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COMMENTARY

Unmet Needs in the Acute Treatment of Migraine

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ABSTRACT

Migraine represents the most common neurologic disorder, ranking second among the world's causes of disability [expressed as years lived with disability (YLDs)]. Patients often do not receive the best therapy because of safety issues, tolerance, and prescription accessibility. General practitioners are not always educated about the disease, and specialists are few and often difficult to reach. Therapies are limited and have many side effects that can impede the prescription. Prophylactic therapy is recommended in case of four or more headaches a month, eight or more headache days a month, debilitating headaches, and medication-overuse headaches. The available therapeutic options are in constant development. The classic one consists of non-specific drugs: β-blockers, tricyclics, antiepileptics, and botulinum toxin. Monoclonal antibodies targeting the calcitonin gene receptor (CGRP) peptide or its receptor are the only ones specifically designed to treat migraine. Their efficiency and convenient safety profile have been demonstrated in a number of trials versus both placebo and classic therapies. The treatment of acute migraine attack consists of medications designed to affect the painful symptoms. For over 30 years, the cornerstones of treatment in clinical practice have continued to be represented by triptans and non-steroidal anti-inflammatory drugs (NSAIDs), with the well-know related adverse effects. Opioids are used inappropriately and overprescribed. Polytherapy is strongly not recommended but is still a common practice because treatment is not optimized and thus not efficient. Great promise comes from gepants, also targeting CGRP, and ditans, 5-HT1F receptor agonists. They seem to outweigh the risk of medication overuse headache because of their efficacy and rapid onset and have no cardiovascular contraindications. Nonetheless, these points remain to be confirmed. Although therapies have been implemented in the last years, significant unmet treatment needs remain a reality in patients' lives. This commentary aims to identify the most important unmet needs in the acute treatment of migraine, analyzing the current status of available therapies and their limits. We also analyzed some of the prophylactic

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therapies available, especially focusing on anti-CGRP monoclonal antibodies, to better understand the importance of setting a therapeutic strategy that includes the two modes, both acute and prophylactic, to reach the best result. We hope that having an overview of the shortcomings will help to provide constructive ideas for improvement.

Keywords: Migraine; Acute migraine treatment; Triptans; Gepants; Ditans; Antimigraine drugs; Migraine education

Key Summary Points

Although migraine represents the most common neurologic disorder, patients often do not receive the best acute phase therapy
The cornerstones of treatment continue to be represented by triptans and NSAIDs, with well-know related adverse effects
Gepants offer great promise, also targeting CGRP and ditans, 5-HT1F receptor agonists
Although therapies have been implemented in the last years, significant unmet treatment needs remain a reality in patients' lives

INTRODUCTION

Migraine represents the most common neurologic disorder and is characterized by recurrent headache attacks of moderate to severe intensity. Treatment is based on preventive and acute attack therapy. Prophylactic therapy has been revolutionized by the use of anti-CGRP monoclonal antibodies because of their efficacy and high safety profile. For over 30 years, the cornerstones of acute phase treatment continue to be represented by triptans and NSAIDs, with the well-know related adverse effects. Opioids are another category of drug with massive inappropriate use in migraine. Gepants and ditans offer great promise; nonetheless, their advantages must be confirmed with longer observation periods.

This commentary intends to underline how correct education on acute migraine therapies has often been neglected, retraces the most important strategies in this context, and aims to stimulate doctors to follow a correct approach in this regard. More education about the disease especially among general practitioners is recommended to set the best therapy strategy, have a better patient adherence, and improve the doctor-patient trust relationship.

Several important unmet needs in the treatment of migraine are still present, and the scientific community should strive to meet them in the coming years.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Migraine

Migraine is a disease with enormous social, economic, and occupational impact. The Global Burden of Disease study 2019 (GBD2019) showed that migraine was the second leading cause of global disability [expressed as years lived with disability (YLDs)] considering all ages and all sexes but became the first considering only young women. In fact, in this population, migraine is the leading cause of DALYs (disability-adjusted life years). Data show that nearly a billion people worldwide are affected by the disease [1]. It is characterized by recurrent headache attacks of moderate to severe intensity accompanied by some characteristic symptoms such as photophobia, phonophobia, and nausea [2]. Treatment is based on preventive and acute attack therapy. Preventive therapy is recommended [3] in case of four or more headaches a month or at least eight headache days a month, debilitating attacks despite appropriate acute management, difficulty tolerating or having a contraindication to acute therapy, medication-overuse headache, patient

preference, or the presence of certain migraine subtypes (i.e., hemiplegic migraine; migraine with brainstem aura; migrainous infarction; or frequent, persistent, or uncomfortable aura symptoms).

ACUTE ATTACK DRUGS OVERVIEW

Triptans and NSAIDs

The treatment of acute migraine attack consists of medications designed to affect the painful symptoms and manifestations that normally accompany the headache. The standard of care in treatment of acute attack is 5-hydroxytryptamine1B /1D (5-HT1B/D) receptor agonists called triptans [3]. This category of drugs was introduced in the early 1990s and still represents the gold standard. Together with nonsteroidal anti-inflammatory drugs (NSAIDs), they represent the first-line drug category [4]. Although triptans are considered an excellent treatment, they have several shortcomings in both efficacy and safety profile [5]. It should be considered that only about 30% of patients are completely free from pain 2 h after taking the treatment [4]; in 30–40% of cases, there is a relapse of symptoms even when the treatment has been effective [6]. Furthermore, the frequent use of triptans can lead to a worsening of the disease characterized by an increase in the frequency and intensity of attacks with progressive evolution to chronic migraine [7]. Regarding the safety profile, there are some contraindications or precautions to consider because of their vasoconstrictive 5-HT1B-mediated effect. Triptans should be used with caution in patients with cardiovascular risk factors, and they are contraindicated in patients with established cerebrovascular or cardiovascular disease [8]. NSAIDs, on the other hand, have a series of well-known adverse effects (nephrotoxicity, gastrointestinal distress, and coagulation alterations), so they cannot be recommended for many patients [9]. Furthermore, repeated use of triptans and NSAIDs, in combination or alone, can lead to medication overuse headache and promote progression from periodic to chronic migraine [10, 11].

Opioids

Another drug category that needs major evaluations regarding its use in migraine is opioids. Although the combination of opioids and NSAIDs may be useful in some categories of patients [12], their routine utilization in migraine should be avoided [13]. The numerous harmful effects of the use of opioids in migraine were highlighted in several studies. Opioids increase release of calcitonin gene-related peptide (CGRP), promote disease progression to chronic form, have a pronociceptive effect, and interfere with the efficacy of triptans [13]. Therefore, the 2019 EHF guidelines [14] advise against the inappropriate use of these drugs, at least partially countering the epidemic of their use. Nonetheless, especially in the USA, there is still massive inappropriate use of these drugs for migraine.

Gepants

CGRP is a peptide whose role in the trigeminal-thalamic system and in genesis of migraine has been well researched. In recent years, a new class of molecules called gepants have been presented for the acute treatment of migraine. Their mechanism of action consists in antagonizing the CGRP receptor [15]. The non-interference with the vasoconstriction mechanism represents a great advantage of this category of drugs. Therefore, gepants have no contraindications in patients with cardiovascular risk factors. After the first generation of gepants that did not spread mainly because of their hepatotoxicity, the second generation (rimegepant, ubrogepant, atogepant, vazegepant) showed promising results [16]. Rimegepant [17, 18] and ubrogepant [19] demonstrated efficacy against placebo in randomized placebo-controlled clinical trials. The first received its approval in the USA for the acute treatment of migraine in February 2020 [20]. It is available in the pharmaceutical form of 75-mg orally disintegrating tablets. It has a very good safety profile; the only recognized adverse effects are hypersensitivity reactions that have arisen in very rare cases while hepatotoxicity appears to involve only a

small percentage of patients (1–2%) with a mild serum aminotransferase elevation [21]. Vazegepant is the first gepant that can be used in intranasal formulation with promising results in terms of bioavailability and rapidity of action [22]. However, its commercial availability remains limited [23]. Atogepant is the only gepants that has been approved for prophylactic treatment of migraine [24]. Given the possible use of gepants in preventive therapy as well as acute phase, it seems reasonable to think that these drugs are not involved in causing medication overuse headache [23, 23]. Furthermore, despite the limited number of data, gepants do not appear to have clear contraindications for patients with cardiovascular risk factors. These characteristics make gepants a valid alternative to fill the important gaps of triptans in the treatment of migraine. However, most of the mentioned advantages remain only speculations as we do not have certain data in this regard, and a longer observation period that can define with certainty their overuse profile is needed.

Ditans

Good news and promises come from another class of drugs directed against 5-HT1f receptors. These drugs, called ditans, appear to have no adverse cardiovascular effects as they do not cause vasoconstriction and thereby could be used in ischemic cardiovascular patients [25]. At present, the only one approved for acute migraine treatment is lasmitidan [26]. Unfortunately, it showed numerous central side effects such as dizziness, nausea, and fatigue, which sometimes make it difficult to tolerate [27, 28]. It is hoped that in the next few years there will be a further evolution of these drugs to improve their tolerance profile [29].

PREVENTIVE THERAPY: OVERVIEW

Monoclonal Antibodies

Although the pathogenesis of migraine has not yet been fully elucidated, the formulation of "the neurovascular theory" has revolutionized the approach to the disease. The trigeminal ganglion fibers that innervate the vessels in the dura mater release inflammatory neuropeptides such as calcitonin gene-related peptide (CGRP) causing inflammation and vasodilation by activating adenylyl cyclase, hence beginning of the migraine attack [30]. Other neuropeptides appear to have the same action, such as pituitary adenylate cyclase-activating peptide 38 (PACAP-38) and nitric oxide. Monoclonal antibodies targeting this pathway have been developed. They are directed against CGRP ligand (fremanezumab, galcanezumab, eptinezumab) or CGRP receptor (erenumab). Their use is indicated in chronic and episodic migraine if a prophylactic strategy is needed also as first-line therapy [31]. As we mentioned before, their approval has been a real breakthrough in migraine prophylactic therapy.

Numerous studies demonstrated a reduction in days with migraine, a good responder rate (at least 50% reduction in migraine days), reduction in the use of acute attack medication, and a good safety profile [32].

Recently, besides its established efficacy in prophylactic therapy, eptinezumab has also been shown to be useful in treating acute migraine attacks [33].

Studies have also shown efficacy in resistant chronic migraine, a very difficult group of patients to treat. Patients reported fewer days with migraine, attacks of lower intensity, and a response rate $> 50\%$, therefore showing a clear improvement in quality of life with negligible adverse effects [34]. The use of CGRP antibodies has unfortunately still not been proved effective in cluster headache [35].

The posology of these drugs is convenient for many reasons both practical and therapeutic. They are administered with a single subcutaneous injection monthly (erenumab, fremanezumab, and galcanezumab); eptinezumab is given intravenously every 3 months.

The onset is rapid; benefits can be observed as early as the first day of therapy for galcanezumab and eptinezumab [36] and the first week for erenumab [37] and fremanezumab [38].

Rates of interaction with other drugs are low. These drugs are metabolized via proteolytic degradation pathways and not by the liver. This greatly reduces the risk of interactions with other drugs such as anticoagulants, antiepileptics, etc. [39].

The response rate is high, and side effects are placebo-like [40].

Use is not recommended in some special populations such as high vascular risk patients and those with overt history of vascular events and Raynaud syndrome [41] because of the blockage of the endogenous vasodilating power of the neuropeptide.

They are also not recommended in pregnant or nursing women. The few data on low exposures seem to confirm safety [42] but erenumab may cross the placenta [43], and CGRP is important in the uteroplacental circulation; hence, its blockage may increase the potential for gestational hypertension, pre-eclampsia, and eclampsia [44]. Further studies need to be conducted to understand the safety of anti-CGRP therapies in these categories of patients.

Constipation also emerged as a frequent adverse event of treatment with galcanezumab [45] and mostly with erenumab [46], even if the reports showed only mild symptoms that did not stop the treatment.

However, considering the short history of the usage of CGRP antibodies, further studies and vigilance during longer treatment periods are needed.

Other Preventive Therapies

Botulinum toxin type A (BoNTA) modulates neurotransmitter release, enhances the opioidergic transmission, and seems to change the surface expression of receptors and cytokines [47].

It is administrated with injections in seven specific head neck muscle areas in fixed doses every 12 weeks [48].

It has been tested and found effective in chronic migraine with changes in headache frequency from baseline compared to placebo and seems to have the same efficacy as topiramate with a better safety profile [49]. Data are missing about the efficacy in episodic migraine [49]. The most common adverse events reported were pain at the injection site, hematoma at the injection site, and muscular weakness.

Topiramate administered in a maximum dose of 100 mg per day led to a reduction in monthly migraine days; although usually well tolerated, it can cause several adverse events like nausea, dizziness, dyspepsia, fatigue, anorexia, taste alteration, and disturbance in attention.

Other therapies that are used in preventive therapy are antiepileptics such as divalproex sodium, amitriptyline and other antidepressants, beta-blockers like propranolol, and antihistamines like cinnarizine [50].

Doctor-patient Relationship

There is much evidence that nothing totally satisfies migraine patients' needs regarding acute phase treatment. A recent US longitudinal population-based study showed that nearly 40% of migraine patients have at least one unmet need for the acute treatment of their disease [51]. Major gaps derive from a lack of personal training of health professionals, mainly general practitioners (GPs), and of patient education about treating the disease and its management in acute phase [52]. Various studies have highlighted the lack of primary care in setting up an effective therapy [53]. Furthermore, many patients do not have satisfactory education about the condition and therapeutic strategies. This leads to an abuse and misuse of acute phase drugs, with the relative harmful consequences in terms of adverse effects and refractoriness to treatments. Some studies have highlighted how migraine patients are often unable to adopt a correct therapeutic strategy, and their degree of satisfaction does not reflect the actual quality of the therapeutic choices adopted [54]. This leads to significant delays in referral to specialized centers where a correct therapeutic strategy can be set. A migraine patient receives the correct diagnosis after about 10 years and attends at least four hospital centers before finding the definitive one where he or she receives the correct therapy [55]. The causes of these delays can be traced back to a widespread lack of

information, services, and culture regarding migraine. The dissemination of more information on the subject within the bodies responsible for managing health resources, GPs, and patient populations would allow for a widespread improvement in treatment from the earliest stages of the disease.

DISCUSSION

The burden of migraine has negative implications involving various aspects of patients' lives as well as socioeconomic and public health aspects.

As previously mentioned, nearly a billion people worldwide suffer from migraines [56]. In this very large number of patients, it is estimated that up to 40% report at least one unmet need.

This occurs because therapies are often not effective but even more because patients do not use the best therapy because of safety issues, tolerance, and prescription accessibility. We tried to focus our analysis on both physician and prescription issues and on the limits of therapeutic options.

It is essential for clinicians to advise patients about the right treatment for both prophylactic therapy and acute attack therapy by prescribing drugs that are the most advanced and effective and have a high safety profile. Specialized headache clinics are few and not optimally geographically distributed, hence the pivotal role of GPs (general practitioners) in early diagnosis and setting optimal therapy.

Unfortunately, this often does not happen. GPs often receive little specialized training on the condition, they are not provided with standardized management guidelines, diagnostic tools, or continuing education on new treatment options that, in addition to being more effective, have fewer side effects and could greatly improve patient satisfaction and the trust relationship between doctor and patient.

Educating GPs about the disease so they can make an early diagnosis and optimize treatment should be a primary goal.

Standard prophylactic therapies such as beta-blockers, antidepressants, and antihistamines have various side effects. Beta-blockers can cause hypotension, bradycardia, impotence, and lethargy. Antiepileptics may provoke nausea, paresthesia, difficulty concentrating, and others. Antidepressants cause QT prolongation, nausea, dizziness, and others. All these possible side effects can cause compliance challenges; in fact, only 10% of the 40% of migraine patients adhere to prophylactic therapy effectively [57]. This leads to acute drug abuse, often polypharmacy, which can lead to chronicity and makes treatment even more complicated. This mode has been strongly discouraged by multiple evidence [58].

The classic drugs available in the acute migraine attack are NSAIDs (nonsteroidal anti-inflammatory drugs) and triptans. The goals of acute treatment of migraine attack were defined in the 2019 AHS Consensus Position Statement [59].

1. Rapid and consistent freedom from pain and associated symptoms without recurrence.
2. Restored ability to function.
3. Minimal need for repeat dosing or rescue medication.
4. Optimal self-care and reduced subsequent use of resources (e.g., emergency department visits, diagnostic imaging, health care provider, and ambulatory infusion center visits).
5. Minimal or no adverse events.

Unfortunately, these goals are not always reached because of ineffectiveness/presence of adverse effects/non-prescription for safety reasons [60].

For example, NSAIDs have many side effects (nephrotoxicity, bleeding tendency, gastrointestinal distress) [9], triptans are effective in 18–50% of patients but should be prescribed with caution in patients with cardiovascular risk factors and are not recommended in those with a history of cerebrovascular disease and established cardiovascular disease because of the vasoconstriction at the basis of their pharmacologic action [61].

In America, 19.1% of men and 18.6% of women with episodic migraine have three or more cardiovascular risk factors (hypertension,

smoking habit, diabetes mellitus, obesity, dyslipidemia); 73.4% and 69.5%, respectively, have at least one [51]. In other countries, the percentages are slightly lower but still substantial [62]. This fact results in a large portion of the population suffering from migraine disease having difficulty treating the acute attack, with a tendency to abuse other categories of drugs that, as we have seen above, are not risk-free or may not be effective.

There is an absolute need to fill these gaps using new molecules that could overcome these limits. There has been an advancement in prophylactic therapy with the introduction of CGRP antibodies while less progress has been made in the search for new drugs for the acute attack. In fact, until recently, all therapies used to treat migraine were not specifically designed for this purpose. New knowledge about neurotransmission mechanisms involved in migraine disease let us discover new pathways that could be used to treat the disease.

Monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) signaling pathway have revolutionized prophylactic therapy by having a superior safety and efficacy profile compared to traditional therapies; the main adverse effects are constipation and injection site reactions [63, 64]. Further studies should be conducted to fully test its safety profile in established cardiovascular disease and in special situations such as pregnancy.

Regarding acute therapy, there are new promising therapeutic opportunities coming from gepants and ditans as they seem to outweigh the risk of medication overuse headache and seem to have no cardiovascular contraindications. Nonetheless, these points remain to be confirmed. The oral CGRP receptor antagonists, the gepants, are a category of drugs that also act on CGRP.

Currently, the only FDA-approved drugs in the class are ubrogepant (Ubrelvy®) as acute therapy, atogepant (Qulipta®) as prophylactic therapy, and rimegepant (Nurtec®, Nurtec ODT®, Vydura®) as both acute and prophylactic therapy. This dual-use feature is particularly appealing as an alternative in no responder patients to other therapies and to simplify administration in patients with poor compliance.

Studies have shown that gepants are effective in acute attack and have an excellent safety profile with a low adverse event profile, placebo-like, and can be prescribed as an alternative to triptans in patients with cardiovascular risk/disease. All can be administered orally, and zavegepant is formulated as a nasal spray [65].

Further studies need to be conducted to demonstrate its safety and efficacy in the long term and in special conditions such as pregnancy and cardiovascular disease, but the results so far are promising [66].

Ditans (the only one approved at the moment is lasmitidan) are the other category of drugs that can help expand the few choices of available treatments in acute therapy. They act on serotonin receptors, like triptans. Triptans work through serotonin5-HT1B/1D receptors. Ditans on 5-HT1F receptor present on the trigeminal ganglion. Activation of this receptor does not appear to cause vasoconstriction, unlike triptans do [67], and thus they do not seem to provoke any cardiovascular risk. This drug category can actively penetrate the blood-brain barrier. This characteristic is the basis for their central therapeutic effect as well as side events (dizziness, vertigo, drowsiness, and fatigue).

Since these drugs have been recently approved, longer clinical post-marketing experience is needed for the accurate determination of adverse events, mainly for people suffering from cardiovascular diseases and during pregnancy [68].

CONCLUSION

Although enormous progress has been made in migraine research, several unmet needs regarding acute migraine treatment remain. We highlighted this topic with a critical view trying to suggest the most successful strategies.

For over 30 years, the cornerstones of treatment in clinical practice continue to be represented by triptans and NSAIDs, with the well-know related adverse effects, cardiovascular for the former, gastrointestinal and coagulative for

the latter. Although the use of triptans and NSAIDs represents a valid strategy for the acute treatment, they have numerous limitations and shortcomings. As already mentioned, triptans do not possess a totally risk-free profile in patients with cardiovascular diseases. NSAIDs, on the other hand, have a series of well-known adverse effects. Combinations of drugs (triptans and NSAIDs, NSAIDs and opioids), although sometimes more effective than single treatments, carry an increased risk of abuse and a greater risk of disease progression in chronic migraine and development of medication overuse headache. The scientific community has moved in this direction recently by promoting a progressive simplification of treatments trying to avoid a multiple therapeutic approach [69]. Great promise is offered by gepants and ditans as they seem to outweigh the risk of medication overuse headache and have no cardiovascular contraindications. Nonetheless, these points remain to be confirmed. There are also large gaps in the world of information and investments that global health services devote to migraines. The examples come from the relationship between migraine patients and primary care. From this point of view, the scientific community should try to disseminate appropriate information about migraines to make the best treatments widely available. Finally, to manage these very frequent disorders, one motto can be cited: "Moving headache into broad clinical medicine," stating that all physicians—and not only the few headache experts—from general medicine to all medical specialties, should be educated to appropriately treat any form of primary headache promptly and appropriately [70]. We aim for ever-new pathophysiologic discoveries regarding the genesis of migraine to create new therapeutic targets and to confirm and expand promising features of the newly released drugs in terms of both safety and efficiency. The hope for the immediate future is to have enough drugs to create tailored therapy according to the patient's needs, preferences, and comorbidities. With this expanded armamentarium, GPs and specialists, correctly informed and educated, can provide the right drug to the right patient, improving patient satisfaction and confidence. Physicians should educate patients and make them part of the decision process regarding the most appropriate therapy, by choosing with them and not for them. With an appropriate therapeutic strategy, there will certainly be greater adherence and hence the use of as few drugs as possible and reduction of polypharmacy and possible chronicity.

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