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Received: 16 March 2021 | Accepted: 9 May 2021

DOI: 10.1111/head.14153

AHS CONSENSUS STATEMENT

The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice

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Abstract

Objective: To incorporate recent research findings, expert consensus, and patient perspectives into updated guidance on the use of new acute and preventive treatments for migraine in adults.

Background: The American Headache Society previously published a Consensus Statement on the use of newly introduced treatments for adults with migraine. This update, which is based on the expanded evidence base and emerging expert consensus concerning postapproval usage, provides practical recommendations in the absence of a formal guideline.

Methods: This update involved four steps: (1) review of data about the efficacy, safety, and clinical use of migraine treatments introduced since the previous Statement was published; (2) incorporation of these data into a proposed update; (3) review and commentary by the Board of Directors of the American Headache Society and patients and advocates associated with the American Migraine Foundation; (4) consideration of these collective insights and integration into an updated Consensus Statement.

Results: Since the last Consensus Statement, no evidence has emerged to alter the established principles of either acute or preventive treatment. Newly introduced acute treatments include two small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists (ubrogepant, rimegepant); a serotonin (5-HT$_{1F}$) agonist (lasmiditan); a nonsteroidal anti-inflammatory drug (celecoxib oral solution); and a neuromodulatory device (remote electrical neuromodulation). New preventive treatments include an intravenous anti-CGRP ligand monoclonal antibody (eptinezumab). Several modalities, including neuromodulation (electrical trigeminal nerve stimulation, noninvasive vagus nerve stimulation, single-pulse transcranial magnetic stimulation) and biobehavioral therapy (cognitive behavioral therapy, biofeedback, relaxation therapies, mindfulness-based therapies, acceptance and commitment therapy) may be appropriate for either acute and/or preventive treatment; a neuromodulation device may be appropriate for acute migraine treatment only (remote electrical neuromodulation).

Abbreviations: AE, adverse event; CGRP, calcitonin gene-related peptide; DHE, dihydroergotamine; FIS, Functional Impairment Scale; HIT, Headache Impact Test; HRQoL, health-related quality of life; ICHD-3, International Classification of Headache Disorders, 3rd edition; IM, intramuscular; IV, intravenous; mAbs, monoclonal antibodies; MFIQ, Migraine Functional Impact Questionnaire; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; Migraine-ACT, Migraine Assessment of Current Therapy; MMD, monthly migraine day; MPFID, Migraine Physical Function Impact Diary; MSQ, Migraine-Specific Quality of Life; mTOQ, Migraine Treatment Optimization Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; PGIC, Patient Global Impression of Change; PPMQ-R, Patient Perception of Migraine Questionnaire-Revised; SC, subcutaneous; WPAI, Work Productivity and Activity Impairment.

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Conclusions: The integration of new treatments into clinical practice should be informed by the potential for benefit relative to established therapies, as well as by the characteristics and preferences of individual patients.

KEYWORDS
acute, consensus, migraine, preventive, principles, treatment

INTRODUCTION

Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting,[1] and, frequently, cutaneous allodynia.[2–6] About one third of those with migraine have migraine with aura, and approximately three quarters experience a premonitory phase prior to the onset of headache.[7] Diagnoses of migraine can be refined based on the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs) (Table 1).[1]

Migraine is widespread, and it can have a substantial burden of illness. The one-year period prevalence is 18% in women and 6% in men, and prevalence peaks between the ages of 25 and 55.[8–10] Migraine attacks can significantly impair functional ability at work or school, at home, and in social situations.[11–13] Among neurologic conditions, it ranks second worldwide in terms of years lost to disability.[14,15] Migraine is associated with a considerable financial burden, with annual total costs estimated at $27 billion in the United States,[16,17] and increased risk for a range of common health conditions, including anxiety, depression, asthma, epilepsy, and stroke.[18]

TABLE 1 ICHD-3 criteria for migraine and chronic migraine[1]

Migraine
(A) At least five attacks fulfilling criteria B–D
(B) Headache attacks lasting 4–72 h (when untreated or unsuccessfully treated)
(C) Headache has at least two of the following four characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
(D) During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
(E) Not better accounted for by another diagnosis
Chronic migraine
(A) Migraine-like or tension-type-like headache on ≥15 days/month for >3 months that fulfill criteria B and C
(B) Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura
(C) On ≥8 days/month for >3 months, fulfilling any of the following:
1. Criteria C and D for migraine without aura
2. Criteria B and C for migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
(D) Not better accounted for by another diagnosis

Abbreviation: ICHD-3, International Classification of Headache Disorders, 3rd edition.

The pain and associated symptoms of migraine, as well as its life consequences, can be addressed with acute treatments, preventive treatments, or both.[19,20] However, because the severity, frequency, and characteristics of migraine vary among persons and, often, within individuals over time,[21] and symptom profiles or biomarkers that predict efficacy and side effects at the individual level have not yet been identified,[22,23] optimizing treatment for particular patients remains challenging. As a result, although the majority of patients with migraine respond to prescribed treatment(s), a process of trial and error is often necessary before a therapeutic plan can be individualized. To account for these challenges while ensuring access to cost-effective medical care, reimbursement decisions concerning migraine treatments must reflect these clinical realities.

The development and introduction of new medications and devices has led to important advances in the acute and preventive treatment of migraine. As a result, the appropriate and cost-effective integration of these new treatments remains a high priority for prescribing clinicians. The American Headache Society, consistent with its mission of improving the lives of individuals impacted by headache, previously established indications for which the initiation and continuation of novel acute and preventive treatments might be appropriate. For this update, the Society convened a task force (the authors JA, RCB, and MSR) to review the literature published since December 2018 and to revise the document based on its findings. The initial literature review was performed by JA, RCB, and MSR in September 2019. Additional relevant information, including subsequently published clinical trials and regulatory updates, was included through February 2021. Commentary on the revision was provided by the Board of Directors of the American Headache Society and patients and patient advocates associated with the American Migraine Foundation. The AHS Board of Directors provided final review of the Consensus Statement in February 2021.

The resulting update to *The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice* is designed to offer prescribing clinicians with guidance in the use of established and recently approved therapies for the acute and preventive treatment of migraine, including the goals of treatment, approved indications for usage, and strategies for developing personalized treatment plans. Like its predecessor, this Statement uses the recommendations of the US Headache Consortium as a

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starting point,[22,24–28] but it incorporates information that has become available since the first Statement was published, including new recommendations about the use of novel treatments approved for the acute and preventive treatment of migraine and an evidence-based update on the long-term safety of monoclonal antibodies (mAbs) to calcitonin gene-related peptide (CGRP) and its receptor for the preventive treatment of migraine.

As in the first Consensus Statement, the objective of this document is to improve outcomes among patients with migraine who have unmet needs by helping clinicians identify and develop successful, evidence-based treatment plans for those most likely to benefit from a trial of a new therapy. Although it provides timely recommendations to clinicians and their patients with migraine, this Consensus Statement is not intended to be, and should not be understood or applied as, a Clinical Practice Guideline. Expert consensus about optimal sequencing and layering of acute and preventive treatments (e.g., migraine-specific vs. nonspecific), as well as definitive guidance distinguishing the efficacy, tolerability, and safety of new treatments relative to established treatments and each other, await the results of studies designed to answer these important questions. In the meantime, the Society recommends that within migraine-specific acute therapies and preventive treatments, generalized step-care strategies be adjusted to meet the medical needs of individual patients. Individualized treatment plans are more likely to provide appropriate therapy at the initial consultation and spare patients a series of failed therapeutic efforts,[29,30] yielding both better clinical outcomes and lower healthcare costs.

Readers are advised that this Statement has been reorganized. The section on acute treatment now precedes preventive treatment, which more closely aligns with the experience of migraine in clinical practice. The previous subcategory of *Patient Identification* now appears under the single subcategory of *Indications*. A new section addresses treatments that provide therapeutic benefits as acute and preventive therapies.

ACUTE TREATMENT

Goals

The goals of the acute treatment of patients with migraine include the following[23]:

- Rapid and consistent freedom from pain and associated symptoms, especially the most bothersome symptom, without recurrence.
- Restored ability to function.
- Minimal need for repeat dosing or rescue medications.
- Optimal self-care and reduced subsequent use of resources (e.g., emergency room visits, diagnostic imaging, clinician and ambulatory infusion center visits).
- Minimal or no adverse events (AEs).
- Cost considerations.

Effective acute treatment can reduce the pain, associated symptoms, and disability associated with attacks. Suboptimal acute treatment is associated with higher migraine-related disability and risk of disease progression.[31]

Indications

All patients with a confirmed diagnosis of migraine should be offered a trial of acute pharmacological and/or nonpharmacologic treatment.

Developing treatment plans

Patient education and lifestyle modification are important tools in the management of patients with migraine, and acute treatment plans should incorporate personalized guidance about the benefits of proper nutrition, regular exercise, adequate hydration, proper sleep, stress management, and maintaining a migraine diary.[32,33] In addition to education and lifestyle recommendations tailored to the individual, the following principles should be used as a guide in developing personalized plans for the acute treatment of patients with migraine.[23]

Use evidence-based treatments

Use nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (e.g., aspirin + acetaminophen + caffeine) for mild-to-moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE], small-molecule CGRP receptor antagonists [gepants], selective serotonin ($5\text{-}HT_{1F}$) receptor agonist [ditan]) for moderate or severe attacks and mild-to-moderate attacks that respond poorly to nonspecific therapy.[19,23] Acute treatments considered effective or probably effective based on reviews of available evidence[19,34–47] are presented in Table 2.

Evidence suggests that about 30% of patients who are given a prescription for a triptan have an insufficient response, resulting in significantly higher healthcare utilization and costs than those who obtain adequate relief.[48] Although some research has shown that individuals in whom an initial triptan medication is ineffective have a better response after being switched to a second drug in the triptan class,[49,50] other studies have found no association between switching triptan regimens or adding acute therapies and improved outcomes.[51,52] Therefore, patients who do not respond to initial therapy with a triptan, or in whom the initial choice of acute treatment is intolerable or contraindicated, may benefit from a second triptan or a different therapy, as shown in Table 3. In this setting, evidence for a migraine-specific therapy supports use of a gepant (ubrogepant[34–36] or rimegepant[37–39]) or a ditan (lasmiditan[40,41]). Neuromodulatory devices can also be considered (electrical trigeminal nerve stimulation [eTNS][53,54]; noninvasive vagus nerve stimulation [nVNS][44]; remote

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TABLE 2 Acute treatments with evidence of efficacy in migraine[19,34–41,47]

Established efficacy[a]	Probably effective
Migraine-specific	
Triptans	Ergotamine
Ergotamine derivatives	Other forms of dihydroergotamine
Gepants	
Lasmiditan	
Nonspecific	
NSAIDs: aspirin, celecoxib oral solution, diclofenac, ibuprofen, naproxen	NSAIDs: flurbiprofen, ketoprofen, IV and IM ketorolac
Combination analgesic: acetaminophen + aspirin + caffeine	IV magnesium[b]
	Isometheptene-containing compounds
	Antiemetics: chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine

Abbreviations: IV, intravenous; IM, intramuscular; NSAID, nonsteroidal anti-inflammatory drug.

[a]Consider neuromodulatory devices in patients who prefer nondrug treatments or in whom drug treatment is ineffective, intolerable, or contraindicated.

[b]In migraine with aura.

TABLE 3 Criteria for initiating acute treatment with gepants, ditans, or neuromodulatory devices[a]

Use is appropriate when ALL the following are met:
(A) Prescribed/recommended by a licensed clinician
(B) Patient is at least 18 years of age[b]
(C) Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
(D) Either of the following:
a. Contraindications to or inability to tolerate triptans[c]
b. Inadequate response to two or more oral triptans, as determined by EITHER of the following
(i) Validated acute treatment patient-reported outcome questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC)
(ii) Clinician attestation

Abbreviations: FIS, Functional Impairment Scale; ICHD-3, International Classification of Headache Disorders, 3rd edition; Migraine-ACT, Migraine Assessment of Current Therapy; mTOQ, Migraine Treatment Optimization Questionnaire; PGIC, Patient Global Impression of Change; PPMQ-R, Patient Perception of Migraine Questionnaire-Revised.

[a]To improve the likelihood of choosing appropriate therapy at the initial consultation[29,30] and adjust these recommendations to the needs of individual patients.

[b]Three neuromodulatory devices (nVNS, REN, sTMS) have also received clearance for the treatment of patients aged 12–17 years.

[c]Gepants, ditans, and neuromodulatory devices may be considered.[55]

electrical neuromodulation [REN][45,46]; or single-pulse transcranial magnetic stimulation [sTMS][42]).

In the absence of real-world data, judgments about prescribing specific agents for acute treatment may benefit from comparing numbers needed to treat and harm, as the use of metrics that fail to account for relative efficacy and safety data (e.g., placebo-subtracted response) may lead to suboptimal outcomes[56] and increased costs. However, because clinical trial populations may not accurately reflect experience in general practice, drug selection should be informed by clinical expertise, the needs of individual patients, and real-world clinical evidence as it becomes available.

Regardless of which acute treatment is prescribed, patients should be instructed to treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability.[57]

Choosing a nonoral route of administration for severe nausea or vomiting

A nonoral formulation should be used in patients whose attacks are associated with severe nausea or vomiting, who do not respond well to traditional oral treatments, or who have trouble swallowing orally administered medications. This includes sumatriptan 3, 4, or 6 mg subcutaneous (SC) and intranasal liquid and powder formulations, as well as ketorolac in intranasal and intramuscular (IM) formulations.[58–62] Alternatives include DHE SC and intranasal spray. Intravenous (IV) DHE and an antiemetic should be considered for especially refractory headaches. In addition, antiemetics, such as prochlorperazine and promethazine suppositories (for both headache and nausea), may be useful. Other nonoral options for acute treatment include the neuromodulatory devices (i.e., eTNS, nVNS, REN, and sTMS). Nonoral routes of administration should also be considered in patients who do not respond well to traditional oral treatments or experience significant nausea or vomiting early during attacks.

Accounting for tolerability and safety issues

The tolerability and safety of certain acute treatments may preclude usage in many patients including those with certain coexistent or comorbid illnesses. For instance, NSAIDs can cause serious gastrointestinal and cardiovascular side effects. Triptans and ergot derivatives should be avoided or used with caution in patients with coronary artery disease, peripheral vascular disease, uncontrolled hypertension, and other vascular risk factors and disorders. In patients with preexisting vascular disease or in whom triptans are otherwise contraindicated, gepants, ditans, or neuromodulatory devices may be useful. However, although the clinical trials of gepants and ditans included subjects with stable cardiovascular disease and showed good safety and tolerability outcomes,[34–41] benefit–risk should be assessed in each patient as the real-world database for these therapies grows. Similarly, when contraindications are not clear-cut (e.g., one to two cardiovascular risk factors, moderate Framingham risk), drug selection must be individualized. Any of the approved neuromodulatory devices may be considered in patients who have experienced moderate to severe tolerability and/or safety issues with pharmacotherapy.[23] Failure

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to account for tolerability and safety issues in prescribing may cause patients to limit, delay, or forego acute treatment.[56]

Considering self-administered rescue

When acute treatment does not bring relief, patients may require rescue medication. Depending on the initial treatment, options for outpatient rescue include SC sumatriptan, DHE IM or intranasal spray, IM ketorolac, or corticosteroids (e.g., dexamethasone); office-based or inpatient options may include parenteral formulations of triptans, DHE, antiemetics, NSAIDs (e.g., ketorolac), anticonvulsants (e.g., valproate sodium [not in women of childbearing potential who are not using an appropriate method of birth control[63,64]]), corticosteroids, magnesium sulfate, and peripheral nerve blocks. Consider recommending a self-administered rescue treatment for patients with severe attacks and those who have a history of nonresponse or variable response to acute treatment.

Avoiding medication overuse

Patients with migraine who need to use acute treatments on a regular basis should be instructed to limit medication use to an average of two headache days per week, and patients who exceed this limit should be offered a preventive treatment. Patients who continue to overuse acute medication while receiving preventive therapy may require an escalation in the preventive dose or a change in acute or preventive therapy; expert consensus generally supports the addition of a second preventive treatment in these patients. Among newer medications, repeated treatment with the CGRP receptor antagonists (i.e., ubrogepant and rimegepant) does not appear to be associated with medication-overuse headache[65–67]; preclinical models suggest repeated use of lasmiditan may induce medication-overuse headache through persistent latent peripheral and central sensitization mechanisms, although clinical studies are lacking.[68,69] Acute treatment with an approved neuromodulatory device may reduce the use of acute medication.[70]

Recently approved acute treatments

Since the publication of the initial Consensus Statement, the FDA has approved or cleared five therapies for the acute treatment of migraine: celecoxib, lasmiditan, REN, rimegepant, and ubrogepant.

Celecoxib

Celecoxib, which has been used to treat acute pain since 1998, was approved for the acute treatment of migraine; the new formulation is supplied as an oral solution. Efficacy is supported by findings from two randomized controlled clinical trials.[47,71] As with other NSAIDs, the prescribing information for celecoxib oral solution carries a boxed warning about risk of serious cardiovascular thrombotic events (e.g., myocardial infarction and stroke), and the drug is contraindicated in the setting of coronary artery bypass graft surgery.[71] Other safety concerns with celecoxib oral solution include an elevated risk of spontaneous bleeding, ulceration, and perforation of the stomach or intestines, particularly among elderly patients and those with a history of peptic ulcer disease and/or gastrointestinal bleeding.[71]

Lasmiditan

Lasmiditan was approved based on positive results from two randomized controlled clinical trials evaluating lasmiditan doses of 50, 100, and 200 mg.[40,41] The most common AEs were dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness. Lasmiditan has been associated with driving impairment and sleepiness, and it is classified as a Schedule V controlled substance (low potential for abuse).[72] Patients given a prescription for lasmiditan should be cautioned not to drive within 8 h after taking their medication. Frequent use of lasmiditan may potentially cause medication-overuse headache.[68] The safety, tolerability, and efficacy of coadministering lasmiditan with a triptan or a gepant has not been assessed.

Remote electrical neuromodulation

The REN device achieves therapeutic effects by delivering transcutaneous electrical stimulation to the upper arm, which induces conditioned pain modulation and activates a descending endogenous analgesia.[73] It was FDA-cleared for the acute treatment of migraine in adults based on positive results in a randomized controlled clinical trial[45]; it was cleared for the acute treatment of migraine and chronic migraine in patients aged 12 years and older based on data from an open-label, single-arm, multicenter study.[74] As with many nondrug therapeutic options, REN has shown good tolerability and safety in clinical trials; paresthesia in the area of the device was the most common side effect.[45,46] This novel approach to acute treatment may also reduce the use of medications and consequent risk of medication-overuse headache.[70]

Rimegepant

Rimegepant has demonstrated efficacy and tolerability in multiple randomized controlled clinical trials.[37–39] It has shown good safety and tolerability when used for up to 1 year, with nausea the most commonly reported AE.[66] The maximum dosage of rimegepant is a single 75 mg dose as needed per 24 h.[75] As stated previously, rimegepant (as with ubrogepant and lasmiditan) does not constrict blood vessels and may have a role in patients with cardiovascular

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contraindications to triptans.[76] Repeated acute treatment with rimegepant does not appear to be associated with medication-overuse headache,[66,67] which makes it similar to ubrogepant[65] and may distinguish it from lasmiditan.[68]

Ubrogepant

Ubrogepant, the first drug in the gepant class to receive FDA approval for the acute treatment of migraine, has shown efficacy in two randomized controlled clinical trials.[34,35] In a 1-year open-label trial, 50 and 100 mg doses of ubrogepant used intermittently (one or two doses per attack) had good safety and tolerability, and the most common AEs were nausea, somnolence, and dry mouth; there was no evidence of medication-overuse headache, hepatotoxicity, or serious AEs.[77] In clinical practice, a substantial subset of patients may require two doses of ubrogepant to treat their attacks, as approximately 40% of ubrogepant-treated patients in clinical trials took an optional second dose of study treatment.[34,35]

To achieve cost-effective care while ensuring access to those most appropriate for these treatments, it is important that the criteria for initiating treatment with novel acute treatments are widely understood and closely followed (Table 3). To determine efficacy and tolerability, at least three attacks should be treated, and response to treatment should be evaluated using a validated acute treatment patient-reported outcome questionnaire or clinical assessment of improvement by the prescribing clinician.

Measuring response to acute treatment

The efficacy endpoints typically used in clinical trials may not fully reflect the outcomes valued by patients[78–80] or the importance of ease of use in forming patient perceptions of treatment. Failure to understand patient preferences may reduce adherence, discourage patients from continuing treatment, and limit the ability to match treatment with patient needs. Patient-oriented, validated outcome measures of acute treatment success can help to verify that patients have experienced a meaningful response and identify the need for adjustments to a therapeutic regimen (Appendix A).

PREVENTIVE TREATMENT

Goals

The goals of migraine prevention are to[22–24]:

- Reduce attack frequency, severity, duration, and disability.
- Improve responsiveness to and avoid escalation in use of acute treatment.
- Improve function and reduce disability.
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments.
- Reduce overall cost associated with migraine treatment.
- Enable patients to manage their own disease to enhance a sense of personal control.
- Improve health-related quality of life (HRQoL).
- Reduce headache-related distress and psychological symptoms.

Preventive treatments—pharmacologic, interventional, biobehavioral, neurostimulation, nutraceuticals, and lifestyle modification—are important parts of the overall approach for a proportion of people with migraine, and multiple evidence-based guidelines are available.[20,23,25–28] None of the currently available oral preventive treatments was designed specifically for migraine, and many oral preventive treatments have limited to moderate efficacy, moderate to high rates of AEs, contraindications, or interactions that limit use. These factors explain in part why few patients with migraine use preventive treatment (3%–13%), even though it is believed that nearly 40% of those with migraine with or without aura, and almost all of those with chronic migraine, in the general population would benefit.[8,81]

Indications

Patients with migraine should be considered for preventive treatment in any of the following situations[22–24]:

- Attacks significantly interfere with patients' daily routines despite acute treatment.
- Frequent attacks (Table 4).
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as follows:
  a. Ten or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused.
  b. Fifteen or more days per month for nonopioid analgesics, acetaminophen, and NSAIDs.
- AEs with acute treatments.
- Patient preference.

TABLE 4 Criteria for identifying patients for preventive treatment[8]

Prevention should be …	Headache days/month	Degree of disability required[a]
Offered	6 or more	None
	4 or more	Some
	3 or more	Severe
Considered	4 or 5	None
	3	Some
	2	Severe

[a]As can be measured by the Migraine Disability Assessment Scale, Migraine Physical Function Impact Diary, or Headache Impact Test.

Prevention should also be considered in the management of certain uncommon migraine subtypes, including hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura (>60 min), and those who have previously experienced a migrainous infarction, even if there is low attack frequency.[22–24]

Patients are most often selected for preventive treatment based on attack frequency and degree of disability. Consensus guidelines identify groups of patients where preventive treatment should be either "offered" or "considered" based on the parameters in Table 4.[8]

Another important element of identification involves reviewing the history of medication use for acute treatment and treatment response. Those with migraine who have poorly controlled attacks are at risk of medication overuse and more likely to develop medication-overuse headache (Table 5) and chronic migraine, and overuse of medications for the acute treatment of headache may reduce the effectiveness of some preventive treatments.[23,82] Several preventive medications have demonstrated evidence of efficacy in patients with migraine who are overusing acute treatments (e.g., topiramate, onabotulinumtoxinA, CGRP mAbs).[19]

Before a preventive treatment plan is developed, measures to ensure appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments coupled with education and lifestyle modifications should be initiated.[1]

Developing treatment plans

As with acute treatment, individualized patient education and lifestyle modification recommendations are important to preventive treatment plans. Patients should be instructed about identification and minimization of exposure to migraine triggers, as well as the benefits of proper nutrition, regular exercise, adequate hydration, proper sleep, stress management, and maintaining a migraine diary.[32] Accordingly, preventive treatment plans for migraine should include education and lifestyle recommendations and use the following principles as a guide to initiating, titrating, and, if necessary, stopping preventive treatment.[22,24,83]

TABLE 5 ICHD-3 criteria for medication-overuse headache[1]

(A) Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder
(B) Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, with medication overuse defined as
1. Ten or more days/month for ergot derivatives, triptans, opioids, combination analgesics,[a] and a combination of drugs from different classes that are not individually overused
2. Fifteen or more days/month for nonopioid analgesics, acetaminophen, and NSAIDs
(C) Not better accounted for by another diagnosis

Abbreviations: ICHD-3, International Classification of Headache Disorders, 3rd edition; NSAID, nonsteroidal anti-inflammatory drug.
[a]Drugs of two or more classes, each with analgesic effect (e.g., acetaminophen + codeine) or acting as adjuvants (e.g., caffeine).

Using evidence-based preventive treatments

The use of evidence-based treatments is essential to the success of migraine prevention. Table 6 shows preventive pharmacologic treatments that are effective or probably effective based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence.[20,84]

Based on reliable evidence supporting efficacy and safety,[87–98] there are now four CGRP mAbs approved for use in the United States: eptinezumab, erenumab, fremanezumab, and galcanezumab. Eptinezumab, fremanezumab, and galcanezumab target the CGRP ligand, and erenumab targets the CGRP receptor. Erenumab, fremanezumab, and galcanezumab are administered as SC injections, and eptinezumab is the first migraine preventive administered as an IV infusion. Following the criteria for initiating treatment with these evidence-based migraine-specific therapies (Table 7) will help medical professionals balance cost-effectiveness with access to care.

Although evidence can narrow the range of therapeutic options, it does not replace clinical judgment; preventive treatment plans must be designed to meet the needs of individual patients with migraine. For example, among those with a history of at least eight MHDs, if the medical risk from a trial of two or more established preventive treatments outweighs the possible benefits, an attestation by the prescribing clinician should take precedence over prospectively defined plans and allow patients access to whatever treatment(s) are deemed medically necessary. Meeting individualized needs may also involve combining older and newer treatments as well as complex or nontraditional approaches.[20] In an observational study of patients with intractable chronic migraine who were receiving onabotulinumtoxinA and treated adjunctively with erenumab,[99] the onabotulinumtoxinA–CGRP mAb combination improved response to treatment and, compared with onabotulinumtoxinA monotherapy, extended the effects by about 2 weeks while demonstrating good tolerability and safety. A trial designed to determine the nature and extent, if any, of a clinically meaningful synergistic effect between these treatments is warranted, although their differential effects on the trigeminovascular system suggest such a possibility.[100] Because adhering to a predetermined course of therapy for every patient may lead to suboptimal outcomes and higher costs, decisions about access to care should be modifiable based on medical need and individual circumstances.

Starting low and titrating

Oral treatments should be started at a low dose and titrated slowly until the target response develops, the maximum or target dose is reached, or tolerability issues emerge.[22,24] When there is a partial but suboptimal response or dose-limiting AEs, combining preventive drugs from different drug classes may be useful.

With the five parenteral preventive therapies available for prescription in the United States,[87–98,101,102] there is no known benefit

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TABLE 6 Medications with evidence of efficacy in migraine prevention[a,20,85]

Established efficacy[b]		Probably effective[c]	
Oral	**Parenteral**	**Oral**	**Parenteral**
Candesartan	Eptinezumab	Amitriptyline	OnabotulinumtoxinA + CGRP mAb[d,e]
Divalproex sodium	Erenumab	Atenolol	
Frovatriptan[f]	Fremanezumab	Lisinopril	
Metoprolol	Galcanezumab	Memantine	
Propranolol	OnabotulinumtoxinA[d]	Nadolol	
Timolol		Venlafaxine	
Topiramate			
Valproate sodium			

Abbreviations: CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody.

[a]The decision to prescribe preventive therapy in women who are pregnant or of childbearing potential should be based on the needs of individual patients and available safety data.

[b]Two or more Class I trials based on American Academy of Neurology evidence classification.[84]

[c]One Class I or 2 Class II trials based on American Academy of Neurology evidence classification.[84]

[d]Prevention of chronic migraine.[86]

[e]One Class IV trial based on American Academy of Neurology evidence classification.[84]

[f]Short-term prevention of menstrual-related migraine; evaluated and rejected by the FDA for this indication.

from gradual dose escalation. The optimal dose of onabotulinumtoxinA (155 units) is given as the initial dose, while a follow-the-pain protocol allowing higher doses is approved in the European Union. Eptinezumab is supplied in therapeutic doses of 100 and 300 mg for quarterly administration. Erenumab is available in two doses (70 and 140 mg), either of which can be used as a starting dose. Fremanezumab is supplied in two doses (225 and 675 mg) to support monthly and quarterly dose regimens, respectively. Galcanezumab is provided in a 120-mg dose intended for monthly use following an initial loading dose of 240 mg.

Reaching a therapeutic dose

With oral treatments, an initial target dose should be set (e.g., topiramate 100 mg) and patients advised to stop the titration if the maximal dose is reached, when efficacy is optimal, or when AEs become intolerable.

With injectable treatments (i.e., onabotulinumtoxinA or any of the CGRP mAbs), patients often experience a rapid onset of therapeutic benefits, but the duration of the transition from established preventive treatment to CGRP mAb (i.e., the interim period when both treatments are taken) has not been defined. Because treatment response in migraine is highly individualized, the decision to stop taking established therapies should rely on assessment of the onset and magnitude of treatment effects with the CGRP mAb at 4, 8, and 12 weeks after treatment with both therapies begins. There are data to suggest continued improvement beyond 3 months.[103–105] Data from a randomized withdrawal trial—in which all subjects initially receive active treatment for 12 weeks and then are randomized in a blinded fashion to continue active treatment or placebo[106] —may help to refine decisions about when patients who have begun treatment with a CGRP mAb can stop taking an established preventive, as well as how long to continue a CGRP mAb or any preventive.

Giving an adequate trial

With oral treatments, prevention plans should be followed for a minimum of 8 weeks at a target therapeutic dose before lack of effectiveness can be determined. If there is no response to treatment after at least 8 weeks at a target or usual effective dose, switching preventive treatments is recommended. Patients with a partial response should be counseled that cumulative benefits may occur over 6–12 months of continued use.

With injectable CGRP mAbs, determinations of clinical benefit should be assessed after at least 3 months of treatment for those administered monthly and at least 6 months after the start of quarterly treatments. Clinicians and patients should reassess the benefits of mAbs and continue treatment only if benefits have been achieved (Table 8).[107]

Establishing realistic expectations

When patients are introduced to migraine prevention, they may expect that attacks will cease soon after starting treatment. Although most established therapies have treatment latencies, observational post hoc studies of CGRP mAbs and onabotulinumtoxinA may demonstrate early benefits, within days or weeks. The patient should be involved in the process to help establish individual treatment goals, expectations, and limitations. Thus, it is crucial that patients

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TABLE 7 Criteria for initiating treatment with monoclonal antibodies to calcitonin gene-related peptide or its receptor

Use is appropriate when A, B, and either C, D, or E are met:
(A) Prescribed by a licensed clinician
(B) Patient is at least 18 years of age
(C) Diagnosis of ICHD-3 migraine with or without aura (4–7 MMDs) and both of the following:
a. Inability to tolerate (due to side effects) or inadequate response to an 8-week trial at a dose established to be potentially effective of two or more of the following:
1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Tricyclic antidepressant: amitriptyline, nortriptyline
5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
6. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
b. At least moderate disability (MIDAS ≥ 11 or HIT-6 > 50)
(D) Diagnosis of ICHD-3 migraine with or without aura[a] (8–14 MMDs) and inability to tolerate (due to side effects) or inadequate response to an 8-week trial of two or more of the following:
a. Topiramate
b. Divalproex sodium/valproate sodium
c. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
d. Tricyclic antidepressant: amitriptyline, nortriptyline
e. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
f. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
(E) Diagnosis of ICHD-3 chronic migraine[a] and EITHER a or b:
a. Inability to tolerate (due to side effects) or inadequate response to an 8-week trial of two or more of the following:
1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Tricyclic antidepressant: amitriptyline, nortriptyline
5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
6. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
b. Inability to tolerate or inadequate response to a minimum of 2 quarterly injections (6 months) of onabotulinumtoxinA

Abbreviations: AAN, American Academy of Neurology; HIT, Headache Impact Test; ICHD-3, International Classification of Headache Disorders, 3rd edition; MHDs, monthly headache days; MIDAS, Migraine Disability Assessment.

[a]With attestation by the prescribing clinician about medical risk, a trial of two established therapies may not be required before initiating treatment with a monoclonal antibody.

understand that any of the following can define success in migraine prevention:

- 50% reduction in the frequency of days with headache or migraine.

TABLE 8 Criteria for continuation of monoclonal antibodies to calcitonin gene-related peptide or its receptor or neuromodulation therapy[a]

Reauthorization after initial use[b] is appropriate when EITHER of the following criteria are met
(A) Reduction in mean MHDs or headache days of at least moderate severity of ≥50% relative to the pretreatment baseline (diary documentation or medical professional attestation)
(B) A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:
a. MIDAS
(i) Reduction of ≥5 points when baseline score is 11–20
(ii) Reduction of ≥30% when baseline score is >20
b. MPFID
(i) Reduction of ≥5 points
c. HIT-6
(i) Reduction of ≥5 points[108]

Note: Reauthorization duration: Indefinite; guided by patient response and medical professional attestation.

Abbreviations: HIT, Headache Impact Test; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MPFID, Migraine Physical Function Impact Diary.

[a]Exceptions to these criteria may be made under circumstances when deemed medically indicated by the prescribing licensed clinician.

[b]Initial authorization: 3 months for treatments administered monthly; for treatments delivered quarterly (every 3 months), two cycles of treatment (6 months).

- Significant decrease in attack duration as defined by patient.
- Significant decrease in attack severity as defined by patient.
- Improved response to acute treatment.
- Reduction in migraine-related disability and improvements in functioning in important areas of life.
- Improvements in HRQoL and reduction in psychological distress due to migraine.

In some patients, a less than 50% reduction in MHDs produces benefits, whereas in others, especially those with daily or continuous headache, a significant reduction in the overall severity of headache may lead to improvements in function and HRQoL and a reduction in headache-related disability.[109] Patients should also understand the most common AEs and their typical frequency and severity, as well as the potential for rare but serious AEs. The success of preventive therapy depends on establishing realistic patient expectations for the given treatment(s).[24]

Optimizing drug selection

The optimal selection of preventive treatment is case-dependent, and decisions about the use of specific medications and non-pharmacologic approaches must account for a range of factors (Table 9).

Comorbid and coexistent conditions are very important; drug selection may involve choosing treatments known to have efficacy

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TABLE 9 Factors in the optimal drug selection of preventive treatment

Evidence of efficacy	Medical professional experience
Tolerability	Patient preference
Headache subtype (episodic or chronic)	Comorbid and coexistent illnesses
Concomitant medications	Physiological factors (e.g., heart rate, blood pressure)
Body habitus	Pregnancy or the potential for pregnancy among women
Ease of use	Response to previous treatments
Contraindications/allergies	Cost/Insurance coverage

for a comorbid condition or avoiding drugs that may exacerbate comorbid or coexisting illness or interact with coadministered medications. A single drug for multiple conditions should be avoided if there is a risk of undertreating any single condition,[110] as optimal treatment may require the use of separate classes of medication.[24] As a general rule, clinicians should avoid preventive pharmacotherapy in pregnant or lactating women and those who are trying to conceive and discuss the potential for AEs on a pregnancy and a developing fetus in women of childbearing potential. Ultimately, treatment of migraine in women who are pregnant, lactating, or trying to conceive should be assessed individually; for many patients, the risks of uncontrolled migraine during pregnancy or lactation may be higher than those associated with a preventive medication. Clinicians should consider the use of a neuromodulatory device in patients who may benefit from preventive treatment but must limit or avoid medications due to comorbid and coexistent illness or concomitant medication. Practitioners should seek alternatives to erenumab in patients with a latex allergy as well as constipation, as its use has been associated with cases of severe constipation. Because erenumab has been shown to precipitate or exacerbate hypertension,[89,111] its use should be evaluated on an individual basis in patients with preexisting hypertension; the relationship between hypertension and other CGRP mAbs is presently unknown.

Because migraine attack frequency fluctuates over time, and migraine may improve or remit, it is important to reevaluate therapeutic response and determine whether to continue or, if possible, taper or discontinue treatment if patients no longer meet the criteria for preventive treatment (Table 4). However, caution must be exercised in patients who have established, long-standing chronic migraine or in those in whom multiple prior attempts at prevention have not been well tolerated or effective. Once control is established, as with the control of any chronic disease, the decision to discontinue or taper treatment should be a shared decision between patient and clinician, as premature discontinuation may lead to exacerbation and control may not be easily recaptured, even after restarting a treatment that was previously effective. A randomized withdrawal trial[106] might provide insight into the natural history of migraine after discontinuation of preventive treatment(s) and identity risk factors for migraine relapse and progression. Preliminary evidence suggests that some patients who respond to preventive treatments from different classes may regress slightly after treatment is stopped, but attack frequency appears to remain below pretreatment levels.[112–114]

Maximizing adherence

Rates of long-term adherence to oral preventive treatment are low, mainly due to suboptimal efficacy and poor tolerability.[81] A study of adherence to 14 oral migraine preventive medications used to treat patients with chronic migraine (N = 8688) found adherence rates between 26%–29% at 6 months and 17%–20% at 12 months.[115] Patient education about dose adjustments, treatment expectations, and AEs may improve adherence.

Because tolerability is among the most important reasons for poor adherence, the potential for treatment-emergent AEs needs to be considered. In some patients, the use of onabotulinumtoxinA or an injectable CGRP mAb may improve adherence, as their tolerability profiles in clinical trials are similar to those observed with placebo, and injection site reactions are the most commonly observed AEs.[87–98] In clinical settings, the incidence of AEs with CGRP mAbs may be higher than in clinical trials.[116]

Adherence can also be affected by dosing frequency,[117,118] and patients who are poorly adherent to orally administered drugs may be less likely to lapse from care with onabotulinumtoxinA (dosed quarterly) or an injectable CGRP mAb, which are dosed monthly (erenumab, galcanezumab) or quarterly (eptinezumab, fremanezumab). Patient preference is important in treatment decisions, and shared decision-making often leads to improved outcomes.

Recently approved preventive treatments

Eptinezumab

Since the previous Statement, eptinezumab was approved by the FDA for the preventive treatment of migraine based on evidence of efficacy and tolerability from multiple randomized, controlled clinical trials in patients with episodic and chronic migraine.[96–98] Eptinezumab is the only CGRP mAb supplied for IV administration, and its preventive benefits have been shown to begin within 24 h of the first administration.[96,97] As seen with other CGRP mAbs,[119] patients treated with eptinezumab also reduced the use of medication for acute treatment, which may reduce the risk of developing medication-overuse headache.

Measuring response to preventive treatment

Determining the efficacy and tolerability of preventive treatment is a patient-driven decision that may not exactly mirror the endpoints used in clinical trials. In general, a significant reduction (e.g., 50%) in MHDs or moderate or severe headache days is a useful

benchmark in both clinical trials and practice.[106,109] However, efficacy varies between patients, and a successful therapeutic outcome depends not only on a reduction in MHD frequency but also on the persistence and severity of pain and associated symptoms, level of disability, and functional capacity. Therefore, patient-centric and validated outcome measures that evaluate the effect of treatment on functional capacity, disability, and quality of life are important for determining whether meaningful change has occurred and, often, guiding clinical decision-making with respect to changes in dose, adding additional preventive treatment, or switching to an alternative treatment. Examples of these measures are included in Appendix B.

A significant proportion of patients who do not achieve at least a 50% reduction in MHDs in the 4 weeks after the first SC dose of a CGRP mAb may achieve a response in the 4 weeks after a second dose. Similarly, a smaller yet significant proportion of patients will respond in 4–8 weeks after a third consecutive SC dose. As a result, it is essential that all preventive pharmacotherapies be given an adequate trial (at least 3 to 6 months) before the benefits of treatment are assessed.

DUAL-USE THERAPIES

Several migraine treatments have been shown to provide meaningful benefits as acute and preventive therapies. For example, neuromodulation and biobehavioral therapies can be used alone or together with pharmacotherapy and/or other modalities in the acute and preventive treatment of appropriately selected patients. Among pharmacotherapies, frovatriptan is an established acute treatment that can have a role in the short-term prevention of menstrual-related migraine,[20] and regular use of drugs in the gepant class, two of which have been approved for acute treatment, has been shown to reduce attack frequency.[66,67,120,121] These “dual-use” therapies transcend the traditional boundary between acute and preventive treatment.

Neuromodulation

Goals

The goals of acute and preventive treatment with neuromodulatory devices are the same as the goals of acute and preventive pharmacotherapy.[22–24]

Indications

All patients with a confirmed diagnosis of migraine may be offered treatment with a neuromodulatory device, which modulates pain mechanisms involved in headache by stimulating the nervous system centrally or peripherally with an electric current or a magnetic field.[122] All four devices that have received FDA clearance (eTNS,[53,54] nVNS,[44] REN,[45,46] and sTMS[42]) can be used alone or together with pharmacotherapy for acute treatment. Three devices are cleared for use as monotherapy or adjunctive therapy for preventive migraine treatment: eTNS, nVNS, and sTMS.[42,43,54] Three devices (nVNS, REN, and sTMS) are also cleared for the acute and preventive treatment of migraine in adolescents between 12 and 17 years of age.[42,74,123,124]

Although the efficacy and safety of neuromodulation is supported by positive results from multiple clinical trials,[42,44–46,53,54,125] the use of neuromodulatory devices in clinical practice has been limited. Patients with an inadequate response to a migraine-specific medication, as well as those with frequent attacks who may be at risk of developing medication-overuse headache and/or chronic migraine due to overuse of acute medication, should be considered for a trial of a neuromodulatory device as an adjunct to the existing treatment plan. Patients who prefer to avoid medication, as well as those with a history of poor tolerability with or contraindications to triptans, may be offered a trial of neuromodulatory monotherapy. For preventive treatment, all patients should be considered for a trial of a neuromodulatory device as an adjunct to the existing treatment plan. Determinations about the precise role of neuromodulation in an overall treatment plan must be individualized.

Developing treatment plans

The use of neuromodulation is highly dependent on the medical needs of the patient. As stated previously and above, neuromodulatory devices can be used alone or concurrently with medication(s) for acute and/or preventive treatment. Neuromodulation may be an especially important alternative for patients who prefer nondrug therapies and those who have failed to respond to, have contraindications to, or have poor tolerability with pharmacotherapy.

Biobehavioral therapies

Goals

The goals for behavioral interventions as preventive treatment for headache include the following[23]:

- Reduced frequency and severity of headache.
- Reduced headache-related disability.
- Reduced reliance on poorly tolerated or unwanted pharmacotherapies.
- Enhanced personal control of migraine.
- Reduced headache-related distress and psychological symptoms.

Biobehavioral therapies—specifically, cognitive behavioral therapy, biofeedback, and relaxation therapies—are effective in the preventive treatment of migraine, with Grade A evidence for their use as preventive therapies and limited evidence and clinical

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experience supporting their use as acute therapies.[126–130] In addition, mindfulness-based therapies (e.g., mindfulness-based cognitive therapy, mindfulness-based stress reduction) and acceptance and commitment therapy are active topics of research and have a growing evidence base for use in migraine.[131–135]

Indications

Biobehavioral therapies have Grade A evidence supporting their use as preventive treatments in patients with migraine, but they are particularly well suited for patients who[23]:

- Prefer nonpharmacologic interventions.
- Have inadequate response, poor tolerance, or medical contraindications to specific pharmacologic treatments.
- Are pregnant, lactating, or planning to become pregnant.
- Have a history of acute medication overuse or medication-overuse headache (Table 5).
- Exhibit significant stress or deficient stress-coping skills.
- Have high migraine-related disability, and/or low HRQoL, and/or comorbidities.

Developing treatment plans

Biobehavioral therapies may be used alone or in conjunction with pharmacologic and interventional treatments for the acute or preventive treatment of migraine. Combining biobehavioral interventions with pharmacotherapy may enhance benefits versus medication or either modality alone.[127,128,136,137] Specific therapies may be selected based on available efficacy data and patient preference. Traditionally, biobehavioral therapies have been delivered using in-person formats, although web-, group-, and application-based approaches have been developed and tested that may be able to increase patient access and participation.[138–140]

Gepants

Preliminary research with telcagepant, a first-generation gepant, suggested a potential role for CGRP receptor antagonism in migraine prevention.[141] Recent investigations of two drugs in the gepant class appear to confirm and extend those findings. Atogepant, an orally administered gepant in development for migraine prevention, demonstrated efficacy and tolerability in the preventive treatment of migraine in a 12-week randomized, double-blind, placebo-controlled, parallel-group study of subjects with episodic migraine.[120] All atogepant doses (10, 30, or 60 mg once daily, 30 or 60 mg twice daily) were more effective than placebo at reducing MMDs (3.6–4.2 per month) and well tolerated, with no evidence of liver toxicity. Rimegepant, which has previously demonstrated efficacy in the acute treatment of migraine, has also shown efficacy in the preventive treatment of migraine. Patients treated with rimegepant 75 mg—the same dose approved by the FDA for acute treatment[75,142]—every other day for up to 1 year had significant reductions in MMDs versus baseline (−4.3 per month), with good tolerability and no sign of medication-overuse headache or liver toxicity.[66,67,121]

The evidence that daily and near-daily long-term use of multiple drugs in the gepant class demonstrate reductions in MMDs with no signs of medication-overuse headache raises the possibility of using a single drug to achieve acute and preventive treatment effects and has important implications for their safety as acute treatments.

Goals

Gepants share the goals of acute and preventive therapy set forth individually above.

Indications

With prior evidence of efficacy as an acute treatment, gepants may represent a continuum between the acute and preventive treatment of migraine.[143] Because some patients with migraine prefer oral formulations to injectable formulations,[144] the optimal use of gepants is likely to evolve as the evidence base grows.

Developing treatment plans

Gepants may be used for the acute treatment of migraine in patients who satisfy the criteria outlined in Table 3. Treatment plans involving the preventive use of gepants should be based on regimens used in clinical trials and personalized according to the needs of individual patients.

PATIENT PERSPECTIVE

The American Headache Society partnered with the American Migraine Foundation, a nonprofit organization dedicated to the advancement of research and awareness surrounding migraine, to understand how the updated Consensus Statement might be perceived by those likely to be affected by its recommendations. The American Migraine Foundation used an online questionnaire to invite members who are patient advocates (N = 21) trained to understand the migraine treatment landscape and whose personal experiences reflect the patient community at large to review and comment on the updated Consensus Statement. Four respondents agreed to participate and were free of conflicts of interest; two patient advocates, both previously diagnosed with migraine and in leadership positions with the American Migraine Foundation, also participated in the review.

Patient reviewers unanimously approved of the goals and indications for using acute treatments and how responses to acute

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treatments are to be measured, and they agreed with the criteria for initiating acute therapies, including newer treatments. They were also unanimous in agreeing that the updated Consensus Statement reasonably describes goals and indications for implementing preventive therapies and in supporting the criteria for continuing treatment with these medications and neuromodulation therapy.

There were some concerns among patient reviewers (50% [3/6]) about recommendations related to preventive treatment. Specifically, one reviewer (17%) had reservations about the requirement that patients try two established preventive medications (e.g., topiramate, beta-blockers, antidepressants) before having access to recently introduced preventive therapies (i.e., mAbs to CGRP or its receptor), citing the historically modest efficacy and poor tolerability of many older agents. Two reviewers (33%) were concerned that the recommended length of a trial of established preventive medication (6–12 months) is too long, especially among individuals exhibiting a partial response to treatment or experiencing treatment-emergent AEs. Two reviewers (33%) believed that the Statement would be improved by more attention to nonpharmacologic and device-related therapies, and one reviewer (17%) suggested that guidance related to exploratory approaches (e.g., cannabis) might be helpful.

CONCLUSIONS

The principles of acute treatment include using evidence-based treatments, choosing nonoral agents for patients with severe nausea or vomiting, accounting for tolerability and safety issues, considering self-administered rescue, and avoiding medication overuse. Many evidence-based medications are available for the acute treatment of migraine, including triptans, ergotamine derivatives, NSAIDs, nonopioid analgesics, and analgesic combinations, as well as the newer gepants and ditans. A number of nonpharmacologic options, such as neuromodulatory devices and biobehavioral approaches, are supported by evidence and may be used alone or as an adjunct to medication in the acute treatment of migraine. To individualize acute treatment plans, decisions should be based on medical needs and treatment history, as well as evidence of efficacy, potential side effects, patient-specific contraindications, and drug interactions. Evaluating response to acute treatment should be a collaborative effort between clinicians and patients that involves the regular use of validated instruments that are reliable, convenient for use in clinical practice, and able to provide information about efficacy, tolerability, and patient satisfaction with treatment and help to identify the need for adjustments.

The principles of preventive treatment include using evidence-based treatments, titrating until clinical benefits are achieved, giving each treatment a trial of at least 2–3 months, and avoiding overuse of acute treatments. Titration is not necessary with injectable preventive treatments, which are initiated at therapeutic doses and have a relatively rapid onset of action. The decision to initiate preventive treatment should be based on the frequency of migraine attacks, average number of days with migraine or moderate/severe headache, and degree of disability. Patients who have severe, disabling, or frequent migraine attacks, as well as those who cannot tolerate or are nonresponsive to acute treatment, should be considered for preventive treatment. The choice of preventive treatment should be based on an individual's history of response to acute and preventive treatment(s), as well as evidence of efficacy, medical professional experience, tolerability, patient preference, headache subtype, comorbid and coexistent disease, concomitant medications, and the potential for childbearing. Nonpharmacologic approaches to preventive treatment, such as neuromodulation and biobehavioral treatments, may be used alone or in combination with pharmacologic treatment. Measuring the benefits of a preventive treatment regimen is based on overall efficacy and tolerability but ultimately is a patient-driven decision made in partnership with their medical professional. Validated patient-centric outcome measures that evaluate the effect of treatment on functional capacity, disability, and quality of life are important for guiding clinical treatment decisions to continue, add, combine, or switch preventive treatments.

Although this revised Consensus Statement continues to recommend adequate trials of established acute and/or preventive treatments before initiating use of newer migraine-specific acute and preventive therapies, in part to due to cost considerations, no published evidence supports or refutes this hierarchical approach. Because the benefit–risk profiles of newer treatments will continue to evolve as clinical trial and real-world data accrue, the American Headache Society intends to review this Statement regularly and update, if appropriate, based on the emergence of evidence with implications for clinical practice.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the time and effort of American Headache Society staff (Howard Rosen and Hayley Swiderski) and the patients, advocates, and leadership of the American Migraine Foundation (Rachel Koh; Ronetta Stokes; Jamie Valendy; Patti Williams; David W. Dodick, MD; Nim Lalvani, MPH; Christine Lay, MD; Deborah Henscheid Lorenz; Lawrence C. Newman, MD; Kenneth H. Shubin Stein, MD, MPH, MS, CPH, CFA). The authors also wish to acknowledge additional contributors to the initial consensus statement including the 2018 American Headache Society Board of Directors and Past President Advisors Richard B. Lipton, MD and Stephen D. Silberstein, MD. Writing and editorial assistance were provided by Christopher Caiazza and supported by the American Headache Society.

CONFLICT OF INTEREST

American Headache Society Board of Directors: Jessica Ailani, MD, has received clinical trial grants as a principal investigator from Allergan/Abbvie, American Migraine Foundation, Biohaven, Eli Lilly, Satsuma, and Zosano; has received stock options for consulting from CtrlM; and has received honoraria from the following: Alder/

Lundbeck (speaking, consulting), Allergan/Abbvie (speaking, consulting), Amgen (speaking, consulting), Biohaven (speaking, consulting), GlaxoSmithKline (consulting), Eli Lilly and company (speaking, consulting), Impel (consulting), Theranica (consulting), Axsome (consulting), Neso (consulting), Aeon (data advisory board), Teva (speaking, consulting), Satsuma (consulting), *Current Pain and Headache Reports* (section editor), NeurologyLive (editorial board), SELF (medical advisory board), Medscape (advisory board). Rebecca C. Burch, MD, receives an editorial stipend for serving as an Associate Editor for *Neurology*. Matthew S. Robbins, MD, serves on the editorial board of *Headache*. He receives an editorial stipend from Springer (*Current Pain and Headache Reports*) and book royalties from Wiley. Dawn C. Buse, PhD, has been compensated as a consultant/advisor for Allergan/Abbvie, Amgen, Biohaven, Eli Lilly, Teva, Lundbeck, and Promius/Dr. Reddy's and as a researcher/independent contractor for Allergan/Abbvie, Amgen, Eli Lilly, and Promius/Dr. Reddy's. Andrew C. Charles, MD, has received compensation for work as a consultant for Alder, Amgen, Biohaven, Eli Lilly, and eNeura. Kathleen B. Digre, MD, has no conflicts to report. Peter J. Goadsby, MD, PhD, reports grants and personal fees from Amgen and Eli Lilly and Company, grant from Celgene, and personal fees from Alder Biopharmaceuticals, Aeon Biopharma, Allergan (Abbvie), Biohaven Pharmaceuticals Inc., Clexio, Electrocore LLC, eNeura, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, MundiPharma, Novartis, Pfizer, Sanofi, Santara Therapeutics, Satsuma, Teva Pharmaceuticals, Trigemina Inc., WL Gore, and personal fees from MedicoLegal work, Massachusetts Medical Society, Up-to-Date, Oxford University Press, and Wolters Kluwer; and Gerson Lehrman Group. Christine Lay, MD (also with American Migraine Foundation), has received honoraria from Allergan and served on advisory boards for Aralez, Eli Lilly, Novartis, and Teva. Morris Levin, MD, has served on advisory boards for Biohaven, Currax, Theranica, Upsher-Smith and receives royalties from Oxford University Press. Noah Rosen, MD, has conducted contracted research and been compensated as a consultant and for Allergan/Abbvie, Amgen, and Eli Lilly. He has received fees as a speaker for Allergan/Abbvie and as an advisor to Supernus, and he has served on advisory boards for Biohaven, Novartis, Lundbeck, and Teva. Todd J. Schwedt, MD, MSCI, has been compensated as a consultant for Alder, Allergan, Amgen, Aural Analytics, Biohaven, Click Therapeutics, Eli Lilly, Equinox, Lundbeck, and Nocira. He has received a research grant from Amgen and owns stock options in Aural Analytics and Nocira. Stewart J. Tepper, MD, reports the following conflicts: Grants for research (no personal compensation): Allergan, Amgen, ElectroCore, Eli Lilly, Lundbeck, Neurolief, Novartis, Satsuma, Zosano. Consultant and/or Advisory Boards (honoraria): Aeon, Align Strategies, Allergan/Abbvie, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, DeepBench, DRG, Eli Lilly, Equinox, ExpertConnect, GLG, Guidepoint Global, Healthcare Consultancy Group, Health Science Communications, HMP Communications, Impel, InteractiveForums, Krog and Partners, Lundbeck, M3 Global Research, Magellan Rx Management, Medicxi, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Pulmatrix, Reckner Healthcare, Relevale, SAI MedPartners, Satsuma, Slingshot Insights, Spherix Global Insights, Sudler and Hennessey, Synapse Medical Communications, System Analytic, Teva, Theranica, Thought Leader Select, Trinity Partners, XOC, Zosano. Salary: Dartmouth-Hitchcock Medical Center, American Headache Society, Thomas Jefferson University. CME honoraria: American Academy of Neurology, American Headache Society, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital, Ontario, Canada, Headache Cooperative of New England, Henry Ford Hospital, Detroit, Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians' Education Resource, Rockpointe, ScientiaCME, WebMD/Medscape. Rebecca Erwin Wells, MD, MPH, has no conflicts to report. **American Migraine Foundation:** David W. Dodick, MD, reports the following conflicts within the past 12 months: Consulting: Aeon, Amgen, Clexio, Cerecin, Ctrl M, Allergan, Alder, Biohaven, Linpharma, Lundbeck, Promius, Eli Lilly, eNeura, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, XoC, Zosano, Upjohn (Division of Pfizer), Pieris, Revance, Equinox. Honoraria: CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, Southern Headache Society (MAHEC), WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board). Patent 17189376.1–1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Rachel Koh has no conflicts to report. Nim Lalvani, MPH, has served on advocacy roundtables for Allergan MINDS, Impel Neuropharma, and Lundbeck Pharmaceuticals on behalf of the American Migraine Foundation. Deborah Henscheid Lorenz has no conflicts to report. Lawrence C. Newman, MD, has been compensated as a consultant for Allergan-Abbvie, Amgen, Biohaven, Eli Lilly and Company, Novartis, Lundbeck, Theranica, Teva, Supernus and owns stock options in ControlM Health. Kenneth H. Shubin Stein, MD, MPH, MS, CPH, CFA has no conflicts to report. Ronetta Stokes has no conflicts to report. Jamie Valendy has no conflicts to report. Patti Williams has no conflicts to report.

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REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
2. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann Neurol*. 2000;47(5):614-624.
3. Kalita J, Yadav RK, Misra UK. A comparison of migraine patients with and without allodynic symptoms. *Clin J Pain*. 2009;25(8):696-698.
4. Guven H, Cilliler AE, Comoglu SS. Cutaneous allodynia in patients with episodic migraine. *Neurol Sci*. 2013;34(8):1397-1402.
5. Louter MA, Bosker JE, van Oosterhout WPJ, et al. Cutaneous allodynia as a predictor of migraine chronification. *Brain*. 2013;136(Pt 11):3489-3496.
6. Lipton RB, Bigal ME, Ashina S, et al. Cutaneous allodynia in the migraine population. *Ann Neurol*. 2008;63(2):148-158.
7. Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: a cross-sectional study in 2714 persons. *Cephalalgia*. 2016;36(10):951-959.
8. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-349.
9. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA*. 1992;267(1):64-69.
10. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-657.
11. Buse DC, Scher AI, Dodick DW, et al. Impact of migraine on the family: perspectives of people with migraine and their spouse/domestic partner in the CaMEO study. *Mayo Clin Proc*. 2016:S0025-6196(16)00126-9. https://doi.org/10.1016/j.mayocp.2016.02.013
12. Buse D, Manack A, Serrano D, et al. Headache impact of chronic and episodic migraine: results from the American Migraine Prevalence and Prevention study. *Headache*. 2012;52(1):3-17.
13. Serrano D, Manack AN, Reed ML, Buse DC, Varon SF, Lipton RB. Cost and predictors of lost productive time in chronic migraine and episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. *Value Health*. 2013;16(1):31-38.
14. World Health Organization. *Global Health Estimates 2015: Disease Burden by Cause, Age, Sex, by Country and by Region, 2000–2015*. Geneva: World Health Organization; 2016. http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html. Accessed March 15, 2021.
15. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16(11):877-897.
16. Raval AD, Shah A. National trends in direct health care expenditures among US adults with migraine: 2004 to 2013. *J Pain*. 2017;18(1):96-107.
17. Munakata J, Hazard E, Serrano D, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2009;49(4):498-508.
18. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the Migraine in America Symptoms and Treatment (MAST) study. *J Headache Pain*. 2020;21(1):23.
19. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
20. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337-1345.
21. Serrano D, Lipton RB, Scher AI, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. *J Headache Pain*. 2017;18(1):101.
22. Silberstein SD. Preventive migraine treatment. *Continuum (Minneap Minn)*. 2015;21(4):973-989.
23. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
24. Dodick DW, Silberstein SD. Migraine prevention. *Pract Neurol*. 2007;7(6):383-393.
25. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2012;39(2 Suppl. 2):S1-S59.
26. Evers S, Áfra J, Frese A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol*. 2009;16(9):968-981.
27. National Institute for Health and Care Excellence. *Headaches in Over 12s: Diagnosis and Management*; 2021 https://www.nice.org.uk/guidance/cg150
28. Lanteri-Minet M, Valade D, Geraud G, Lucas C, Donnet A. Revised French guidelines for the diagnosis and management of migraine in adults and children. *J Headache Pain*. 2014;15:2.
29. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: a randomized trial. *JAMA*. 2000;284(20):2599-2605.
30. Lipton RB, Silberstein SD. The role of headache-related disability in migraine management: implications for headache treatment guidelines. *Neurology*. 2001;56(6 Suppl. 1):S35-S42.
31. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology*. 2015;84(7):688-695.
32. Robblee J, Starling AJ. SEEDS for success: lifestyle management in migraine. *Cleve Clin J Med*. 2019;86(11):741-749.
33. Robbins MS, Victorio MC, Bailey M, et al. Quality improvement in neurology: headache quality measurement set. *Neurology*. 2020;95(19):866-873.
34. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med*. 2019;381(23):2230-2241.
35. Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial. *JAMA*. 2019;322(19):1887-1898.
36. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant, an acute treatment for migraine, improved patient-reported functional disability and satisfaction in 2 single-attack phase 3 randomized trials, ACHIEVE I and II . *Headache*. 2020;60(4):686-700.
37. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019;381(2):142-149.
38. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10200):737-745.
39. Lipton LB, Conway CM, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the acute treatment of migraine: results from a phase 3, double-blind, randomized, placebo-controlled trial, study 301 (PS123LB). *Headache*. 2018;58:1287-1337.

15264610, 2021, 7, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14153 by Test, Wiley Online Library on [15/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

40. Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. *Neurology*. 2018;91(24):e2222-e2232.
41. Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142(7):1894-1904.
42. Starling AJ, Tepper SJ, Marmura MJ, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study). *Cephalalgia*. 2018;38(6):1038-1048.
43. Stanak M, Wolf S, Jagos H, Zebenholzer K. The impact of external trigeminal nerve stimulator (e-TNS) on prevention and acute treatment of episodic and chronic migraine: a systematic review. *J Neurol Sci*. 2020;412:116725.
44. Tassorelli C, Grazzi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: the randomized PRESTO study. *Neurology*. 2018;91(4):e364-e373.
45. Yarnitsky D, Dodick DW, Grosberg BM, et al. Remote electrical neuromodulation (REN) relieves acute migraine: a randomized, double-blind, placebo-controlled, multicenter trial. *Headache*. 2019;59(8):1240-1252.
46. Rapoport AM, Bonner JH, Lin T, et al. Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications. *J Headache Pain*. 2019;20(1):83.
47. Lipton RB, Munjal S, Brand-Schieber E, Tepper SJ, Dodick DW. Efficacy, tolerability, and safety of DFN-15 (celecoxib oral solution, 25 mg/ml) in the acute treatment of episodic migraine: a randomized, double-blind, placebo-controlled study. *Headache*. 2020;60(1):58-70.
48. Marcus SC, Shewale AR, Silberstein SD, et al. Comparison of healthcare resource utilization and costs among patients with migraine with potentially adequate and insufficient triptan response. *Cephalalgia*. 2020;40(7):639-649.
49. Russell MB, Holm-Thomsen OE, Rishøj Nielsen M, Cleal A, Pilgrim AJ, Olesen J. A randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. *Cephalalgia*. 1994;14(4):291-296.
50. Leroux E, Buchanan A, Lombard L, et al. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: a systematic literature review. *Adv Ther*. 2020;37(12):4765-4796.
51. Serrano D, Buse DC, Kori SH, et al. Effects of switching acute treatment on disability in migraine patients using triptans. *Headache*. 2013;53(9):1415-1429.
52. Buse DC, Serrano D, Reed ML, et al. Adding additional acute medications to a triptan regimen for migraine and observed changes in headache-related disability: results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2015;55(6):825-839.
53. Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): a randomized controlled trial. *Cephalalgia*. 2019;39(1):3-14.
54. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology*. 2013;80(8):697-704.
55. Dodick D, Lipton RB, Martin V, et al. Consensus statement: cardiovascular safety profile of triptans (5-$HT_{1B/1D}$ agonists) in the acute treatment of migraine. *Headache*. 2004;44(5):414-425.
56. Tajti J, Majlath Z, Szok D, Csati A, Vecsei L. Drug safety in acute migraine treatment. *Expert Opin Drug Saf*. 2015;14(6):891-909.
57. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs. non-early intervention in acute migraine-'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia*. 2008;28(4):383-391.
58. Cady RK, McAllister PJ, Spierings EL, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). *Headache*. 2015;55(1):88-100.
59. Tepper SJ, Cady RK, Silberstein S, et al. AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS Study): a comparative randomized clinical trial across multiple attacks. *Headache*. 2015;55(5):621-635.
60. Munjal S, Gautam A, Offman E, Brand-Schieber E, Allenby K, Fisher DM. A randomized trial comparing the pharmacokinetics, safety, and tolerability of DFN-02, an intranasal sumatriptan spray containing a permeation enhancer, with intranasal and subcutaneous sumatriptan in healthy adults. *Headache*. 2016;56(9):1455-1465.
61. Cady RK, Munjal S, Cady RJ, Manley HR, Brand-Schieber E. Randomized, double-blind, crossover study comparing DFN-11 injection (3 mg subcutaneous sumatriptan) with 6 mg subcutaneous sumatriptan for the treatment of rapidly-escalating attacks of episodic migraine. *J Headache Pain*. 2017;18(1):17.
62. Munjal S, Brand-Schieber E, Allenby K, Spierings ELH, Cady RK, Rapoport AM. A multicenter, open-label, long-term safety and tolerability study of DFN-02, an intranasal spray of sumatriptan 10 mg plus permeation enhancer DDM, for the acute treatment of episodic migraine. *J Headache Pain*. 2017;18(1):31.
63. Medicines and Healthcare Products Regulatory Agency. *Guidance: Valproate Use by Women and Girls*. https://www.gov.uk/guidance/valproate-use-by-women-and-girls. Accessed March 15, 2021.
64. *FDA Drug Safety Communication: Children Born to Mothers Who Took Valproate Products While Pregnant May Have Impaired Cognitive Development*. https://www.fda.gov/Drugs/DrugSafety/ucm261543.htm. Accessed March 15, 2021.
65. Navratilova E, Behravesh S, Oyarzo J, Dodick DW, Banerjee P, Porreca F. Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. *Cephalalgia*. 2020;40(9):892-902.
66. Lipton RB, Berman G, Kudrow D, et al. Long-term, open-label safety study of rimegepant 75 mg for the treatment of migraine (Study 201): interim analysis of safety and exploratory efficacy (IHC-PO-127). *Cephalalgia*. 2019;39(1_suppl):1-337.
67. McGinley JS, L'Italien GJ, Thiry A, Croop R, Coric V, Lipton RB. Rimegepant 75 mg results in reductions in monthly migraine days: secondary analysis of a multicenter, open label long-term safety study of rimegepant for the acute treatment of migraine (1793). *Neurology*. 2020;94(15 Suppl):1793.
68. Rau JC, Navratilova E, Oyarzo J, et al. Evaluation of LY573144 (lasmiditan) in a preclinical model of medication overuse headache. *Cephalalgia*. 2020;40(9):903-912.
69. Saengjaroentham C, Strother LC, Dripps I, et al. Differential medication overuse risk of novel anti-migraine therapeutics. *Brain*. 2020;143(9):2681-2688.
70. Marmura MJ, Lin T, Harris D, Ironi A, Rosen NL. Incorporating remote electrical neuromodulation (REN) into usual care reduces acute migraine medication use: an open-label extension study. *Front Neurol*. 2020;11:226.
71. *Drug Approval Package: Elyxyb*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212157Orig1s000TOC.cfm. Accessed March 15, 2021.
72. *Drug Approval Package: Reyvow*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211280Orig1s000TOC.cfm. Accessed March 15, 2021.
73. Rapoport AM, Lin T, Tepper SJ. Remote electrical neuromodulation (REN) for the acute treatment of migraine. *Headache*. 2020;60(1):229-234.
74. Hershey AD, Lin T, Gruper Y, et al. Remote electrical neuromodulation for acute treatment of migraine in adolescents. *Headache*. 2021;61(2):310-317.

15264610, 2021, 7, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14153 by Test, Wiley Online Library on [15/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

75. *Drug Approval Package: Nurtec ODT*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212728Orig1s000TOC.cfm. Accessed March 15, 2021.
76. Berman G, Croop R, Kudrow D, et al. Safety of rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. *Headache*. 2020;60(8):1734-1742.
77. Ailani J, Lipton RB, Hutchinson S, et al. Long-term safety evaluation of ubrogepant for the acute treatment of migraine: phase 3, randomized, 52-week extension trial. *Headache*. 2020;60(1):141-152.
78. Sheftell FD, Fox AW. Acute migraine treatment outcome measures: a clinician's view. *Cephalalgia*. 2000;20(Suppl. 2):14-24.
79. Malik SN, Hopkins M, Young WB, Silberstein SD. Acute migraine treatment: patterns of use and satisfaction in a clinical population. *Headache*. 2006;46(5):773-780.
80. Smelt AFH, Louter MA, Kies DA, et al. What do patients consider to be the most important outcomes for effectiveness studies on migraine treatment? Results of a Delphi study. *PLoS One*. 2014;9(6):e98933.
81. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache*. 2013;53(4):644-655.
82. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache*. 2008;48(8):1157-1168.
83. Katsarava Z, Holle D, Diener HC. Medication overuse headache. *Curr Neurol Neurosci Rep*. 2009;9(2):115-119.
84. Gronseth GH, Cox J, Getchius TSD. *Amendments to the 2011 American Academy of Neurology Clinical Practice Guideline Process Manual*. https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/2.Clinical_Guidelines/4.About_Guidelines/1.How_Guidelines_Are_Developed/14%20Process%20Manual%20Amendment_v203.pdf. Accessed March 15, 2021.
85. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia*. 2014;34(7):523-532.
86. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818-1826.
87. Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017;377(22):2123-2132.
88. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38(6):1026-1037.
89. Kudrow D, Pascual J, Winner PK, et al. Vascular safety of erenumab for migraine prevention. *Neurology*. 2020;94(5):e497-e510.
90. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425-434.
91. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA*. 2018;319(19):1999-2008.
92. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377(22):2113-2122.
93. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211-e2221.
94. Skljarevski V, Oakes TM, Zhang QI, et al. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: a randomized clinical trial. *JAMA Neurol*. 2018;75(2):187-193.
95. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75(9):1080-1088.
96. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40(3):241-254.
97. Dodick DW, Lipton RB, Silberstein S, et al. Eptinezumab for prevention of chronic migraine: a randomized phase 2b clinical trial. *Cephalalgia*. 2019;39(9):1075-1085.
98. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020;94(13):e1365-e1377.
99. Yuan H, Baggaley S, Ozudogru S, Digre K. CGRP antibodies as adjunctive prophylactic therapy for prolonging the therapeutic effect of onabotulinumtoxinA injections among chronic migraine patients (P09). *Headache*. 2020;59(Suppl. 1):1-208.
100. Pellesi L, Do TP, Ashina H, Ashina M, Burstein R. Dual therapy with anti-CGRP monoclonal antibodies and botulinum toxin for migraine prevention: is there a rationale? *Headache*. 2020;60(6):1056-1065.
101. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30(7):793-803.
102. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30(7):804-814.
103. Tepper SJ, Ashina M, Reuter U, et al. Long-term safety and efficacy of erenumab in patients with chronic migraine: results from a 52-week, open-label extension study. *Cephalalgia*. 2020;40(6):543-553.
104. Camporeale A, Kudrow D, Sides R, et al. A phase 3, long-term, open-label safety study of galcanezumab in patients with migraine. *BMC Neurol*. 2018;18(1):188.
105. Goadsby PJ, Silberstein SD, Yeung PP, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. *Neurology*. 2020;95(18):e2487-e2499.
106. Diener H-C, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. *Cephalalgia*. 2020;40(10):1026-1044.
107. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59(1):1-18.
108. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. *J Clin Epidemiol*. 2006;59(4):374-380.
109. Tassorelli C, Diener H-C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia*. 2018;38(5):815-832.
110. Silberstein SD, Dodick D, Freitag F, et al. Pharmacological approaches to managing migraine and associated comorbidities–clinical considerations for monotherapy versus polytherapy. *Headache*. 2007;47(4):585-599.
111. Ashina M, Kudrow D, Reuter U, et al. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: a pooled analysis of four placebo-controlled trials with long-term extensions. *Cephalalgia*. 2019;39(14):1798-1808.

15264610, 2021, 7, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14153 by Test, Wiley Online Library on [15/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

112. Raffaelli B, Mussetto V, Israel H, Neeb L, Reuter U. Erenumab and galcanezumab in chronic migraine prevention: effects after treatment termination. *J Headache Pain*. 2019;20(1):66.
113. Stauffer VL, Wang S, Voulgaropoulos M, Skljarevski V, Kovacik A, Aurora SK. Effect of galcanezumab following treatment cessation in patients with migraine: results from 2 randomized phase 3 trials. *Headache*. 2019;59(6):834-847.
114. Diener H-C, Agosti R, Allais G, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2007;6(12):1054-1062.
115. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia*. 2015;35(6):478-488.
116. Kanaan S, Hettie G, Loder E, Burch R. Real-world effectiveness and tolerability of erenumab: a retrospective cohort study. *Cephalalgia*. 2020;40(13):1511-1522.
117. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. https://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed March 15, 2021.
118. Cowan R, Cohen JM, Rosenman E, Iyer R. Physician and patient preferences for dosing options in migraine prevention. *J Headache Pain*. 2019;20(1):50.
119. Alasad YW, Asha MZ. Monoclonal antibodies as a preventive therapy for migraine: a meta-analysis. *Clin Neurol Neurosurg*. 2020;195:105900.
120. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol*. 2020;19(9):727-737.
121. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(10268):51-60.
122. Puledda F, Shields K. Non-pharmacological approaches for migraine. *Neurotherapeutics*. 2018;15(2):336-345.
123. Grazzi L, Egeo G, Liebler E, Padovan AM, Barbanti P. Non-invasive vagus nerve stimulation (nVNS) as symptomatic treatment of migraine in young patients: a preliminary safety study. *Neurol Sci*. 2017;38(Suppl. 1):197-199.
124. Irwin SL, Qubty W, Allen IE, Patniyot I, Goadsby PJ, Gelfand AA. Transcranial magnetic stimulation for migraine prevention in adolescents: a pilot open-label study. *Headache*. 2018;58(5):724-731.
125. Chou DE, Gross GJ, Casadei CH, Yugrakh MS. External trigeminal nerve stimulation for the acute treatment of migraine: open-label trial on safety and efficacy. *Neuromodulation*. 2017;20(7):678-683.
126. Nestoriuc Y, Martin A, Rief W, Andrasik F. Biofeedback treatment for headache disorders: a comprehensive efficacy review. *Appl Psychophysiol Biofeedback*. 2008;33(3):125-140.
127. Andrasik F. Biofeedback in headache: an overview of approaches and evidence. *Cleve Clin J Med*. 2010;77(Suppl. 3):S72-S76.
128. Harris P, Loveman E, Clegg A, Easton S, Berry N. Systematic review of cognitive behavioural therapy for the management of headaches and migraines in adults. *Br J Pain*. 2015;9(4):213-224.
129. Holroyd KA, Penzien DB. Psychosocial interventions in the management of recurrent headache disorders. 1: overview and effectiveness. *Behav Med*. 1994;20(2):53-63.
130. Cousins S, Ridsdale L, Goldstein LH, Noble AJ, Moorey S, Seed P. A pilot study of cognitive behavioural therapy and relaxation for migraine headache: a randomised controlled trial. *J Neurol*. 2015;262(12):2764-2772.
131. Seng EK, Singer AB, Metts C, et al. Does mindfulness-based cognitive therapy for migraine reduce migraine-related disability in people with episodic and chronic migraine? A phase 2b pilot randomized clinical trial. *Headache*. 2019;59(9):1448-1467.
132. Sansone E, Grazzi L, Raggi A, Leonardi M, D'Amico D. Mindfulness as an add-on treatment for patients with chronic migraine and medication overuse: a preliminary analysis. *Neurol Sci*. 2020;41(Suppl. 2):469-471.
133. Vasiliou VS, Karademas EC, Christou Y, Papacostas S, Karekla M. Acceptance and commitment therapy for primary headache sufferers: a randomized controlled trial of efficacy. *J Pain*. 2021;22(2):143-160.
134. Grazzi L, Bernstein C, Raggi A, et al. ACT for migraine: effect of acceptance and commitment therapy (ACT) for high-frequency episodic migraine without aura: preliminary data of a phase-II, multicentric, randomized, open-label study. *Neurol Sci*. 2019;40(Suppl. 1):191-192.
135. Wells RE, O'Connell N, Pierce CR, et al. Effectiveness of mindfulness meditation vs headache education for adults with migraine: a randomized clinical trial. *JAMA Intern Med*. 2021;181(3):317-328.
136. Holroyd KA, Cottrell CK, O'Donnell FJ, et al. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. *BMJ*. 2010;341:c4871.
137. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. *JAMA*. 2013;310(24):2622-2630.
138. Minen MT, Adhikari S, Padikkala J, et al. Smartphone-delivered progressive muscle relaxation for the treatment of migraine in primary care: a randomized controlled trial. *Headache*. 2020;60(10):2232-2246.
139. Stubberud A, Tronvik E, Olsen A, Gravdahl G, Linde M. Biofeedback treatment app for pediatric migraine: development and usability study. *Headache*. 2020;60(5):889-901.
140. Matsuzawa Y, Lee YSC, Fraser F, et al. Barriers to behavioral treatment adherence for headache: an examination of attitudes, beliefs, and psychiatric factors. *Headache*. 2019;59(1):19-31.
141. Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology*. 2014;83(11):958.
142. Rimegepant (Nurtec ODT) for acute treatment of migraine. *Med Lett Drugs Ther*. 2020;62(1597):70-72.
143. Al-Hassany L, MaassenVanDenBrink A. Targeting CGRP in migraine: a matter of choice and dose. *Lancet Neurol*. 2020;19(9):712-713.
144. Mitsikostas DD, Belesioti I, Arvaniti C, et al. Patients' preferences for headache acute and preventive treatment. *J Headache Pain*. 2017;18(1):102.
145. Lipton RB, Kolodner K, Bigal ME, et al. Validity and reliability of the Migraine-Treatment Optimization Questionnaire. *Cephalalgia*. 2009;29(7):751-759.
146. Dowson AJ, Tepper SJ, Baos V, Baudet F, D'Amico D, Kilminster S. Identifying patients who require a change in their current acute migraine treatment: the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire. *Curr Med Res Opin*. 2004;20(7):1125-1135.
147. Revicki DA, Kimel M, Beusterien K, et al. Validation of the revised Patient Perception of Migraine Questionnaire: measuring satisfaction with acute migraine treatment. *Headache*. 2006;46(2):240-252.
148. Silberstein SD, Cady RK, Sheftell FD, Almas M, Parsons B, Albert KS. Efficacy of eletriptan in migraine-related functional impairment: functional and work productivity outcomes. *Headache*. 2007;47(5):673-682.
149. Diener H-C, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: fourth edition. *Cephalalgia*. 2019;39(6):687-710.
150. Dodick DW, Silberstein S, Saper J, et al. The impact of topiramate on health-related quality of life indicators in chronic migraine. *Headache*. 2007;47(10):1398-1408.

15264610, 2021, 7, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14153 by Test, Wiley Online Library on [15/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

151. Mannix S, Skalicky A, Buse DC, et al. Measuring the impact of migraine for evaluating outcomes of preventive treatments for migraine headaches. *Health Qual Life Outcomes*. 2016;14(1):143.
152. Bagley CL, Rendas-Baum R, Maglinte GA, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. *Headache*. 2012;52(3):409-421.
153. Kawata AK, Hsieh R, Bender R, et al. Psychometric evaluation of a novel instrument assessing the impact of migraine on physical functioning: the Migraine Physical Function Impact Diary. *Headache*. 2017;57(9):1385-1398.
154. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology*. 2001;56(6 Suppl. 1):S20-S28.
155. Murray CJ. Quantifying the burden of disease: The technical basis for disability-adjusted life years. *Bull World Health Organ*. 1994;72(3):429-445.
156. EEC note for guidance: good clinical practice for trials on medicinal products in the European Community. CPMP Working Party on Efficacy of Medicinal Products. *Pharmacol Toxicol*. 1990;67(4):361-372.

How to cite this article: Ailani J, Burch RC, Robbins MS; the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61:1021–1039. https://doi.org/10.1111/head.14153

APPENDIX A

VALIDATED INSTRUMENTS FOR MEASURING RESPONSE TO ACUTE TREATMENT

These assessment tools have been shown to be reliable, accurate, and easy to use, and their regular application in clinical practice has the potential to improve efficacy outcomes and patient satisfaction with treatment.

- Migraine Treatment Optimization Questionnaire (mTOQ), a validated, self-administered questionnaire that assesses efficacy based on four aspects of response to acute treatment.[145]
- Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire, a four-item assessment tool that evaluates how a recently prescribed acute treatment is working and identifies patients who might benefit from a change in acute treatment.[146]
- Patient Perception of Migraine Questionnaire (PPMQ-R), a reliable and valid measure of patient satisfaction with acute migraine treatment in patients with frequent migraine attacks.[147]
- Functional Impairment Scale (FIS), a four-item assessment of function that has demonstrated sensitivity in clinical trials.[148,149]

The prescribing licensed clinician's judgment on the best treatment option for a selected patient is sufficient to initiate a new treatment.

APPENDIX B

VALIDATED INSTRUMENTS FOR MEASURING RESPONSE TO PREVENTIVE TREATMENT

Disease-specific instruments are more likely to be sensitive to change and reflect the impact of a particular treatment on migraine-related disability.

- Patient Global Impression of Change Scale (PGIC).[150]
- Migraine Functional Impact Questionnaire (MFIQ), a 26-item self-administered instrument for the assessment of the impact of migraine on physical functioning, usual activities, social functioning, and emotional functioning over the past 7 days.[151]
- Migraine-Specific Quality of Life questionnaire version 2.1 (MSQ v2.1).[152]
- Migraine Physical Function Impact Diary (MPFID), a 13-item self-administered instrument that assesses the impact of migraine on everyday activities and physical impairment in the past 24 h.[153]
- Headache Impact Test (HIT-6).[108]
- Migraine Disability Assessment (MIDAS).[154]
- Work Productivity and Activity Impairment (WPAI), a general instrument adapted for migraine that evaluates migraine-related disability and costs.
- Generic measures of HRQoL reflect the overall effect of an illness and the impact of treatment on a subject's perception of their ability to live a useful and fulfilling life.[155,156]

As with acute treatment, the prescribing licensed clinician's judgment on the best treatment option for a selected patient is sufficient to initiate a new treatment.

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