Migraine 3

Migraine: integrated approaches to clinical management and emerging treatments

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Migraine is a highly disabling neurological disorder that directly affects more than 1 billion individuals worldwide. Available treatment options differ between countries and include acute, preventive, and non-pharmacological therapies. Because of major progress in the understanding of migraine pathogenesis, novel mechanism-based medications have emerged and expanded the armamentarium of treatments. We provide a comprehensive overview of the current standard of care that will enable informed clinical management. First, we discuss the efficacy, tolerability, and safety profile of various pharmacological therapies for acute and preventive treatment of migraine. Second, we review the current knowledge on non-pharmacological therapies, such as neuromodulation and biobehavioural approaches, which can be used for a multidisciplinary approach to clinical management. Third, we emphasise that any effective treatment strategy starts with building a therapeutic plan tailored to individual clinical characteristics, preferences, and needs. Finally, we explore the outlook of emerging mechanism-based treatments that could address unmet challenges in clinical management of migraine.

Introduction

Migraine is a major public health challenge that is insufficiently recognised and incurs considerable individual and societal costs.[1] Migraine ranks as the leading cause of years lived with disability worldwide in individuals younger than 50 years.[2] The current armamentarium of treatments includes acute medications, preventive medications, and non-pharmacological therapies. Despite an array of available treatment options, there are ongoing challenges with undertreatment, adherence, and access. In 2018, these challenges were highlighted by population-based data from six European countries.[3] In individuals with migraine, triptans were used by only 3–22%, whereas preventive medications were used by 2–14% of eligible patients. Therefore, improvements need to be made so that the current standard of care is applied consistently and effectively in clinical practice. In this Series paper, we discuss available evidence in the context of optimising patient care and minimising unnecessary treatment exposure and failure. We present each therapeutic approach sequentially, with a review of available evidence in terms of efficacy, tolerability, and safety profile. We also discuss how recently approved (over the past 3 years) and emerging treatments could be integrated into clinical practice.

Acute treatment

Medication therapy is the mainstay of acute treatment of migraine (table 1). The International Headache Society has defined two clinical outcomes for treatment success in randomised controlled trials (RCTs). The first outcome is defined as freedom from pain within 2 h after treatment. The second outcome is defined as absence of the most bothersome migraine-associated symptom (ie, nausea, vomiting, photophobia, or phonophobia) within 2 h after treatment.[24] Acute medications include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and triptans, whereas use of ergot alkaloids and adjunct antiemetics is less frequent. Since 2019, two new drug classes, gepants and ditans, have been approved by the US Food and Drug Administration (FDA) for the acute treatment of migraine. Routine use of opioids and barbiturates are discouraged by practice guidelines because of poor safety and tolerability profiles.[22,23,25]

To minimise unnecessary exposure, all patients should be provided with an optimal acute treatment strategy (figure 1) that accounts for previous treatment failures and individual migraine characteristics, such as usual headache intensity, time to peak intensity, and severity of associated symptoms (eg, nausea and vomiting). Choice of strategy should also reflect patient preference because

Search strategy and selection criteria

We searched MEDLINE (from database inception to Jan 1, 2020), and Embase (from database inception to Jan 1, 2020) for original research articles, and systematic reviews and meta-analyses. We used the search terms "migraine" in combination with the terms "acute", "preventive", "treatment", "medication", "drug, "complimentary", "management", "cognitive", "therapy", "device", "diet", "sleep", "acupuncture", "education", "novel", "economics" and "emerging". We mainly selected publications from the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

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a considerable proportion of individuals with migraine are dissatisfied with their acute medication.[26] Additionally, access to medications differs between countries and any treatment strategy should be tailored to local resources and availability.

Simple analgesics

Paracetamol and NSAIDs are widely used acute medications for migraine, although paracetamol monotherapy is not considered a first-line medication.[27,28] Effective NSAIDs include ibuprofen, aspirin, and diclofenac

	Route	Recommended dose	Number needed to treat	EAN level of recommendation	AAN level of recommendation	Cautions and contraindications
Analgesics						
Paracetamol[4]	Oral	1000 mg	12·0	High	High	Hepatic disease, renal failure
NSAIDs						
Aspirin[5]	Oral	900–1000 mg	8·1	High	High	Gastrointestinal bleeding, heart failure, renal failure
Diclofenac[6]	Oral (soluble)	50 mg	7·4	High	High	Gastrointestinal bleeding, heart failure, renal failure
Ibuprofen[7]	Oral	400 or 600 mg	7·2 for 400 mg, 6·3 for 600 mg	High	High	Gastrointestinal bleeding, heart failure
Triptans						
Almotriptan[8]	Oral	12·5 mg	5·2	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Eletriptan[9]	Oral	20, 40, or 80 mg	9·9 for 20 mg, 4·0 for 40 mg, 3·7 for 80 mg	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Frovatriptan[10]	Oral	2·5 mg	11·9	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Naratriptan[11]	Oral	2·5 mg	8·2	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Rizatriptan[12]	Oral	10 mg	3·1	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Rizatriptan[12]	Oral (disintegrating)	5 or 10 mg	5·0 for 5 mg, 3·0 for 10 mg	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Sumatriptan[13]	Intranasal	20 mg	4·7	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Sumatriptan[13]	Oral	50 or 100 mg	6·1 for 50 mg, 4·7 for 100 mg	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Sumatriptan[13]	Subcutaneous	6 mg	2·3	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Zolmitriptan[14]	Intranasal	5 mg	4·6	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Zolmitriptan[14]	Oral	2·5 or 5 mg	5·0 for 2·5 mg, 4·8 for 5 mg	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Zolmitriptan[14]	Oral (disintegrating)	2·5 mg	5·2 (4·2–6·9)	High	High	Coronary heart disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease
Gepants						
Rimegepant*[15]	Oral (disintegrating)	75 mg	9·4	Not rated	Not rated	Hypersensitivity reactions, hepatic impairment
Ubrogepant*[16,17]	Oral	50 or 100 mg	13·3 or 13·6 for 50 mg, 10·7 for 100 mg	Not rated	Not rated	Concomitant use with strong CYP3A4 inhibitors

(Table 1 continues on next page)

	Route	Recommended dose	Number needed to treat	EAN level of recommendation	AAN level of recommendation	Cautions and contraindications
(Continued from previous page)						
Ditans						
Lasmiditan*[18-20]	Oral	50, 100, or 200 mg	13·7 for 50 mg, 7·7 or 9·9 for 100 mg, 5·7 or 5·9 for 200 mg	Not rated	Not rated	Operating a vehicle or machinery within 8 h after drug intake, concomitant use with drugs that are P-glycoprotein substrates, concomitant use with alcohol or other CNS depressants
Ergot alkaloids						
Dihydroergotamine[21]	Intranasal	0·5–2 mg	Not available	Not rated	High	Coronary heart disease, peripheral vascular disease, uncontrolled hypertension

Selection of acute medications were based on guidelines that have been published by the EAN and the AAN.[22,23] A modified GRADE system was used to determine the level of recommendation for each medication that was assessed by AAN. AAN=American Academy of Neurology. EAN=European Academy of Neurology. GRADE=Grading of Recommendations Assessment, Development and Evaluation. NSAIDs=non-steroidal anti-inflammatory drugs. *Acute medications that had been approved by the US Food and Drug Administration within the past 10 years.

Table 1: **Selected acute medications for migraine in adults**

For the **GRADE system of rating evidence** see https://www.gradeworkinggroup.org/

potassium.[29,30,31] During migraine attacks of moderate or severe headache intensity, ibuprofen provided freedom from pain within 2 h of treatment in 26% of individuals with migraine, compared with 12% after placebo.[29] Similarly, pain freedom by 2 h is reached in 24% of individuals taking aspirin, compared with 11% after placebo.[30]

Triptans

Triptans are migraine-specific drugs that exist in various formulations, with sumatriptan being accessible in most countries worldwide.[27] Triptans are often used for attacks of moderate or severe headache intensity, although drug administration is recommended while the pain intensity is still mild—ie, early in the headache phase of a migraine attack. During migraine attacks of moderate or severe headache intensity, oral sumatriptan provides freedom from pain by 2 h in 32% of individuals with migraine, compared with 11% after placebo.[13] Based on currently available studies, all oral triptans have proven beneficial compared with placebo.[23] If sumatriptan is injected subcutaneously, freedom from pain is reached in 59% of individuals with migraine, compared with 15% after placebo.[13] However, use of subcutaneous sumatriptan is not widespread because oral formulations are less expensive and more accessible. Nonetheless, a non-oral route of administration is preferred in patients who need a rapid drug effect, have attacks of moderate or severe headache intensity upon awakening, or have attacks with considerable nausea or vomiting.[28] If nausea or vomiting does occur, adjunct prokinetic antiemetics might also be advisable.[28] In patients who do not respond to a particular triptan, other triptans can prove beneficial.[32] Additionally, sumatriptan can be used effectively in combination with naproxen.[33] Migraine recurrence after initial pain freedom ranges from 17% to 40% and is affected by the half-life and receptor potency of the triptan drug.[34] If a single dose of triptan provides inadequate pain relief, clinicians tend to recommend a repeat dose, although this approach is not supported by the currently available evidence.[13] Adverse events to triptans include transient paraesthesia, flushing, and palpitations. Less common is neck and chest tightness, but these symptoms are rarely associated with serious cardiovascular events. In fact, there is very little evidence of an increased risk of vascular events in triptan users.[35] However, the theoretical risk remains because triptans are vasoconstrictors; therefore,

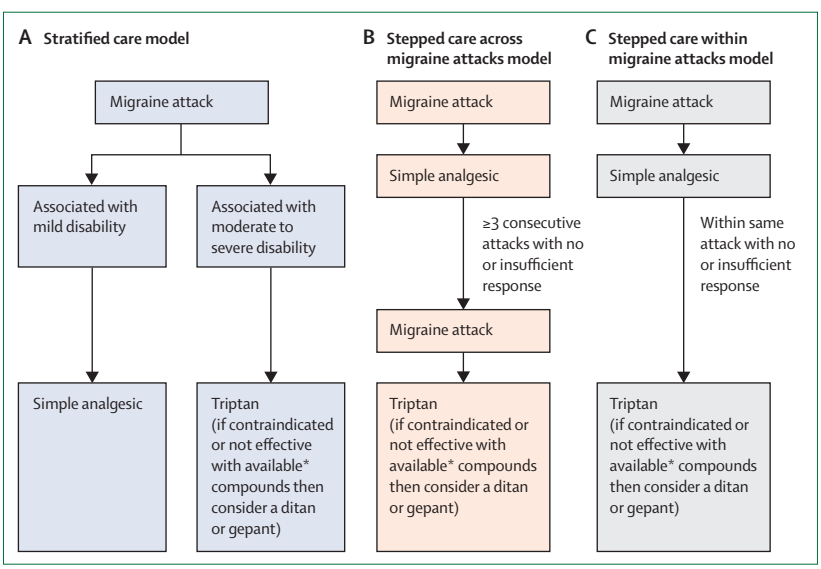

Figure 1: **Treatment strategies for delivery of acute treatment for migraine**
There are three treatment strategies used for delivery of acute treatment for migraine: stratified care (A), stepped care across migraine attacks (B), and stepped care within attacks (C). In stratified care, choice of acute medication is based on the degree of migraine-related disability. In stepped care across migraine attacks, choice of acute medication starts with a simple analgesic. If a simple analgesic is insufficient after three consecutive attacks, patients are offered a migraine-specific drug for subsequent attacks, starting with a triptan. In stepped care within migraine attacks, a simple analgesic is used to initially treat an attack. If insufficient, patients should take a migraine-specific drug within the same attack. *Depending on local practice guidelines.

Panel 1: Medication overuse headache and migraine

Medication overuse headache is a secondary headache disorder attributed to frequent use of analgesics or migraine-specific medications (eg, triptans, ergotamines).[41] Medication overuse headache is more common in individuals with a high frequency of migraine, by comparison with those who have low frequency of migraine, and constitutes a modifiable risk factor of transformation from episodic to chronic migraine.[42,43]

According to the International Headache Society, medication overuse headache is defined as follows:[41]

- Headache occurring on at least 15 days per month in an individual with a pre-existing headache disorder
- Regular overuse for over 3 months of one or more medications that can be taken for acute or symptomatic treatment of headache (overuse for ≥10 days per month or ≥15 days per month, depending on the medication)
- Headache that is not better accounted for by another diagnosis in the third edition of the International Classification of Headache Disorders

An important consideration is that regular overuse of acute medications is an indicator of suboptimal clinical management.[41] Triptans, opioids, and barbiturates are associated with the highest risk of medication overuse headache, whereas non-steroidal anti-inflammatory drugs (such as ibuprofen) have been shown to have less risk.[44,45]

Clinical management of medication overuse headache has three components:

- Patient education and counselling
- Discontinuation of the overused medication
- Use of preventive medications or non-pharmacological prevention[43]

Although this three-step approach is widely used, it is not based on high-quality evidence and more research is needed to establish the best practices for clinical management of medication overuse headache in individuals with migraine. Monoclonal antibodies against calcitonin gene-related peptide, or its receptor, reduce the use of migraine-specific medications in patients with chronic migraine and medication overuse headache.[46,47] Similar data on onabotulinumtoxinA are more discordant and further investigations are warranted.[48,49]

it is considered advisable to be cautious and not recommend triptans for patients who have a history of coronary heart disease, cerebrovascular disease, or uncontrolled hypertension.[28]

Gepants (small-molecule calcitonin gene-related peptide receptor antagonist)

The first gepant, ubrogepant, was approved by the FDA in 2019. In patients with migraine attacks of moderate or severe headache intensity, one phase 3 trial found that 100 mg ubrogepant provided freedom from pain by 2 h in 21% of individuals with migraine, while 50 mg ubrogepant did so in 19%, compared with 12% after placebo.[36] In another phase 3 trial, 50 mg ubrogepant provided pain freedom by 2 h in 22% of individuals with migraine while 25 mg ubrogepant did so in 21%, compared with 14% after placebo.[16] Rimegepant is another gepant recently approved by the FDA as an orally disintegrating tablet. In attacks of moderate or severe headache intensity, one phase 3 trial found that 75 mg rimegepant provided pain freedom by 2 h in 21% of individuals with migraine, compared with 11% after placebo.[37] Based on data from phase 3 trials, ubrogepant and rimegepant were well tolerated but their therapeutic benefits are modest, as measured by numbers needed to treat for pain freedom by 2 h (table 1).[16,36,37] Therefore, use of these drugs will be limited to patients for whom NSAIDs and triptans are contraindicated or ineffective.[38]

Ditans

The first ditan, lasmiditan, was approved by the FDA in 2019. In patients with migraine attacks of moderate or severe headache intensity, one phase 3 trial found that 200 mg lasmiditan provided pain freedom by 2 h in 32% of people with migraine, and 100 mg lasmiditan did so in 28%, compared with 15% after placebo.[39] These results were subsequently confirmed in another phase 3 trial.[18] Lasmiditan is associated with temporary driving impairment and inability to self-assess the degree of impairment. It is therefore not advisable to operate a vehicle or other machinery for at least 8 h following drug intake. Thus, lasmiditan is likely to be limited to patients for whom NSAIDs and triptans are contraindicated or ineffective.

Ergot alkaloids

Ergot alkaloids are one of the oldest drug classes for the acute treatment of migraine. Ergotamine tartrate is available in an oral formulation and dihydroergotamine is available as intranasal, subcutaneous, and intramuscular formulations. Oral ergot alkaloids are less effective than triptans and have poor overall tolerability, with nausea as a frequent adverse event.[40] Because of an increased risk of vascular events, their use is contraindicated in patients with a history of coronary heart disease, cerebrovascular disease, or uncontrolled hypertension.[28] This has led to a recommendation from the European Headache Federation that routine use of ergot alkaloids should be avoided.[28] Nonetheless, ergot alkaloids remain widely used outside of Europe and are regarded as an alternative to triptans in the USA.[27]

Antiemetics

Antiemetics are recommended as an adjunct therapy in patients who experience severe nausea or vomiting related to their migraine attacks. In an evidence-based guideline document from the Canadian Headache Society, domperidone and metoclopramide were recommended for use as an adjunct treatment of migraine.[23]

Treatment strategy

Although there is a broad armamentarium of acute medications, migraine-specific drugs are used by less than one-quarter of patients worldwide.[3] In the USA, a similar proportion of patients use opioids or barbiturates despite moderate efficacy (at best) and a considerable risk of medication overuse headache (panel 1), habituation, dependency, and addiction.[50] The use of non-migraine drugs is alarming because suboptimal acute treatment, inducing excessive and disordered medication use (ie,

Panel 2: Clinical management of migraine in specific populations

Paediatric migraine

Migraine is a common headache disorder in children and adolescents.[52] The typical headache features tend to be of more frequent bilateral localisation and shorter duration compared with migraine in adults.[28] Recommended acute medications include simple analgesics, whereas almotriptan, zolmitriptan nasal spray, and sumatriptan combined with naproxen have been approved by the US Food and Drug Administration for use in children aged 12 years or older.[53] Recommended preventive medications include propranolol and topiramate, and amitriptyline can be used in combination with cognitive behavioural therapy.[54] However, no randomised controlled trial (RCT) has reported clinical efficacy of any preventive medication for paediatric migraine,[55] which could be partly explained by the high placebo response in children and adolescents.[55] One RCT found that neither topiramate nor amitriptyline was superior to placebo, but the placebo response rate was 61%.[56] This high placebo response rate along with the low number of participants included in the placebo group (n=66) compared with the amitriptyline (n=132) and topiramate groups (n=130) might explain the negative findings.

Menstrual migraine

Menstrual migraine is divided into two subtypes (pure menstrual migraine and menstrually related migraine) according to the International Headache Society.[41] Pure menstrual migraine is defined as migraine attacks that occur exclusively on day 1 (±2 days) of menstruation in at least two out of three menstrual cycles. Menstrually related migraine is defined as migraine attacks that occur exclusively on day 1 (±2 days) of menstruation in at least two out of three menstrual cycles, and additionally at any other time of the cycle.

Population-based data have estimated that 8% of women with migraine have pure menstrual migraine, whereas an even higher proportion (13%) of women with migraine have menstrually related migraine.[57,58] If standard of care acute medications are ineffective, perimenstrual preventive therapy should be considered. For this purpose, long-lasting triptans (eg, naratriptan, frovatriptan) can be administered daily during the perimenstrual period (ie, day –2 to day +5 of menstruation).[59] Hormone replacement therapy is also used by some clinicians, but the quality of evidence is very low.[60] Further investigations are needed to determine the effectiveness of hormone replacement therapy for recommendations to be made.

Pregnancy and breastfeeding

In most women with migraine, pregnancy is associated with an attenuation of migraine.[61] As such, treatment might be unnecessary for some women during their entire pregnancy. In those who continue to have migraine attacks, paracetamol should be used as a first-line acute medication.[62] Ibuprofen, diclofenac, and naproxen should be used with caution (because of risk of miscarriage and congenital malformations) and only during the second trimester.[62] Use of triptans during pregnancy has not been well documented, with only few studies reporting safety data to support the use of sumatriptan under specialist supervision.[62] Similarly, other acute medications cannot be recommended because of scarce safety data. Preventive medications should be avoided if possible, although β blockers are often considered safe to use during pregnancy.[62] Amitriptyline is frequently considered a second-line medication, although available safety data are scarce.[62]

Similar to pregnancy, there is a scarcity of safety data on medication use in breastfeeding women. Paracetamol is often the drug of choice, and ibuprofen and sumatriptan are also considered safe.[62]

Migraine in older people

Migraine tends to remit with age and, in those who continue to have migraines, its clinical presentation is more often of bilateral localisation and associated with autonomic symptoms—eg, tachycardia, facial flushing.[63] Another important consideration is the ability to differentiate migraine aura without headache from transient ischaemic attacks (TIAs). In this context, it should be noted that onset of migraine aura symptoms is typically gradual and spreads over minutes, whereas TIA symptoms generally occur simultaneously from onset. To guide clinicians, clear diagnostic criteria have been developed to differentiate between migraine with aura and TIA.[64] Standard treatment options can be considered, but it is crucial to use these medications with caution in older people because this population has a higher risk of side-effects by comparison with younger people.

medication overuse), is a key risk factor for transformation into chronic migraine.[42] Thus, there is a pressing need for clinicians to provide an adequate treatment strategy. In one randomised, controlled, parallel-group trial, stratified care (ie, choosing treatment on the basis of attack severity) was shown to be better than stepped care across attacks (ie, start with a simple analgesic and, if unsuccessful, treat subsequent attacks with a migraine-specific drug) and stepped care within attacks (ie, start with a simple analgesic and, if pain progresses, proceed to a migraine-specific drug).[51] However, the findings should be interpreted with caution as patients who have little or infrequent migraine-related disability were excluded—there was a bias against stepped care. It could be argued that patients who are less adversely affected by migraine might have an adequate treatment response from use of simple analgesics. Clinical practice guidelines encourage that clinicians offer acute medications to everyone who has migraine attacks.[28] Patients should be advised to take their acute medication early in the headache phase of an attack and avoid regular overuse, as this can lead to the development of medication overuse headache.[28,43] From clinical experience, substitution

with another acute medication is typically recommended after treatment failure of three consecutive attacks with a given acute medication. Nonetheless, treatment strategies should always be individualised to address the needs specific to each patient (panel 2). Additionally, any change of acute medication should be preceded by a review of underlying reasons for treatment failure (eg, inadequate dose, inappropriate route of administration). In terms of gepants and ditans, these drugs did not show superiority to triptans by indirect comparison with RCT data. Their use will also currently be limited by high costs and restricted availability, although they remain (wherever available and affordable) a viable substitute for NSAIDs and triptans. It should be noted that validated patient-reported outcome tools are currently available to aid the evaluation of treatment response, such as the Headache Under-Response to Treatment Questionnaire (HURT) and the Migraine Treatment Optimization Questionnaire (M-TOQ).[65,66,67]

Preventive treatment

Preventive medications are used to reduce the frequency, severity, or duration of migraine attacks in affected individuals in whom use of acute medications does not

	Route	Recommended dose	EAN level of recommendation	AAN level of recommendation	Cautions and contraindications
β blockers					
Atenolol	Oral	25–100 mg once daily	Not rated	Moderate	Asthma, cardiac failure, Raynaud's disease, atrioventricular block, depression
Bisoprolol	Oral	5–10 mg once daily	Moderate	Inadequate or conflicting	Asthma, cardiac failure, Raynaud's disease, atrioventricular block, depression
Metoprolol	Oral	50–100 mg twice daily or 200 mg (modified-release) once daily	High	High	Asthma, cardiac failure, Raynaud's disease, atrioventricular block, depression
Nadolol	Oral	20–160 mg once daily	Not rated	Moderate	Asthma, cardiac failure, Raynaud's disease, atrioventricular block, depression
Propranolol	Oral	80–160 mg (long acting) once to twice daily	High	High	Asthma, cardiac failure, Raynaud's disease, atrioventricular block, depression
Candesartan	Oral	16 mg once daily	Low	Low	Co-administration of aliskiren
Antidepressants					
Amitriptyline	Oral	50–100 mg once daily at night	Moderate	Moderate	Children under 6 years old, heart failure, co-administration with MAOIs, glaucoma
Anticonvulsants					
Sodium valproate	Oral	600–1500 mg once daily	High	High	Liver disease, thrombocytopenia, women of childbearing potential
Topiramate	Oral	50–100 mg once daily	High	High	Nephrolithiasis, pregnancy, lactation, glaucoma
Other drug classes					
Flunarizine	Oral	5–10 mg once daily	Not rated	High	Parkinson's disease, depression
OnabotulinumtoxinA*	Intramuscular	155–195 units to multiple site injections every 12 weeks	Not rated	Not rated	Hypersensitivity reactions, infection at injection site
Monoclonal antibodies against CGRP or its receptor					
Eptinezumab	Intravenous	100 mg or 300 mg once quarterly	Not rated	Not rated	Hypersensitivity reactions, coronary heart disease, cerebrovascular disease, inflammatory bowel disease
Erenumab	Subcutaneous	70 or 140 mg once monthly	Not rated	Not rated	Hypersensitivity reactions, coronary heart disease, cerebrovascular disease, inflammatory bowel disease
Fremanezumab	Subcutaneous	225 mg once monthly or 675 mg once quarterly	Not rated	Not rated	Hypersensitivity reactions, coronary heart disease, cerebrovascular disease, inflammatory bowel disease
Galcanezumab	Subcutaneous	120 mg once monthly (240 mg initial loading dose)	Not rated	Not rated	Hypersensitivity reactions, coronary heart disease, cerebrovascular disease, inflammatory bowel disease

Selection of preventive medications were based on guidelines that have been published by the EAN and AAN.[24,68] Dose recommendations are based on a treatment guideline that was developed by the European Headache Federation and the Lifting The Burden campaign.[28] It should be emphasised that dose recommendations differ between countries and regions; thus, any treatment plan should be made in accordance with local practice guidelines. A modified GRADE system was used to determine the level of recommendation for each medication that was assessed by AAN. AAN=American Academy of Neurology. EAN=European Academy of Neurology. CGRP=calcitonin gene-related peptide. GRADE=Grading of Recommendations Assessment, Development and Evaluation. MAOI=monoamine oxidase inhibitors. *Preventive medications that had been approved by the US Food and Drug Administration within the past 10 years.

Table 2: **Selected preventive medications for migraine in adults**

suffice as a standalone treatment strategy. According to consensus guidelines from the European Headache Federation, initiation of preventive therapy is recommended for individuals who have migraine attacks that occur at least 2 days per month and are associated with impaired quality of life.[28] Additionally, their migraine should either be inadequately regulated despite optimised acute medication use or cause over-frequent use of acute medications.[28] It should be emphasised that initiation of preventive therapy should be made on a case-by-case basis and in accordance with local practice guidelines. Choice of a specific preventive medication is based on multiple factors, such as efficacy, tolerability, availability, cost, medical comorbidities, and patient preference (table 2). It should be emphasised that most medications used for the preventive treatment of migraine were tested in RCTs that were underpowered and poorly designed. Evidence-based effectiveness for chronic migraine has been documented for topiramate, onabotulinumtoxinA, and monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor.[69,70,71]

Active follow-up is recommended shortly after initiation or change of preventive medication and should be done regularly thereafter.[28] Treatment response is best evaluated by assessment of the reduction in monthly headache or migraine days, treatment adherence, and adverse events. Other important outcome measures are the reduction in pain intensity during attacks, migraine-related disability, and acute medication use. For this purpose, patients should be encouraged to use headache calendars with entries only needed on symptomatic days. This would, in turn, enable informed clinical decision making on when dose escalation is necessary (or unnecessary). If preventive therapy fails, specialist referral should be considered after a thorough review of underlying reasons.

Antidepressants

Two antidepressants, amitriptyline and venlafaxine, are currently being used in clinical practice. Amitriptyline has shown beneficial effects similar to topiramate for migraine prevention, whereas there are few studies that support the use of venlafaxine.[72,73] Common adverse events to amitriptyline include weight gain, dizziness, and constipation. Worldwide, amitriptyline remains widely used and can be considered in individuals with migraine who have comorbid depression or sleep disturbances.[28]

Antihypertensives

The use of antihypertensives for migraine prevention is well known, with β blockers being common migraine preventive drugs that are used worldwide.[27] A multitude of β blockers (eg, propranolol, metoprolol, and atenolol) have proven beneficial for the preventive treatment of migraine, and candesartan was equally as effective as propranolol in one randomised, triple-masked, crossover study.[74,75] Less evidence exists for the use of lisinopril,[23] and the effectiveness of other antihypertensives (eg, losartan and amlodipin) have not been investigated for migraine prevention.

Anticonvulsants

Two anticonvulsants, topiramate and valproate, are considered effective for migraine prevention, although their safety profiles vary considerably.[28] Valproate should not be used in women of childbearing potential because of the risk of teratogenicity. Topiramate is also preferred because of the existence of high-quality evidence and the absence of weight gain. In a meta-analysis of nine RCTs, topiramate was superior to placebo, as measured by reduction in monthly number of headache days.[76] Common adverse events to topiramate include weight loss, fatigue, nausea, depression, cognitive problems, and paraesthesia. Topiramate has also proven beneficial in preventive treatment of chronic migraine.[77]

Flunarizine

Flunarizine is a calcium channel blocker used for preventive treatment of migraine in some countries, although it is unavailable in the USA.[28] In a comparative effectiveness meta-analysis of RCTs, flunarizine was found to provide clinical benefits in the prevention of episodic migraine.[78] Common adverse events to flunarizine include weight gain, fatigue, nausea, and constipation, whereas drug-induced parkinsonism is an infrequent, but important, side-effect.

OnabotulinumtoxinA

The efficacy of onabotulinumtoxinA is well established for the prevention of chronic migraine, whereas no difference was found on efficacy outcomes when compared with placebo in individuals with episodic migraine.[69] Additionally, one comparator trial found that onabotulinumtoxinA was better tolerated than topiramate, as measured by dropout rates due to insufficient efficacy or adverse events.[79] No systemic adverse events have been reported for onabotulinumtoxinA.[69] The most common adverse events include neck pain, muscle weakness, and injection-site pain.[69]

Anti-CGRP monoclonal antibodies

The integral role of CGRP in migraine pathophysiology has led to the development of four monoclonal antibodies that target CGRP (fremanezumab, galcanezumab, and eptinezumab) or its receptor (erenumab). They are comparably effective, safe, and well tolerated for the prevention of both episodic and chronic migraine.[70] Erenumab (70 or 140 mg once monthly), fremanezumab (225 mg once monthly), and galcanezumab (120 mg once monthly, 240 mg loading dose) are subcutaneously administered, whereas eptinezumab is intravenously administered on a quarterly basis (100 mg or 300 mg once quarterly), although fremanezumab can be administered

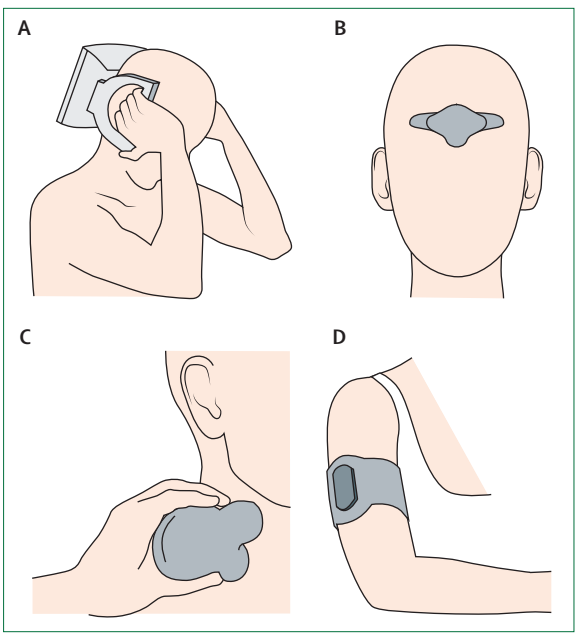

Figure 2: **Neuromodulatory devices**
Several neuromodulatory devices are available for the treatment of migraine. (A) Single-pulse transcranial magnetic stimulation. (B) External trigeminal nerve stimulation. (C) Non-invasive vagus nerve stimulation. (D) Remote electrical neuromodulation.

quarterly in higher doses. Erenumab, fremanezumab, and galcanezumab are also effective in individuals with more than two preventive medication failures because of efficacy or tolerability issues.[80,81,82] The most frequent adverse events are injection-site-related reactions (eg, pain and erythema)[70] and, for erenumab, constipation. Furthermore, use of monoclonal antibodies against CGRP or its receptor has potential immunogenicity and theoretical concerns of cardiovascular safety (eg, cerebro- or cardiovascular events) have been raised.[83] Real-world data are needed to adequately assess tolerability and long-term safety because 6-month follow-up data is scarce.[84,85] Clinical use of monoclonal antibodies against CGRP or its receptor are currently limited by high costs and regulatory restrictions that require documented failure of at least two other preventive medications.

Miscellaneous options

There are several miscellaneous therapeutic options used for migraine prevention, such as melatonin, feverfew, ubidecarenone (also known as coenzyme Q10), magnesium, and riboflavin. These supplements are easily accessible, but studies supporting their use are scarce.[74]

Non-pharmacological therapeutic approaches

Several non-pharmacological therapies have benefits for individuals with migraine and can be used alone or as adjunct therapy to pharmacological drugs. They provide a multidisciplinary approach to clinical management while also minimising unnecessary drug exposure. The non-pharmacological therapies with the strongest evidence include neuromodulation and biobehavioural therapies, such as cognitive behavioural therapy (CBT), biofeedback, and relaxation training. Less evidence supports the use of physical therapy, sleep management, acupuncture, and dietary modifications.

Neuromodulatory devices

Neuromodulation for migraine includes implantable devices and non-invasive devices (figure 2). Implantable devices are considered highly controversial and show little benefit.[86] By contrast, non-invasive neuromodulatory approaches are beneficial and well tolerated in individuals with migraine.[87] The FDA has approved several non-invasive treatments including single-pulse transcranial magnetic stimulation (s-TMS) and external trigeminal nerve stimulation (e-TNS) for both acute and preventive treatment of migraine.[87] Non-invasive vagus nerve stimulation and remote electrical neuromodulation have been approved for acute treatment of migraine.[87] Benefits of neuromodulation might be limited to the short term as there is insufficient data on the long-term effects. The quality of evidence is considered high for non-invasive vagus nerve stimulation and moderate for e-TNS in relation to acute treatment of migraine.[87] In terms of preventive treatment, the quality is classified as moderate for e-TNS and low for s-TMS.[87] As research in neuromodulatory devices progresses, promising treatments are likely to emerge and provide an important alternative to pharmacological therapy.

Biobehavioural therapies

Established biobehavioural therapies for migraine include CBT, biofeedback, and relaxation training. The American Headache Society recommends their use for the preventive treatment of migraine and report Grade A evidence.[38] A meta-analysis from The Cochrane Collaboration reported that 54% of individuals with migraine had at least 50% reduction in migraine frequency following psychological therapy, compared with 24% of controls.[88] However, the authors highlighted the absence of high-quality evidence. This Cochrane review contrasts with the conclusions of another systematic review[89] and partly assessed outcomes as defined by guidelines for drug trials.[88] There is a need for pragmatic solutions to optimise study designs and ensure consistency in reported outcomes. However, biobehavioural therapies continue to provide an important treatment option for many patients, including those with symptoms of psychological disability or special considerations, such as pregnancy or a preference for non-pharmacological therapy.

Dietary approaches

The emphasis on diet in management of migraine is popular among some individuals with migraine and media outlets. Well known dietary approaches include

elimination diets and avoidance of dietary triggers. However, there is very little evidence to support the effect of dietary interventions on migraine. In terms of avoidance of dietary triggers, clinicians should avoid inferring causality of particular foods in the development of migraine attacks. False attribution and recall bias might lead to unnecessary avoidance of specific dietary items.[28,90] Similarly, it is premature to ascribe food diets with beneficial effects on migraine because studies have found that patients benefited from both the intervention diet and control diets.[91,92] Additionally, some evidence suggests that weight loss might reduce the frequency of headache days in individuals with migraine.[93,94] Thus, high-quality research is needed to confirm the effect of dietary approaches in the clinical management of migraine.

Physical therapy

Widespread musculoskeletal pain is common in individuals with migraine. Consequently, it has been suggested that physical therapies (eg, manual therapy and stretching manoeuvres) might improve clinical outcomes. However, one RCT found no additional benefits of physical therapy as an adjunct treatment to medications for migraine.[95] Furthermore, a meta-analysis of controlled trials found that physical therapy techniques reduced the duration of migraine attacks, but had no effect on pain intensity and attack frequency.[96] Thus, firm conclusions cannot be drawn on the potential benefits of physical therapy for patients with migraine.

Quality of sleep

Symptoms of poor sleep quality are frequently found in patients with migraine. Insufficient sleep is reported by 46% of individuals with migraine, compared with 20% of individuals without headache disorders.[97] Despite the widespread prevalence, research into sleep management is still in its infancy, with only few RCTs that show benefits of CBT interventions in individuals with chronic migraine who have comorbid insomnia.[98] Future studies should assess the benefits of various sleep therapies in those with and without comorbid insomnia.

Acupuncture

The use of acupuncture for migraine has been debated for two decades without any consensus being reached. Three large RCTs found either no benefit or minimal benefit of acupuncture on migraine outcomes when compared with sham acupuncture.[99,100,101] However, a 2016 Cochrane review concluded that acupuncture is likely to reduce headache frequency in individuals with episodic migraine if used as an adjunct to acute medications.[102] The evaluation of acupuncture for migraine treatment is further complicated by limitations related to sham acupuncture (a procedure that avoids acupuncture points and often uses fewer penetrative needles). Consequently, most available data is inherently biased, suggesting that benefits from acupuncture might be attributed to a placebo effect. Nonetheless, acupuncture is associated with few adverse events and can be used as a substitute in patients for whom preventive medications are ineffective or contraindicated.

Patient centricity

Migraine is a heterogeneous disorder and its clinical manifestations can vary within and between patients over time. To optimise clinical care, there is an urgent need for therapeutic approaches to recognise the clinical characteristics, preferences, and needs of individual patients, thereby avoiding a general standardised approach. Agreed realistic objectives are important and any therapeutic strategy must also account for local resources and access to medications.

Patient preference

Patient preference is an important factor that affects treatment adherence and patient-reported satisfaction. For acute medications, one clinic-based study[103] found that patients emphasised a preference for drugs that provided rapid pain-freedom (within 30 min). Regarding preventive medications, patients rated effectiveness as the most important aspect, followed by rapidity of the effect and absence of adverse events.[104] Although these data are informative, clinicians should always individualise their treatment strategy to the specific needs of each patient.

Patient education

Patient education is of considerable importance in reaching long-term therapeutic success and treatment adherence.[105] Clinicians must strive to implement timely educational strategies, preferably before the start of treatment. Additionally, educational strategies should be personalised and repeated to reduce the risk of non-adherence. Patients should also be counselled on the expected benefits of their treatment and the possible treatment-related adverse events.[28] At follow-up consultations, clinicians should evaluate treatment response and adherence, and include a discussion of the patient's own expectations and satisfaction with the current treatment strategy. Early alignment of expectations is recommended to establish realistic and appropriate treatment goals. Although some data are available, more studies are needed to establish evidence-based educational interventions for migraine.

Physician–patient communication

An important reason for non-adherence and poor clinical outcomes is ineffective physician–patient communication. Active follow-up is recommended within a few weeks after initiation or change of treatment. Some studies suggest that physician–patient communication is often inadequate and can benefit from using open-ended questions and validated tools (eg, HURT and M-TOQ)

for treatment evaluation.[106] Nurses and other caregivers could be used to improve the delivery of adequate care and patient education.[107]

Simplified dosing schedules

Medication adherence can be improved by using simplified dosing schedules that are tailored to fit individual patient characteristics and preferences.[108] This method has not been systematically investigated in patients with migraine, but knowledge from other disorders could be used.[109] Medical studies have shown that once daily medication regimens and use of 7-day pill boxes are valuable resources.[109] Additionally, the use of electronic headache diaries and automated reminder systems could promote adherence and should be a future research priority.

Future research for intervention studies and guideline development

Prospective, randomised, controlled clinical trials are the gold standard to assess the efficacy and safety of interventions for migraine. The International Headache Society guidelines for controlled trials of acute and preventive treatments for migraine[25,110] have assured the continued viability of RCTs. However, RCT data are from carefully selected migraine populations that might not adequately reflect patients in real-world practice. Thus, concerted efforts are needed to optimise RCT data and provide complementary data from large-scale registry studies in clinical practice. First, future RCTs should report both the monthly reduction in migraine and a panel of patient-reported outcomes to fully capture the benefits of a specific intervention. Second, appropriate outcome measures are needed to adequately assess the effect of novel therapies on aura symptoms. Third, health technology assessments should be implemented to evaluate the cost-effectiveness and indirect effects of specific interventions (eg, effect on family life, work productivity, and risk of disorders secondary to treatment, particularly medication overuse headache). Finally, large-scale clinical registries that provide a platform for independent RCT data verification in clinical settings are needed. For this purpose, registry-based RCTs and well designed, non-randomised, observational studies should be viable options to ensure high-quality evidence. In this framework, it should also be possible to do comparative studies between therapeutic approaches. These studies would enable development of informed clinical practices and an ascertainment of the efficacy, tolerability, and safety of available therapies. Additionally, trial costs can be reduced if innovative approaches (eg, at-home testing or Bayesian statistics) and digital technologies (eg, electronic patient-reported outcomes) are fully embedded in the data acquisition workflow.

Emerging treatments

The past decade has seen major progress in the development of novel treatments for migraine, with results from ongoing trials still pending (NCT03855137, NCT03700320, NCT04197349, and NCT03238781). Emerging therapies for migraine prevention include two CGRP receptor antagonists, atogepant and rimegepant, and a monoclonal antibody (Lu-AG09222) that inhibits the signalling molecule pituitary adenylate cyclase-activating polypeptide (PACAP).

Atogepant

Ongoing RCTs are evaluating the efficacy and safety profile of oral atogepant for migraine prevention (NCT03855137, NCT03700320). A phase 2b/3 trial published in 2020 found that multiple dosing regimens of atogepant were superior to placebo, with the most common adverse events being nausea and fatigue.[111] However, more data are needed to adequately determine efficacy, tolerability, and safety.

Rimegepant

In 2020, the use of rimegepant as an orally disintegrating tablet was approved for the acute treatment of migraine.[112] A phase 2b/3 trial reported oral rimegepant 75 mg every other day was superior to placebo, with the most common adverse events being nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection. Further data are needed to adequately determine efficacy, tolerability, and safety.[113]

Anti-PACAP monoclonal antibodies

Over the past decade, monoclonal antibodies targeting signalling molecule PACAP or its pituitary adenylate cyclase-activating polypeptide type 1 (PAC_1) receptor have been considered as possible drug targets. ALD1910 (also known as Lu-AG09222) binds to the PACAP ligand and is currently being evaluated in a phase 1 clinical trial (NCT04197349). AMG301—a monoclonal antibody targeting the PAC_1 receptor—did not show therapeutic benefit when compared with placebo in a phase 2 clinical trial (NCT03238781).[114] However, PACAP acts on two other receptors in addition to the PAC_1 receptor.[115] As such, Lu-AG09222 might still hold promise as a novel medication for migraine prevention.

Conclusion

There have been great advances in the treatment of migraine over the past 5 years, with novel mechanism-based treatments that complement standard of care and mitigate the disease burden attributed to migraine. Many therapeutic options are available to effectively treat migraine but several obstacles remain, including the current knowledge gap related to tailored treatment for individual patients. First, there needs to be more research on the biological underpinnings of migraine to identify potential mechanism-based drug targets. Second, precision medicine strategies that tailor new therapies to each patient's unique migraine profile need to be developed. Finally, clinicians should use

evidence-based multidisciplinary approaches to optimise clinical practices and address unmet treatment needs.

Contributors

MA, HA, TPD, and DWD initiated the concept and designed the scope of this Series paper. MA and DWD wrote the first draft of the introduction. HA, MA, and DWD wrote the first draft of the section on acute treatment. RHS, DDM, and MA wrote the first draft of the section on preventive treatment. DDM, DCB, and DWD wrote the first draft of the section on non-pharmacological therapeutic approaches. DDM, DCB, and DWD wrote the first draft of the section on patient centricity. PP-R, GMT, and MA wrote the first draft of the section on future research for intervention studies and guideline development. TPD, MJL, and MA wrote the first draft of the section on emerging treatments. MA and DWD wrote the first draft of the conclusion. MFPP, CT, and MA wrote the first draft of the section on medication overuse headache. MFPP, CT, and MA wrote the first draft of the section on clinical management of migraine in specific populations. All authors reviewed and approved the final version.

Declaration of interests

MA is a consultant, speaker, or scientific advisor for AbbVie, Allergan, Amgen, Alder, Biohaven, Eli Lilly, Lundbeck, Novartis, and Teva, and primary investigator for Alder, Amgen, Allergan, Eli Lilly, Lundbeck, Novartis, and Teva trials. MA has no ownership interest and does not own stocks of any pharmaceutical company. MA serves as associate editor of *Cephalalgia* and associate editor of the *Journal of Headache and Pain*. MA is president of the International Headache Society. DCB has served as a consultant to and received research funding from Amgen–Novartis, Allergan, Avanir, Biohaven, Eli Lilly, Promius–Dr Reddy's, and Teva. DCB is on the editorial board of *Current Pain and Headache Reports*. PP-R has received honoraria for participation in clinical trials and contribution to advisory boards or medical education from Allergan, Almirall, Amgen, Biohaven, Chiesi, Electrocore, Eli Lilly, Medscape, Novartis, and Teva. PP-R's headache research is supported by La Caixa Foundation, AGAUR, Instituto Investigacion Carlos III, Migraine Research Foundation, and PERIS. MFPP reports grants from Fapesp and CNPq, and personal fees from Allergan, Eurofarma, Eli Lilly, Libbs, Novartis, Pfizer, and Teva, during the conduct of the study. MJL reports grants from the National Research Foundation of Korea, Korean Society of Neurosonology, and Yuhan Company. MJL is a consultant, speaker, or scientific advisor for Eli Lilly and has received speaker honoraria from Sanofi–Aventis and YuYu Pharma, outside the submitted work. MJL serves as junior editor of *Cephalalgia*. GMT reports grants or consultancy support from Novartis, Lilly, Teva, and Allergan, and independent support from the Dutch Research Council, National Institutes of Health, European Community, Dutch Heart Foundation, and Dutch Brain Foundation. RHS reports personal fees from Impel, Teva, BioHaven Pharmaceuticals, and Supernus Pharmaceuticals, and grants from Amgen and Eli Lilly. CT has participated in advisory boards for Allergan, ElectroCore, Eli Lilly, Novartis and Teva, has lectured at symposia sponsored by Allergan, Eli Lilly, Novartis, and TEVA, and is principal investigator or collaborator in clinical trials sponsored by Alder, Eli-Lilly, IBSA, Novartis, and Teva. CT has also received research grants from the European Commission, the Italian Ministry of Health, the Italian Ministry of University, and the Migraine Research Foundation. DDM reports grants and personal fees from Cefaly, Electrocore, Eli Lily, Novartis, Merz, Teva, Specifar, Amgen, Biogen, and Genesis Pharma. DWD reports personal fees from Allergan, Amgen, Alder, Arteaus, Pfizer, Colucid, Merck, NuPathe, Eli Lilly Autonomic Technologies, Praxis, Cerecin, CTRLM, Cooltech, XoC, Pieris, Revance, Equinox, GSK, Linpharma, AEON, Ethicon, Zogenix, Supernus, Labrys, Boston Scientific, Medtronic, St Jude, Bristol-Myers Squibb, Lundbeck, Impax, MAP BioPharma, electroCore, Tonix, Novartis, Teva, Alcobra, Zosano, ZP Opco, Insys, Ispen, Acorda, eNeura, Charleston Laboratories, Gore, Biohaven, Biocentric, Magellan, Foresight, IntraMed, SAGE Publishing, Oxford University Press, American Academy of Neurology, UptoDate, Theranica, Decision Resources, Xenon, Dr Reddy's–Promius Pharma, Vedanta, CC Ford West Group, Foresight, Wolters Kluwer Health, Wiley Blackwell, Axsome, Neurolief, Satsuma, and Impel, outside the submitted work. DWD reports personal fees and non-financial support from West Virginia University Foundation, Canadian Headache Society, Healthlogix, Universal Meeting Management, WebMD/Medscape, Oregon Health Science Center, Albert Einstein University, University of Toronto, Synergy, MedNet, Peer View Institute for Medical Education, Medicom, Medlogix, Chameleon Communications, Academy for Continued Healthcare Learning, Haymarket Medical Education, Global Scientific Communications, Miller Medical, MeetingLogiX, University of British Columbia, University of Southern California, University of California (Los Angeles), American Academy of Neurology, and Canadian Headache Society, outside the submitted work. DWD reports options from Epien, GBS/Nocira, Second Opinion Health, Healint, NeuroAssessment Systems, Myndshft, King-Devick Technologies, Aural Analytics, and Ontologics, outside the submitted work. DWD reports non-financial support from Starr Clinical, International Headache Society, American Headache Society, American Brain Foundation, and American Migraine Foundation. DWD has an issued patent entitled Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis (patent number 17189376.1-1466:v). All other authors declare no competing interests.

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