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Emerging Therapies and Preventive Treatments for Migraine

A migraine is often perceived as "just a bad headache." However, to those suffering from this disabling neurologic disease, it is an incapacitating and chronic illness.[1,2] Viewed as a hereditary disease that disproportionately affects females, migraines often begin in childhood. Puberty is a common trigger for their onset, and the frequency only increases with age.[1] Characterized as a throbbing headache, there are often accompanying sensory abnormalities, the most notable of which is an aversion to light.[3] According to the Migraine Research Foundation, migraines make up the third most prevalent disease in the world, affecting 1 billion people worldwide; in the United States, they affect 18% of women, 6% of men, and 10% of children.[1] In 2013, the World Health Organization updated the ranking of migraine among other conditions in the gloal burden of disease, placing it at the No. 6 spot for years lost to disability worldwide.[4] It is estimated that nearly 90% of migraine sufferers experience moderate to severe pain during an attack and 75% of suffers have a reduced ability to function normally during their attack.[5]

PATHOPHYSIOLOGY

Despite a growing amount of research, the underlying mechanisms that trigger and propagate the migraine cycle are not well understood. It is well known that migraine attacks are associated with triggers , which include stress, hormonal fluctuations, sleep disturbances, skipping meals, and sensory overload; however, the neural and vascular pathophysiology of a migraine is not well understood.[6] As such, the pathophysiology behind migraines is a highly debated topic. One theory for the origin of a migraine headache is that it is a vascular disorder and focuses on the dilation of blood vessels as the root cause during an attack.[6] However, newer evidence suggests the involvement of underlying mechanisms of the trigeminovascular system.[6] In this model, a migraine headache is thought to occur when meningeal pain networks are activated by signals emanating from the trigeminovascular system.[7] The cortex, brainstem, trigeminal nerve, meninges, and hypothalamus are also thought to play a role in migraine pathophysiology.[3] The hypothalamus is of particular interest for its role in maintaining homeostasis. While it not known whether the disease itself causes alterations in brain structure and function or if there is a genetic component, the brain of a migraine sufferer has abnormalities and differences from that of a person who does not experience migraines. It is believed that these abnormalities result in a greater sensitivity to changes in the neurochemical balance maintained within the brain, along with a decreased ability to adapt to fluctuations, which ultimately lead to repeated attacks.[7] Evidence suggests that repeated headaches are involved in the progression of disease and are linked to changes in brain anatomy and function.[7]

ROLE OF CALCITONIN GENE-RELATED PEPTIDE

Advancements in migraine research over the past few decades have led researchers to identify the possible role of calcitonin gene-related peptide (CGRP) in migraine pathophysiology. CGRP is a neuropeptide and a potent dilator of both peripheral and cerebral blood vessels.[3,8] Its effects vary widely; however, where migraines are concerned, it is most notably involved in the regulation of the cardiovascular

system, the modulation of nociceptive receptors and blood vessels, pain signaling, vasodilation, and mediation of neurogenic inflammation.[8,9] Early evidence implicating CGRP in migraine came from groundbreaking research in 1990, which demonstrated a rise in CGRP levels in jugular outflow during attacks. Elevated serum and saliva levels of CGRP have also been reported in spontaneous and induced migraines. Additionally, it has been noted that when a migraine is treated with 5-hydroxytryptamine receptor 1B/D agonists, commonly referred to as triptans, there was either a reduction of CGRP or pain relief.

Despite a mounting body of evidence, the significance of increased blood levels of CGRP remains controversial due to 1 well-controlled trial that failed to demonstrate elevations during migraine.[9] However, compelling evidence points to an increased sensitivity to CGRP in patients who experience migraines. Researchers came to this conclusion based on a study of CGRP injections in both healthy individuals and those who suffer from migraines. Between 57% and 75% of the migraine study group experienced a delayed migraine-like headache, while similar effects were not seen in the healthy group.[8] Despite having vasodilatory effects similar to those of nitroglycerin and pituitary adenylate cyclase-activating polypeptide, which are both used to induce delayed migraine-like headaches, CGRP is not considered to be within a class of vasodilators.[3] This is evidenced by other strong cerebral vasodilators, such as vasoactive intestinal peptide, which do not result in migraine induction. However, although the mechanism of action of CGRP in migraine induction involves more than just vasodilation, vasodilation still occurs at some level during an episode and therefore its role in migraine propagation remains controversial.[3]

Given this line of evidence, it is not surprising that there have been multiple attempts to develop pharmacologic agents directed at decreasing CGRP levels or blocking CGRP receptors. There have been 6 CGRP receptor antagonists researched and tested, and other agents are in development.[9] Although the actual site of action of this class is unknown, it is thought that CGRP receptor antagonists act on the central nervous system (CNS). Despite the fact that many drugs do not cross over well into the CNS because of the blood-brain barrier, it is likely that small amounts can penetrate the CNS to act centrally. However, the efficacy of CGRP-blocking antibody therapy, which acts in the periphery, in clinical trials suggests that CGRP has a peripheral site of action as well.[9]

Olcegepant, an intravenous drug formulation, was the first of the CGRP receptor antagonists studied. Results of a study showed a 66% response rate in reducing headache. Olcegepant at a dose of 2.5 mg was also successful at reducing nausea and sensitivity to light and sound.[9]

In 2007, telcagepant, an orally bioavailable drug, was developed and studied in multiple clinical trials, including in head-to-head trials against triptans. One of those trials was a large phase 3 study that evaluated telcagepant against zolmitriptan and placebo. Telcagepant was found to have a similar efficacy to triptans, with an adverse effect (AE) profile consistent with the placebo. In another long-term study, telcagepant was found to have fewer AEs than rizatriptan. However, development was halted in 2011 after increased liver enzymes were detected in 2 patients in a phase 2 study evaluating the prophylactic use of telcagepant. Additionally, 4 other CGRP antagonists (MK-3207, MK-1602, BI44370 TA, BMS-927711) have been studied in phase 2 clinical trials. An additional 2 drugs have been developed with better pharmacokinetic and pharmacodynamic properties, but they have not been tested clinically. The current CGRP antagonist pipeline appears to be at a standstill.[9]

CLASSIFICATION

Migraine headache episodes can have serious and debilitating effects on a patient, which include a pulsating headache of moderate to severe pain intensity accompanied by nausea and/or vomiting and photophobia or phonophobia. The episodes may be aggravated by movement, such as walking or climbing stairs, which may lead to the avoidance of these activities during an episode.[3,10]

A migraine can be categorized based on its frequency of occurrence. An episodic migraine (EM) occurs when a patient with a migraine has fewer than 15 headache days per month.[11,12] Conversely, very frequent attacks are characterized as chronic migraine (CM) headaches. The International Classification of Headache Disorders (ICHD-II) system defines CM as headaches that occur 15 or more days per month for more than 3 months. These headaches must have the features of a migraine headache for at least 8 days of the month to be considered a CM.[10]

In population-based studies, the prevalence of CMs in the global population has been shown to be between 1.4% and 2.2%.[11] However, using data from the American Migraine Prevalence and Prevention (AMPP) study, the United States was at 0.91%, with a higher prevalence in females (1.29% vs 0.48% of males).[11]

A CM is categorized as a complication of an EM. In patients with EMs, 2.5% per year will progress to CMs.[13] Evidence suggests that an increase in the frequency of EM headaches and the repetitive state of headaches can lead to progression.[7] Excessive symptomatic medication use has also been proposed as a theory to explain the transformation to CMs.[13] Reports show that 1.5% of CM sufferers use acute medications more than 10 to 15 days per month.[13] Use of opioids and barbiturates has been associated with an overall increase in risk for progressing to CMs, although the use of nonsteroidal anti-inflammatory drugs (NSAIDs) appears to have a protective effect in some migraine sufferers, albeit only in those who had fewer than 10 to 14 headache days per month.[13]

COMORBIDITIES

Comorbidities associated with EMs have been well documented and include psychiatric disorders, neurological disorders, chronic pain, asthma, and heart disease.[11] In another examination of the differences in the rates of comorbidities between EMs versus CMs, Buse et al found significant differences in a wide range of conditions after adjusting for age, gender, and income (**Table 1**[14]).[11] Individuals with CMs were found to be twice as likely to suffer from anxiety and depression.[14] There was a greater frequency of other comorbidities in patients with CMs compared with patients with EMs.[14] Prior to this study, there was a general lack of evidence contrasting the comorbidities associated

with the 2 classifications. These data support the fact that CMs are more burdensome, with their increased rates of comorbidities, and provide a greater insight into the overall impact and treatment of CMs. The associated increased risk of comorbidities may influence healthcare providers in clinical decision making and therapy with regard to concomitantly treating multiple disease states, optimizing drug therapy, and minimizing AEs.[15]

TREATMENT APPROACHES

There are 2 goals to migraine therapy: shortening or stopping an acute attack, and preventing future attacks to decrease migraine frequency and possible severity.[7,16] Because migraine attacks are best treated with preventive therapy, patients with CMs or EMs are candidates for this type of treatment.[5] Evidence suggests that migraine sufferers in the United States are consistently undertreated, with focus placed on acute treatments rather than preventive measures.

Despite discussion in the US Headache Consortium Guidelines about indications for preventive treatment, prevention therapy largely remains a therapeutic area with many opportunities.[5] As of March 2017, an estimated 32 million adults in the United States have been affected by a migraine; one-third of those meet the criteria for preventive therapy.[17] However, of those 32 million patients, only 3.5 million are currently receiving preventive therapy, further illustrating an existing opportunity to improve care.[17] Proposed rationales for the lack of preventive therapy include low confidence in the contents of clinical guidelines and a lack of provider awareness of the methodology and quality of clinical guidelines.[12] To date, there is no cure; however, improvements in health outcomes and quality of life have been demonstrated through the use of preventive treatments.[12]

Literature recommends preventive migraine therapies for patients who have 4 or more days of migraines per month with at least some impairment.[5] As part of the AMPP study, Lipton et al established guidelines for preventive medication based on migraine frequency and level of impairment during an acute migraine using a panel of 12 physicians specializing in headaches along with leading experts in the field of headache research.[5] In these guidelines, level of impairment was defined as severe impairment, some impairment, and no impairment. This guideline classified patients into 1 of 3 categories: 1) patients who should be offered preventive treatment, 2) patients who should have preventive treatment considered, and 3) patients who do not need preventive treatment (**Table 2**).[5]

No migraine treatments have been developed with prevention in mind. Prevention treatments with the most evidence of established efficacy are anticonvulsants and beta-blockers. Other medications that are considered effective include tricyclic and serotonin and norepinephrine reuptake inhibitor antidepressants (**Table 3**).[12,15]

Hepp et al examined pharmacy claims for 8688 patients with diagnosed CMs from Truven MarketScan Databases in order to assess adherence to oral migraine prophylaxis medications. The proportion of days covered (PDC), a nationally recognized standard for measuring adherence, was 26% to 29% at 6 months, a rate that fell over time. At 12 months, the PDC had declined to 17% to 20%.[18]

Table 1. Comparison of Comorbidities in Chronic versus Episodic Migraine[14]

Condition	CM (%)	EM (%)
Allergies/hay fever	60	51
Anxiety	30	19
Arthritis	34	22
Asthma	24	17
Bipolar disorder	5	3
Bronchitis	19	13
Chronic bronchitis	9	5
Chronic pain	31	15
Circulation problems	17	11
Depression (using Patient Health Questionnaire-9)	30	17
Depression (self-reported physician diagnosis)	41	26
Emphysema or chronic obstructive pulmonary disease	5	3
Heart disease or angina	10	6
High blood pressure	34	28
High cholesterol	34	26
Obesity	26	21
Sinusitis	45	37
Stroke	4	2
Ulcers	15	8

CM indicates chronic migraine; EM, episodic migraine.

Table 2. Criteria for Preventive Treatment[5]

Patient Group	Criteria for Preventive Treatment Recommendation
Prevention should be offered	6 or more headache days per month, 4 or more headache days with at least some impairment, or 3 or more headache days with severe impairment or requiring bed rest.
Prevention should be considered	4 or 5 migraine days per month with normal functioning, 3 migraine days with some impairment, or 2 migraine days with severe impairment.
Prevention not indicated	less than 4 headache days per month and no impairment or no more than 1 headache day per month regardless of the impairment level

In the second International Burden of Migraine Study, Blumenfeld et al evaluated survey responses from 1165 adults with EMs and CMs during 2010. A total of 43.4% of respondents with CMs reported current treatment with a preventive migraine drug, while 65.9% reported current or prior preventive treatment.[19] The number of respondents reporting discontinuation of 1 or more preventive medication was significant, especially when comparing EMs to CMs (24% vs 40.8%,

Table 3. Drugs Established as Effective Migraine Prevention Treatments[12,15]

Established efficacy		
Drug class	**Drug**	**Dose**
Anticonvulsants	divalproex sodium/ sodium valproate	400-1000 mg daily
	topiramate	25-200 mg daily
Beta-blockers	metoprolol	47.5-200 mg daily
	propranolol	120-240 mg daily
	timolol	10-15 mg twice daily
Probably effective		
Drug class	**Drug**	**Dose**
Antidepressants	amitriptyline	25-150 mg daily
	venlafaxine extended release	150 mg daily
Nonsteroidal anti-inflammatories	fenoprofen	200-600 mg 3 times daily
	ibuprofen	200 mg twice daily
	naproxen	500-1100 mg daily
	naproxen sodium	550 mg twice daily
Beta-blockers	atenolol	100 mg daily

respectively).[20] Complete discontinuation, defined as prior preventive therapy use but no current use, was reported by 21.1% and 15.2% of EM and CM respondents, respectively. AE and lack of efficacy were the most common reasons for discontinuing preventive treatment.[20]

Headache accounts for 5 million emergency department (ED) visits per year, with a majority of those visits associated with migraine occurrence. More than 50% of these visits result in treatment with an opioid instead of a migraine-specific medication.[21] A retrospective cohort study using claims from January 2008 to June 2013 from Truven MarketScan Databases found migraine-related ED visits were more common in patients without acute or prophylactic use (29.9%) than patients receiving only acute treatment (13.2%), prevention-only treatment (9.1%), or acute and preventive therapy (11.1%).[22] This study also noted opioid use occurred in almost half of patients with migraines and that these patients had an average supply exceeding 90 days. Annual costs also were higher in patients with migraines who used an opioid (approximately $20,000 vs $70,000, respectively). ED visits and opioid use could be minimized by utilizing appropriate prevention therapy. Data from the 2009 AMPP study showed that of the 5591 patients with EMs, 32% met the ICHD-II criteria for excessive opioid or barbiturate use and may have had opioid dependence.[23]

ECONOMIC BURDEN

As mentioned previously, a majority of headache visits to the ED can be attributed to migraines. Because of this, the healthcare system incurs $700 million in costs each year, or $775 per visit, from migraine-related ED visits.[21]

A retrospective cohort study used Truven MarketScan Databases to compare the incremental direct and indirect costs of patients with migraines versus matched controls between January 2008 and June 2013. Patients with a migraine diagnosis and/or migraine medications who had 12 months of continuous enrollment before and after the day claim dates occurred were included in the analysis, and patients with HIV or cancer during the study period were excluded. Direct costs were defined as costs incurred for inpatient stays, outpatient visits, ED visits, and medication, while indirect costs were defined as costs incurred from absenteeism and short- and long-term disability. Approximately 84,000 patients with migraines were included in the analysis. The researchers reported these patients had significantly higher indirect costs ($11,294 vs $8945) and direct costs ($10,363 vs $4619) compared with matched controls without migraine. In this study, patients suffering from migraines were 2.5 times more likely to have a short-term disability claim compared with matched controls (16.7% vs 6.7%, P <.001) and 2.4 times more likely to have a long-term disability claim. The average short-term disability claim for patients with migraines was over $1000 more expensive than the average claim of those without migraines. The average cost of a long-term disability claim for patients with migraines was $26,543.[24]

Migraine sufferers lose a considerable amount of worktime, which is another notable indirect cost in patients with CMs. Lost productive time (LPT) is a measure that uses both reduced performance at work (presenteeism) and absence from work (absenteeism) to quantify the impact of decreased productivity in the workplace.[25] Studies estimate that 74 to 96 hours of lost work per year per sufferer can be attributed to migraines.[26] Analyses using AMPP data showed that an average of 88.4 hours of work were lost per year per migraine sufferer,[26] and, as expected, an increase in headache days per month was associated with an increase in LPT.[25]

Absence from work is not the primary issue impacting LPT in migraine sufferers, however. Approximately 75% of LPT can be linked to presenteeism.[26] Further analysis of AMPP data in survey respondents evaluated the cost of lost productivity in EM versus CM sufferers. The highest LPT costs were seen in men and women aged 45 to 54 years: approximately $200 more per week for men with CM than for men with EM; for women, costs for CM were $90 more per week than for EM.[25]

SOCIAL BURDEN

Significant impacts on functional and physical impairment can be caused by migraines, with rates of impaired function occurring in more than 90% and reduced work productivity occurring in 50% of all migraine sufferers.[27] Negative impacts on day-to-day life, as well as health-related quality of life, are also observed in patients with migraines, with 61.1% of patients with EMs and 85.2% of patients with CMs experiencing substantial or severe adverse impact from migraine attacks.[11,20] The prevalence of migraine is highest in those aged 30 to 50 years and lowest in those 60 years and over, and women have a disproportionally higher prevalence of migraine than men.[5] Research also indicates Caucasians are more likely to be

affected than African Americans.[5] Regardless of race or sex, the prevalence of migraines is higher in individuals with lower household incomes, which was approximately twice that of migraine sufferers with the highest income studied.[5]

The results of a study utilizing telephonic and mailed questionnaires indicated that 15.8% of participants reported attacks with a duration of less than 4 hours, 6.4% reported attacks lasting longer than 72 hours, and 43% reported recovering completely between episodes. Participants were considered to have migraines from using an algorithm based on the International Headache Society's migraine criteria. Additionally, respondents were considered to have a migraine if recurring headaches were reported with at least 2 of the following features: unilateral pain, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and at least one of the following: nausea and/or vomiting, phonophobia, and photophobia.[28] Respondents were asked to report if a migraine had a very negative influence, quite a negative influence, some negative influence, or no influence on certain aspects of their life, including establishing a career, work attendance, pursuing studies, family situation, and leisure time (**Figure 1**[11]).[28] The questionnaire also asked about missed time from school and work (**Figure 2**).[28]

Figure 1. Impact of Migraine on Certain Aspects of Life[11]

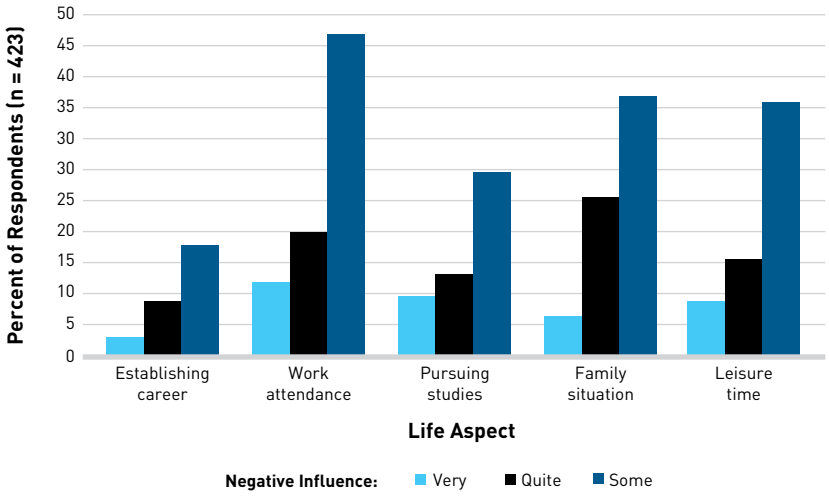
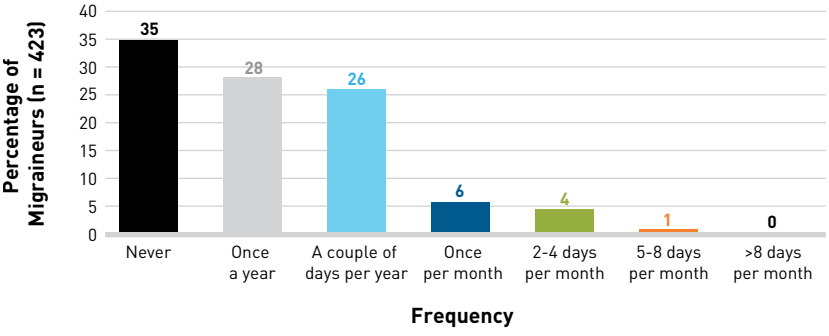


Figure 2. Absenteeism From School or Work as a Result of Migraine[28]



PHASES

While the headache itself has been the most identifiable and the most studied feature of migraines, research has also investigated the phases of migraine generation. The phases that precede the headache include the premonitory or prodrome phase, with or without aura, while the postdrome phase follows the headache.[29] In the past, the phases of a migraine have been viewed as distinct and sequential; however, evidence now suggests that phases represent overlapping chemical, physiological, and anatomical processes.[29]

During the premonitory phase and up to 48 hours prior to the migraine headache, a variety of predictive signs can occur.[10] Common premonitory symptoms include fatigue, mood change, neck stiffness, depression, food cravings, and repetitive yawning.[7] Results from studies utilizing an electronic headache diary suggest that certain patients are able to predict that a headache is going to occur up to 12 hours before its onset due to an awareness of their premonitory symptoms. More than 80% of adults will experience some type of premonitory symptom.[29] In addition, while not all migraine sufferers experience an aura preceding a migraine headache, aura does occur in approximately 25% of migraine sufferers.[1] Symptoms may occur from 5 to 60 minutes prior to the actual headache and can include auditory and visual sensory changes, as well as motor function and somatosensory impacts.[10] Symptoms manifest in a variety of ways, including those of an excitatory or inhibitory nature, that can lead to paresthesia, numbness of the face and hands, speech difficulties, unilateral muscle weakness, and scintillating lights and scotomas.[7] Autonomic, sensory, and cognitive abnormalities traditionally linked to the headache phase have been shown to occur during the aura (**Table 4**[7]).[6,7] The actual migraine headache can last anywhere from 4 hours to 3 days and is characterized by pulsating, unilateral pain that is worsened by routine activities.[7,10] Evidence is contradictory as to whether vasodilation is the cause for the evoked headache, which may merely be as a result of similar mechanisms causing the headache.[29]

After the headache resolves, there is the period known as the postdrome, or recovery, phase, which is defined as lsting from the time when the headache terminates to when the migraine sufferer

Table 4. Symptoms Associated with Migraine[7]

Sensory	Cognitive	Autonomic	Affective
• Photophobia • Phonophobia • Osmophobia • Allodynia	• Transient amnesia • Attention-deficit disorder • Difficulty finding words • Decreased ability to navigate familiar environments	• Yawning • Increased urination • Nausea • Vomiting • Diarrhea • Congestion (nasal/sinus) • Rhinorrhea • Lachrymation	• Irritability • Depression

feels completely normal.[30] One study stated that patients reported symptoms during the postdrome phase that were unrelated to headache and resolved within 6 hours; however, the symptoms can persist for up to 48 hours.[30] There have been fewer studies conducted on the postdrome phase than the prodrome and aura phases.[29] The most commonly reported postdrome symptoms included mood changes, tiredness and weakness, and cognitive difficulties, such as poor concentration. Residual head pain, lightheadedness, and gastrointestinal symptoms have also been reported.[29,30]

While not covered definitively in the ICHD, the postdrome phase can cause significant disability in some patients.[30] The postdrome phase has been thought of as separate and unique in the past; however, it is now viewed as a continuation of symptoms often present in the premonitory phase. One school of thought is that these postdrome symptoms are present throughout the attack, but that their presence is minimized because the headache, nausea, and aura symptoms are more significant. Consequently, when patients receive migraine treatment therapies, they may misperceive the postdrome symptoms as AEs of the migraine treatment.[29] The idea of symptoms beginning in the premonitory phase and persisting throughout the continuum of the migraine is a relatively new concept that warrants further investigation.[30] Although treatment with triptans can abort the actual headache phase, a review of the current literature indicates that triptans do not impact nonheadache symptoms.[30] In addition to the symptoms described above, migraine sufferers can also experience neck stiffness, light sensitivity, auditory sensitivity, thirst, frequent urination, and nausea.[30]

When assessing the overall impact that migraines have on patients, it is important to consider not only the migraine headache, but also the entire cycle of events. The migraine headache itself may only last from 4 to 72 hours, but the overall cycle can last as long as 7 days. Patients may experience relief from the actual headache with or without treatment, but they may not fully recover in between episodes. This may limit their participation in everyday activities; therefore, the effect of the overall migraine cycle should be factored into treatment considerations.

THE FUTURE OF MIGRAINE TREATMENT

Given the complexity of migraines, their economic burden and impact on patients' ability to function at normal capacity, and the fact that many patients are undertreated and not receiving appropriate preventive therapy, there is a need for more effective migraine treatments. This is especially important in light of the fact that patients suffering from migraines who fail or switch therapy have a tendency to continually present with severe disability as their headache frequency increases.[31] Due to both the direct and indirect costs of migraine headaches to the payers and employers, it is important that newer preventive therapies be utilized appropriately when they become available. Adherence to new effective migraine prevention treatments could impact both the health system and employers by decreasing absenteeism, presenteeism, and overall migraine-related healthcare costs.

Humanized monoclonal antibodies (mAbs) have expanded the therapeutic possibilities in a number of diseases and may have a role in treating migraines in the future. With an extended length of action, mAbs directed at CGRP or its receptor have enormous potential in the realm of migraine prophylaxis. A number of mAbs have been engineered and are in various stages of clinical trials. Three humanized anti-CGRP mAbs have been studied primarily in phase 1 trials for their efficacy in preventing EMs. However, only one has been studied in CM, and results are still pending.[3] Perhaps the most intriguing of the mAbs under development is AMG 334, which is designed to target the receptor as opposed to the ligand. AMG 334 has completed both phase 1 safety and tolerability studies and a phase 2 trial.[3] Although concerns exist regarding potential pathological effects of longstanding receptor antagonism, evidence suggested in previous studies involving small molecule antagonists showed a favorable AE profile. Despite the involvement of CGRP in multiple areas of the body as a potent vasodilator, research to date demonstrates a good safety profile for AMG 334. However, it is possible that mAbs directed at CGRP receptors may be contraindicated in hypertensive patients, given that recent evidence has shown the long-term protective effects of CGRP against hypertension.[3]

CONCLUSION

With an estimated 1 billion sufferers globally, migraines affect almost a seventh of the world's population.[1] Given that the majority of these individuals cannot function normally during attacks, the effects on society are sobering. It is not surprising that migraine sufferers have a greater risk of suicide.[7] The high prevalence of migraines, coupled with their devastating effects and the lack of preventive treatments, highlights a significant unmet need in effectively reducing the functional and physical impairments and economic impact of migraine. The past 20 years of research have yielded little progress toward a cure or an effective preventive treatment.

Although the benefits seen with triptans in terminating attacks cannot be overstated, they are effective only for 60% of migraine sufferers, can cause substantial AEs, and do little to prevent the progression from EMs to CMs.[3] It is no wonder that migraine sufferers end up in the ED, which often results in a patient being prescribed

an opioid. Given the national opioid crisis and the increased risk for progression to CMs, opioid therapy does not present an effective and sustainable model of care. Cost-effective preventive medications are underutilized by prescribers for various reasons. Educating providers, developing new treatment algorithms, and utilizing disease-state management programs could be viable approaches for managed care organizations. However, the current options available are associated with low patient adherence rates, partially due to associated AEs. This further demonstrates an unmet need in the preventive migraine treatment arena.

Research continues to point to CGRP as playing a central role in migraine pathophysiology. Small molecule CGRP receptor antagonists have shown great promise, but concerns over liver toxicity have slowed, if not halted, their development.[3] The focus of research has shifted in another potentially more effective and promising direction. Emerging mAbs directed toward either the GCRP receptor or its ligand could revolutionize the treatment options available for preventing migraines. However, it should be noted that the effectiveness seen in small molecule drug trials showed efficacy on par with the triptans. Given our current understanding that migraines collectively do not constitute a single disorder, but represent a heterogenous collection of diseases, there is likely an unmet need in regard to finding a multifaceted approach to therapy.

With new treatments on the horizon, the potential impact to society could be substantial. Whether through a reduction in lost days at work, lost productivity, or visits to the ED, the impact of even a slight reduction in migraine-related complications cannot be overlooked. While the potential societal benefits of migraine treatments are enormous, however, it is important to consider the economic implications of the new medications, too. Given that the current pipeline of migraine drugs in development comprise mAbs, these new therapies may be costly. Cost-benefit analyses will be necessary to improve cost-management issues for payers. Payers, in turn, will need to create utilization management strategies, such as prior authorizations, to ensure that medications will be limited to the patients with migraines who will most likely to benefit from their use. Despite the debilitating effects of migraines on patients and their tremendous impact on healthcare costs, the area of migraine treatment and therapy is an exciting and ever-evolving therapeutic field that has great potential to improve the lives and health of patients worldwide. •

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