traditional treatments, but they have shown increased safety and tolerability.[78] These medications have also been approved to be effective in patients with comorbid anxiety and depression.[77]

PHARMACOKINETICS & PHARMACODYNAMICS

Pharmacokinetic and pharmacodynamic data for intranasal Zavegepant is limited at this time. The compound is a full competitive antagonist of the CGRP receptor, and binded to the human CGRP receptor endogenously expressed in SK-N-MC cell membranes with a mean Ki of 23+/- 2pM and displayed over 10,000 fold selectivity for CGRP compared to adrenomedullin receptors 1 and 2, calcitonin, and amylin receptors 1 and 3. It demonstrated potent, full reversal of CGRP-induced dilation of ex vivo human intracranial arteries (EC50 = 880 +/- 50 pM). It didn't show constriction of ex vivo human coronary artery up to 10μM, compared to sumatriptan which does show concentration dependent constriction. In marmoset facial blood flow testing, 0.03mg/kg SC produced strong inhibition of CGRP-induced increases in facial blood flow at 15 (48%), 60 (80%), and 105 (75%) minutes. In vitro rat models were well tolerated and showed low potential for hepatic, cardiovascular, or genotoxic adverse effect. Zavegepant showed low oral bioavailability in monkey (F=0.3%), mouse (F=1.4%), and rat (F=1.7%) models, but showed rapid intranasal ab-

sorption in a rabbit model with Tmax 15-20 minutes at all doses. It also had a low probability of CYP-related drug interactions based on IC50 compared to several CYPs.[69,75,79]

The preliminary pharmacokinetic profile from the Zavegepant Phase 1 clinical trial indicated that Zavegepant achieved targeted therapeutic exposures with significantly earlier Tmax than observed with other small molecule CGRP receptor antagonists.[68]

SAFETY & EFFICACY

In the randomized, dose ranging, placebo-controlled Phase 2/3 clinical trial, the efficacy and tolerability of intranasal Zavegepant in 5, 10, and 20 mg doses compared to placebo was evaluated in 1,673 patients. The coprimary endpoints were 2-hour freedom from pain and freedom from the most bothersome symptom (MBS) of the migraine, which were either nausea, photophobia, or phonophobia, using a single dose. The 5mg dose was not statistically significant [n = 387, pain freedom 19.6%, p: 0.1214; freedom from MBS 39%, p: 0.1162]. The 10mg dose [n = 391, pain freedom 22.5%, p: 0.0113; freedom from MBS 41.9%, p: 0.0155] and the 20mg dose [n = 402, pain freedom 23.1%, p: 0.0055; freedom from MBS 42.5%, p: 0.0094] were both statistically superior compared to placebo [n = 401, pain freedom 15.5%; freedom from MBS 33.7%]. These benefits were sustained without the rescue medication requirement for 48 hours (nominal p>0.05). This included sustained pain freedom 2 to 24 hours (5, 10, 20mg doses), sustained pain relief 2 to 48 hours (5, 10, and 20mg doses), and sustained pain relief 2 to 24 hours (5, 10, 20mg), and sustained pain relief 2 to 48 hours (5, 10mg). There was evidence of the rapid onset of pain relief as early as 15 minutes and return to normal function at 30 minutes. Adverse events included dysgeusia (13.5 to 16.1% in treatment arms and 3.5% in placebo), and nasal discomfort (1.3 to 5.2% in treatment arms and 0.2% in placebo arm). Over 80% of adverse events were mild in intensity. No study participants had hepatotoxicity, defined as aspartate aminotransferase or alanine aminotransferase greater than three times the upper limit of normal or total bilirubin greater than two times the upper limit of normal.[80,81]

A long-term Phase 2/3 safety study of Zavegepant for the acute treatment of migraine using 10mg intranasal up to 8 times per month, for up to 1 year is currently in progress with an actual enrollment of 608 participants and an estimated study completion date in January 2022. Inclusion criteria include adults with 2-8 moderate to severe migraines per month within the last three months lasting on average 4-72 hours if untreated, migraine attacks present for more than 1 year with the age of onset prior to 50 years of age, less than 15 days with headaches per month in each of the three months prior to the screening visit, and ability to distinguish migraine attacks from tension/cluster headaches. Exclusion criteria include history of HIV disease, basilar or hemiplegic migraine, nasal surgery in 6 months preceding the screening visit, gallstones of cholecystectomy, gastric or small intestinal surgery, BMI ⩾33, HgA1c ⩾6.5%, and current diagnosis of certain psychiatric conditions.[82]

CONCLUSION

Migraine headaches are a complex neurobiological disorder causing significant detriment to quality of life to approximately 15% of adults each year. Many migraine sufferers have decreased functionality during episodes, missing work and school, and ultimately leading to greater financial burden to the patient and the healthcare system.[83] Traditional treatment options for migraines include non-specific analgesics such as NSAIDs or acetaminophen +/- caffeine supplementation for mild to moderate migraines. For moderate to severe migraines, traditional herapies include triptans and ergot alkaloids, as well as ditans as a newer drug class. Prophylactic medications include amitriptyline, valproate, topiramate, and propranolol.[84]

A new class of medications for the treatment of migraines acts on the CGRP receptor. CGRP is released from sensory nerves and is a potent vasodilator, giving it a key role in wound healing and cardiovascular physiology. CGRP cannot cross the blood-brain barrier, and when its release is induced by trigeminal nerve stimulation, it causes meningeal blood vessels vasodilation, which can lead to pain. CGRP receptor antagonists inhibit this peripherally acting pathway and cause neuronal circuit desensitization, improving symptoms of migraine headaches.[4,85] Monoclonal antibodies targeting the CGRP receptor, including erenumab, fremanezumab, and galcanezumab, have already received FDA approval for the prevention of episodic migraines.[86]

Zavegepant is a novel third-generation, high affinity, selective small molecule CGRP receptor antagonist that makes it potentially a candidate for nasal, subcutaneous, inhalational, or oral routes of delivery.[68] Recently released Phase 2/3 clinical trial data on the safety and efficacy of one time intranasal 5mg, 10mg, and 20mg Zavegapant dosing indicate that the 10mg and 20mg doses are significantly more efficacious than placebo in the coprimary endpoints of 2-hour freedom from pain and freedom from most bothersome symptom. The time of onset was as early as 15 minutes. The safety profile included no hepatotoxicity and relatively mild adverse events including dysgeusia and nasal discomfort. A Phase 2/3 trial studying the long-term safety of 10mg intranasal doses of Zavegepant up to 8 times per month, up to 1 year, is currently in progress.[80,82]

CGRP-receptor antagonists are a new and promising drug class that has shown efficacy in treating migraine pain and has great potential to improve the quality of life for patients. Trials are still pending to analyze the safety and efficacy of Zavegepant, a novel intranasal third-generation CGRP receptor antagonist. Afterward, further studies should be conducted to establish the efficacy and adverse effects of Zavegepant's intranasal application in comparison to the oral route of delivery of earlier generation direct CGRP receptor antagonists, to the anti-CGRP monoclonal antibody drug class, and to traditional treatment options for migraine headaches.

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REFERENCES

1. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol Rev*. 2017;97(2):553-622. doi:10.1152/physrev.00034.2015

2. Amin FM, Asghar MS, Hougaard A, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study. *Lancet Neurology*. 2013;12(5):454-461. doi:10.1016/s1474-4422(13)70067-x

3. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. *J Headache Pain*. 2019;20(1). doi:10.1186/s10194-019-1066-0

4. 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

5. Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive Pharmacologic Treatments for Episodic Migraine in Adults. *J Gen Intern Med*. 2013;28(9):1225-1237. doi:10.1007/s11606-013-2433-1

6. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. *Lancet Neurology*. 2010;9(3):285-298. doi:10.1016/s1474-4422(10)70005-3

7. Evans RW, Linde M. Expert Opinion: Adherence to Prophylactic Migraine Medication. *Headache*. 2009;49(7):1054-1058. doi:10.1111/j.1526-4610.2009.01471.x

8. 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

9. Uddman R, Tajti J, Hou M, Sundler F, Edvinsson L. Neuropeptide Expression in the Human Trigeminal Nucleus Caudalis and in the Cervical Spinal Cord C1 and C2. *Cephalalgia*. 2002;22(2):112-116. doi:10.1046/j.1468-2982.2002.00324.x

10. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol*. 2010;6(10):573-582. doi:10.1038/nrneurol.2010.127

11. 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

12. Miller S, Liu H, Warfvinge K, et al. Immunohistochemical localization of the calcitonin gene-related peptide binding site in the primate trigeminovascular system using functional antagonist antibodies. *Neuroscience*. 2016;328:165-183. doi:10.1016/j.neuroscience.2016.04.046

13. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. *Ann Neurol*. 1988;23(2):193-196. doi:10.1002/ana.410230214

14. Burch RC, Loder S, Loder E, Smitherman TA. The Prevalence and Burden of Migraine and Severe Headache in the United States: Updated Statistics From Government Health Surveillance Studies. *Headache*. 2015;55(1):21-34. doi:10.1111/head.12482

15. Migraine Facts. Migraine Research Foundation.

16. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/s0140-6736(18)32279-7

17. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-349. doi:10.1212/01.wnl.0000252808.97649.21

18. Smitherman TA, Burch R, Sheikh H, Loder E. The Prevalence, Impact, and Treatment of Migraine and Severe Headaches in the United States: A Review of Statistics From National Surveillance Studies. *Headache*. 2013;53(3):427-436. doi:10.1111/head.12074

19. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and Burden of Migraine in the United States: Data From the American Migraine Study II. *Headache*. 2001;41(7):646-657. doi:10.1046/j.1526-4610.2001.041007646.x

20. Lipton RB, Bigal ME. Migraine: Epidemiology, Impact, and Risk Factors for Progression. *Headache*. 2005;45(s1):S3-S13. doi:10.1111/j.1526-4610.2005.4501001.x

21. Jiménez-Trujillo I, López-de-Andrés A, del Barrio JL, Hernández-Barrera V, Valero-de-Bernabé M, Jiménez-García R. Gender Differences in the Prevalence and Characteristics of Pain in Spain: Report from a Population-Based Study. *Pain Med*. 2019;20(12):2349-2359. doi:10.1093/pm/pnz004

22. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. *J Pain*. 2009;10(5):447-485. doi:10.1016/j.jpain.2008.12.001

23. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB. Cumulative Lifetime Migraine Incidence in Women and Men. *Cephalalgia*. 2008;28(11):1170-1178. doi:10.1111/j.1468-2982.2008.01666.x

24. Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and Indirect Healthcare Resource Utilization and Costs Among Migraine Patients in the United States. *Headache*. 2018;58(5):700-714. doi:10.1111/head.13275

25. Lantéri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. *Cephalalgia*. 2011;31(7):837-850. doi:10.1177/0333102411398400

26. Mitsikostas DD, Thomas AM. Comorbidity of Headache and Depressive Disorders. *Cephalalgia*. 1999;19(4):211-217. doi:10.1046/j.1468-2982.1999.019004211.x

27. Buse DC, Scher AI, Dodick DW, et al. Impact of Migraine on the Family: Perspectives of People With Migraine and Their Spouse/Domestic Partner in the CaMEO Study. *Mayo Clin Proc*. 2016;91(5):596-611. doi:10.1016/j.mayocp.2016.02.013

28. Tolner EA, Houben T, Terwindt GM, de Vries B, Ferrari MD, van den Maagdenberg AMJM. From migraine genes to mechanisms. *Pain*. 2015;156(Supplement 1):S64-S74. doi:10.1097/01.j.pain.0000460346.00213.16

29. Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. *BMJ*. 1995;311(7004):541-544. doi:10.1136/bmj.311.7004.541

30. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurology*. 2017;16(1):76-87. doi:10.1016/s1474-4422(16)30293-9

31. Kruit MC. Migraine as a Risk Factor for Subclinical Brain Lesions. *JAMA*. 2004;291(4):427. doi:10.1001/jama.291.4.427

32. Scher IA, Stewart FW, Ricci AJ, Lipton BR. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. 2003;106(1):81-89. doi:10.1016/s0304-3959(03)00293-8

33. Katsarava Z, Schneeweiss S, Kurth T, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology*. 2004;62(5):788-790. doi:10.1212/01.wnl.0000113747.18760.d2

34. Couch JR, Bearss C. Chronic Daily Headache in the Posttrauma Syndrome: Relation to Extent of Head Injury. *Headache*. 2001;41(6):559-564. doi:10.1046/j.1526-4610.2001.041006559.x

35. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann Neurol*. 2000;47(5). doi:10.1002/1531-8249(200005)47:5<614::AID-ANA9>3.0.CO;2-N

36. Yarnitsky D, Goor-Aryeh I, Bajwa ZH, et al. 2003 Wolff Award: Possible Parasympathetic Contributions to Peripheral and Central Sensitization During Migraine. *Headache*. 2003;43(7):704-714. doi:10.1046/j.1526-4610.2003.03127.x

37. Pavlovic JM, Buse DC, Sollars CM, Haut S, Lipton RB. Trigger Factors and Premonitory Features of Migraine Attacks: Summary of Studies. *Headache*. 2014;54(10):1670-1679. doi:10.1111/head.12468

38. Kelman L. The Triggers or Precipitants of the Acute Migraine Attack. *Cephalalgia*. 2007;27(5):394-402. doi:10.1111/j.1468-2982.2007.01303.x

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

40. Borkum JM. Migraine Triggers and Oxidative Stress: A Narrative Review and Synthesis. *Headache*. 2016;56(1):12-35. doi:10.1111/head.12725

41. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202

42. Kelman L. The Premonitory Symptoms (Prodrome): A Tertiary Care Study of 893 Migraineurs. *Headache*. 2004;44(9):865-872. doi:10.1111/j.1526-4610.2004.04168.x

43. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The Prevalence of Premonitory Symptoms in Migraine: A Questionnaire Study in 461 Patients. *Cephalalgia*. 2006;26(10):1209-1213. doi:10.1111/j.1468-2982.2006.01195.x

44. 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

45. 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). doi:10.1186/s10194-015-0495-7

46. Karsan N, Goadsby PJ. Biological insights from the premonitory symptoms of migraine. *Nat Rev Neurol*. 2018;14(12):699-710. doi:10.1038/s41582-018-0098-4

47. Karsan N, Goadsby PJ. Imaging the Premonitory Phase of Migraine. *Front Neurol*. 2020;11. doi:10.3389/fneur.2020.00140

48. Evans RW. Diagnostic Testing for Migraine and Other Primary Headaches. *Neurol Clin*. 2019;37(4):707-725. doi:10.1016/j.ncl.2019.08.001

49. 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. doi:10.1111/j.1526-4610.2006.00631.x

50. Viana M, Sances G, Terrazzino S, Sprenger T, Nappi G, Tassorelli C. When cervical pain is actually migraine: an observational study in 207 patients. *Cephalalgia*. 2018;38(2):383-388. doi:10.1177/0333102416683917

51. Goadsby PJ, Holland PR. Pathophysiology of Migraine. *Neurol Clin*. 2019;37(4):651-671. doi:10.1016/j.ncl.2019.07.008

52. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990;28(2):183-187. doi:10.1002/ana.410280213

53. van Dongen RM, Zielman R, Noga M, et al. Migraine biomarkers in cerebrospinal fluid: a systematic review and meta-analysis. *Cephalalgia*. 2017;37(1):49-63. doi:10.1177/0333102415625614

54. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. *Neurol Sci*. 2017;38(S1):125-130. doi:10.1007/s10072-017-2866-0

55. Gazerani P. Migraine and Diet. *Nutrients*. 2020;12(6):1658. doi:10.3390/nu12061658

56. 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

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

58. Rizzoli P. Preventive Pharmacotherapy in Migraine. *Headache*. 2014;54(2):364-369. doi:10.1111/head.12273

59. Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive Pharmacologic Treatments for Episodic Migraine in Adults. *J Gen Intern Med*. 2013;28(9):1225-1237. doi:10.1007/s11606-013-2433-1

60. Silberstein SD. Topiramate in Migraine Prevention: A 2016 Perspective. *Headache*. 2017;57(1):165-178. doi:10.1111/head.12997

61. Brown BL, Craycraft LK, Justice SB. Valproic Acid in the Treatment of Migraines. *Adv Emerg Nurs J*. 2020;42(4):243-253. doi:10.1097/tme.0000000000000319

62. Hosseinzadeh M, Khosravi A, Saki K, Ranjbar R. Evaluation of Helicobacter pylori infection in patients with common migraine headache. *Arch Med Sci*. 2011;5:844-849. doi:10.5114/aoms.2011.25560

63. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin Gene-Related Peptide: Physiology and Pathophysiology. *Physiol Rev*. 2014;94(4):1099-1142. doi:10.1152/physrev.00034.2013

64. Hargreaves R, Olesen J. Calcitonin Gene-Related Peptide Modulators – The History and Renaissance of a New Migraine Drug Class. *Headache*. 2019;59(6):951-970. doi:10.1111/head.13510

65. Huang D, Ren L, Qiu CS, et al. Characterization of a mouse model of headache. *Pain*. 2016;157(8):1744-1760. doi:10.1097/j.pain.0000000000000578

66. Hong P, Liu Y. Calcitonin gene-related peptide antagonism for acute treatment of migraine: a meta-analysis. *Int J Neurosci*. 2017;127(1):20-27. doi:10.3109/00207454.2015.1137915

67. Schytz HW, Olesen J. Laboratory tests of headache disorders – dawn of a new era? *Cephalalgia*. 2016;36(13):1268-1290. doi:10.1177/0333102415612585

68. Biohaven Pharmaceuticals. *Zavegepnt*.

69. Mercer SE, Chaturvedula PV, Conway CM, et al. Azepino-indazoles as calcitonin gene-related peptide (CGRP) receptor antagonists. *Bioorg Med Chem Lett*. 2021;31:127624. doi:10.1016/j.bmcl.2020.127624

70. 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

71. Urits I, Jones MR, Gress K, et al. CGRP Antagonists for the Treatment of Chronic Migraines: a Comprehensive Review. *Curr Pain Headache Rep*. 2019;23(5). doi:10.1007/s11916-019-0768-y

72. Edvinsson L. The Trigeminovascular Pathway: Role of CGRP and CGRP Receptors in Migraine. *Headache*. 2017;57:47-55. doi:10.1111/head.13081

73. 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

74. Ha DK, Kim MJ, Han N, Kwak JH, Baek IH. Comparative Efficacy of Oral Calcitonin-Gene–Related Peptide Antagonists for the Treatment of Acute Migraine: Updated Meta-analysis. *Clin Drug Investig*. 2021;41(2):119-132. doi:10.1007/s40261-020-00997-1

75. Chaturvedula PV, Mercer SE, Pin SS, et al. Discovery of (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BMS-742413): a potent human CGRP antagonist with superior safety profile for the treatment of migraine through intranasal delivery. *Bioorg Med Chem Lett*. 2013;23(11):3157-3161. doi:10.1016/j.bmcl.2013.04.012

76. Pellesi L, Guerzoni S, Pini LA. Spotlight on Anti-CGRP Monoclonal Antibodies in Migraine: The Clinical Evidence to Date. *Clin Pharmacol Drug Dev*. 2017;6(6):534-547. doi:10.1002/cpdd.345

77. Raffaelli B, Neeb L, Reuter U. Monoclonal antibodies for the prevention of migraine. *Expert Opin Biol Ther*. 2019;19(12):1307-1317. doi:10.1080/14712598.2019.1671350

78. Mitsikostas DD, Reuter U. Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: comparisons across randomized controlled studies. *Curr Opin Neurol*. 2017;30(3):272-280. doi:10.1097/wco.0000000000000438

79. Dubowchik GM, Conway CM, Xin AW. Blocking the CGRP Pathway for Acute and Preventive Treatment of Migraine: The Evolution of Success. *J Med Chem*. 2020;63(13):6600-6623. doi:10.1021/acs.jmedchem.9b01810

80. Presse release: Biohaven achieves positive topline results in pivotal phase 2/3 study of vazegepant, the first and only intranasal CGRP receptor antagonist in clinical development for the acute treatment of migraine. Biohaven Pharmaceuticals. Published 2019. Accessed July 16, 2021. https://www.biohavenpharma.com/investors/news-events/press-releases/12-17-2019#:~:text=12%2F17%2F2019-,Biohaven%20Achieves%20Positive%20Topline%20Results%20in%20Pivotal%20Phase%202%2F3,unique%2C%20small%20molecule%20CGRP%20receptor

81. Moreno-Ajona D, Pérez-Rodríguez A, Goadsby PJ. Small-molecule CGRP receptor antagonists: a new approach to the acute and preventive treatment of migraine. *Med Drug Discov*. 2020;7:100053. doi:10.1016/j.medidd.2020.100053

82. Long-term Safety Study of BHV-3500 (Zavegepant*) for the Acute Treatment of Migraine. ClinicalTrials.gov. Published 2021. Accessed August 1, 2021. https://clinicaltrials.gov/ct2/show/record/NCT04408794

83. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin*. 2019;37(4):631-649. doi:10.1016/j.ncl.2019.06.001

84. Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive pharmacologic treatments for episodic migraine in adults. *J Gen Intern Med*. 2013;28(9):1225-1237. doi:10.1007/s11606-013-2433-1

85. 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

86. 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. doi:10.1111/head.13583