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AHS Consensus Statement

The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice

American Headache Society

Objective.—To provide healthcare professionals with updated guidance in the use of novel preventive and acute treatments for migraine in adults.

Background.—The principles of preventive and acute pharmacotherapy for patients with migraine have been outlined previously, but the emergence of new technologies and treatments, as well as new formulations of previously established treatments, has created a need for an updated guidance on the preventive and acute treatment of migraine.

Methods.—This statement is based on a review of existing guidelines and principles for preventive and acute treatment of migraine, as well as the results of recent clinical trials of drugs and devices for these indications. Input was sought from health insurance providers, employers, pharmacy benefit service companies, device manufacturers, pharmaceutical and biotechnology companies, patients, and patient advocates. Expert clinicians and researchers in the field of headache medicine from across North America and the European Union provided input and feedback.

Results.—The principles of pharmacologic preventive treatment of migraine with oral treatments have been as follows: use evidence-based treatments when possible and appropriate; start with a low dose and titrate slowly; reach a therapeutic dose if possible; allow for an adequate treatment trial duration; establish expectations of therapeutic response and adverse events; and maximize adherence. Newer injectable treatments may work faster and may not need titration. The principles of acute treatment include: use evidence-based treatments when possible and appropriate; treat early after the onset of a migraine attack; choose a nonoral route of administration for selected patients; account for tolerability and safety issues; consider self-administered rescue treatments; and avoid overuse of acute medications. Neuromodulation and biobehavioral therapy may be appropriate for preventive and acute treatment, depending on the needs of individual patients. Neuromodulation may be useful for patients who prefer nondrug therapies or who respond poorly, cannot tolerate, or have contraindications to pharmacotherapy.

Conclusions.—This statement updates prior recommendations and outlines the indications for initiating, continuing, combining, and switching preventive and acute treatments of migraine.

Key words: migraine, treatment, acute, preventive, principles

Abbreviations: AE adverse event, CBT cognitive behavioral therapy, CGRP calcitonin gene-related peptide, DHE dihydroergotamine, FIS Functional Impairment Scale, HIT Headache Impact Test, HRQoL health-related quality of life, ICHD International Classification of Headache Disorders, 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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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, in many patients, cutaneous allodynia.[2-6] About one third of patients have migraine with an aura that precedes or occurs during some attacks, while approximately three quarters of patients 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); patients with fewer than 15 MMDs or MHDs have episodic migraine, and those with at least 15 MHDs, of which at least 8 are MMDs, have chronic migraine (Table 1).[1]

Migraine is very common, and the burden of illness is often substantial. The 1-year period prevalence in women and men is 18 and 6%, respectively, and prevalence peaks between the ages of 25 and 55.[8-10] Attacks can significantly impair functional ability at work or school, at home, and in social situations.[11-13] Migraine ranks as the second most disabling neurologic condition globally 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]

The pain and associated symptoms of migraine, as well as its life consequences, can be addressed with acute treatments, preventive treatments, or both.[18,19] However, because the severity, frequency, and characteristics of migraine vary among persons and, often, within individuals over time,[20] and symptom profiles or biomarkers that predict efficacy and side effects for individuals have not yet been identified,[21,22] optimizing treatment for particular patients remains challenging. At present, treatment plans are individualized based on patient preference; status with respect to pregnancy, lactation, or plans to conceive; the frequency and severity of attacks; the presence, type, and severity of associated symptoms; attack-related disability; prior treatment response; the presence of comorbid and coexistent illness; contraindications (eg, cardiovascular disease); factors such as body habitus and physiological measures (eg, blood pressure, heart rate); and the use of concomitant medications. A process of trial and error is often necessary before treatment can be optimized.

Table 1.—ICHD-3 Criteria for Episodic and Chronic Migraine[1]

Episodic migraine
A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least 1 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 5 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 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

ICHD, International Classification of Headache Disorders.

The development and emergence of novel medications, device technologies, novel formulations of established drug therapies, and biologics has led to much needed advances in the acute and preventive treatment of migraine. The appropriate and cost-effective integration of these new treatments is of utmost importance to prescribing healthcare providers and their patients. The American Headache Society, in keeping with its mission of improving the lives of people with headache, and in response to requests from multiple stakeholders, sought to establish clinical parameters for the initiation and continuation of novel acute and preventive treatments. Input was therefore elicited from multiple stakeholders, including health insurance providers, employers, pharmacy benefit service companies, device manufacturers, pharmaceutical and biotechnology companies, patients, patient advocates, and experts in headache medicine from North American and Europe.

This statement on the principles of migraine medical care is designed to provide healthcare professionals with guidance in the use of preventive and acute treatments. It contains information about:

- Preventive and acute treatment goals
- Indications for preventive treatment
- Identification of patients who need prevention
- Identification of patients who need a novel acute or preventive treatment
- Successful treatment plans

Much of this information has been previously described[21,23-27] and is based on the pioneering work of Silberstein and the US Headache Consortium. Since then, studies of new neuromodulation technologies and medical therapies require updated expert guidance on the use of preventive treatment for patients with migraine. In addition, neuromodulation, pharmacotherapies, biologics, new formulations of previously established acute, migraine-specific treatments, and biobehavioral therapies have recently been evaluated. This statement updates prior recommendations. The hope is that providers will find this document helpful in selecting the appropriate patient for selected acute and preventive treatments to improve outcomes among their migraine patients with unmet needs.

PREVENTIVE TREATMENT

The goals of migraine prevention are to:[21-23]

- 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 are an important part of the overall approach for a proportion of people with migraine, and multiple evidence-based guidelines are available.[19,22,24-27] None of the currently available oral preventive treatments were designed specifically for migraine, and many oral preventive treatments have limited to moderate efficacy, moderate to high rates of adverse events (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 episodic migraine, and almost all of those with chronic migraine, in the general population would benefit.[8,28]

Indications for Preventive Treatment.—The recommendations for when to initiate preventive treatment are unchanged. Patients with migraine should be considered for preventive treatment in any of the following situations:[21-23]

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks (≥4 MHDs)
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as:
  - 10 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

Table 2.—Identifying Patients for Preventive Treatment[8] – Modified Criteria

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

[†]As measured by scores on the Migraine Disability Assessment scale.[29]

  - o 15 or more days per month for nonopioid analgesics, acetaminophen, and nonsteroidal antiinflammatory drugs (NSAIDs [including aspirin])
- AEs with acute treatments
- Patient preference

Prevention should also be considered in the management of certain uncommon migraine subtypes, including hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and those who have previously experienced a migrainous infarction, even if there is low attack frequency.[21-23]

Patient Identification.—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 these parameters (Table 2).[8] Another element of identification involves reviewing the history of medication use for acute treatment and treatment response. Those with migraine with poorly controlled attacks are at risk of acute medication overuse, medication overuse headache (Table 3) and progression to chronic migraine, and it is possible that overuse of medications for the acute treatment of headache may reduce the effectiveness of some preventive treatments.[22,30] Before a preventive treatment plan is developed, measures to ensure appropriate use (eg, drug type, route and timing of administration, frequency) of acute treatments coupled with education and lifestyle modifications should be initiated.[1]

Developing Treatment Plans for Traditional Oral Preventive Therapies.—Preventive treatment selection is based on evidence of efficacy, provider experience, tolerability, patient preference, headache subtype, and comorbidities, taking into account women of childbearing potential, especially those who are currently pregnant, breastfeeding or attempting to conceive. There are several basic principles to guide the initiation, titration, and, if necessary, cessation of preventive treatment.[21,23,31]

*Use Evidence-Based Preventive Treatments.—*The use of evidence-based treatments (Table 4) is important to the success of migraine prevention. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine). An important exception to the use of valproate sodium and

Table 3.—ICHD-3 Criteria for Medication Overuse Headache

A) Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder

B) Regular overuse for >3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache, with medication overuse defined as:

1. 10 or more days/month for ergot derivatives, triptans, opioids, combination analgesics[†], and a combination of drugs from different classes that are not individually overused
2. 15 or more days/month for nonopioid analgesics, acetaminophen, and NSAIDs (including aspirin)

C) Not better accounted for by another diagnosis

ICHD, International Classification of Headache Disorders; NSAID, nonsteroidal antiinflammatory drug.
[†]Drugs of 2 or more classes, each with analgesic effect (eg, acetaminophen+codeine) or acting as adjuvants (eg, caffeine).

Table 4.—Treatments With Evidence of Efficacy in Migraine Prevention (Adapted from Silberstein et al[19])

Established efficacy[†]	Probably effective[‡]	Possibly effective[§]
Antiepileptic drugs[‖]	Antidepressants	ACE inhibitors: Lisinopril
Divalproex sodium[‖]	Amitriptyline	Alpha-agonists
Valproate sodium[‖]	Venlafaxine	Clonidine
Topiramate[‖]	Beta-blockers	Guanfacine
Beta-blockers	Atenolol	Antiepileptic drugs: Carbamazepine
Metoprolol	Nadolol	Beta-blockers
Propranolol		Nebivolol
Timolol		Pindolol
Triptans: Frovatriptan[¶]		Antihistamines: Cyproheptadine
OnabotulinumtoxinA[32]		Angiotensin receptor blockers: Candesartan

ACE, angiotensin-converting enzyme.
[†]More than 2 Class I trials based on AAN Scheme for Classification of Evidence.[33]
[‡]One Class I or 2 Class II studies based on AAN Scheme for Classification of Evidence.[33]
[§]One Class II study based on AAN Scheme for Classification of Evidence.[33]
[‖]Not for use in women of childbearing potential who are not using an appropriate method of birth control.[34,35]
[¶]Short-term prevention of menstrual migraine.
[‡‡]For prevention of chronic migraine.

topiramate is that, due to risk of birth defects, it must not be prescribed to women of childbearing potential who are not using a reliable method of birth control.[34,35] The following treatments available by prescription are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan).[19,33] 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, and they may involve combining older and newer treatments as well as complex or nontraditional approaches.[19] In addition, evidence-based medicine is dynamic, and current practices may reflect the incorporation of more recent clinical trial results before they reach the creation or revision of existing treatment guidelines.

Start Low and Titrate.—Start oral treatments at a low dose and titrate slowly until the target response develops, the maximum or target dose is reached, or tolerability issues emerge.[21,23] When there is a partial but suboptimal response or dose-limiting AEs, combining preventive drugs from different drug classes may be useful.

Reach a Therapeutic Dose.—With oral treatments, set an initial target dose (eg, 100 or 200 mg topiramate) and advise patients to stop the titration if the maximal dose is reached, when efficacy is optimal, or when AEs become intolerable.

Give an Adequate Trial.—Give oral preventive treatments an adequate trial of at least 8 weeks at a target or usual effective dose to optimize the possibility of a therapeutic response. Before lack of effectiveness can be determined in patients with chronic migraine, prevention plans should be followed for a minimum of 8 weeks at a target therapeutic dose for oral treatments. If there is no response to treatment after 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 to 12 months of continued use.

Establish Realistic Expectations.—When patients are introduced to migraine prevention, they may expect that attacks will cease soon after starting treatment but most established therapies have treatment latencies. The patient should be involved in the process to help establish individual treatment expectations. Thus, it is crucial that patients understand that any of the following can define success in migraine prevention:

- 50% reduction in the frequency of days with headache or migraine
- 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 health related quality of life and reduction in psychological distress due to migraine

In some patients, a less than 50% reduction in monthly headache days (MHDs) produces benefits while 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.[36] 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).[23]

Optimize Drug Selection.—The selection of preventive treatment should be based on evidence for efficacy; provider experience; tolerability; patient preference; headache subtype; comorbid and coexistent illnesses; concomitant medications; physiological factors (eg, heart rate, blood pressure); body habitus; and pregnancy or the potential for pregnancy among women. Comorbid and coexistent conditions are very important; drug selection may involve choosing treatments known to have efficacy for a comorbid condition or by 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 undertreatment of any single condition,[37] as optimal treatment may require the use of a separate class of medication.[23] Try to avoid preventive treatments (especially valproate sodium and topiramate[34,35]) 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 age. Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue treatment if patients no longer meet the criteria for offering preventive treatment. However, caution must be exercised in patients who have established, longstanding chronic migraine or in those who have failed multiple prior attempts with preventive treatments. Once control is established, like the control of any chronic disease, the decision to discontinue or taper treatment should be a shared decision between patient and clinician, as it is possible that premature discontinuation can lead to exacerbation and control may not be easily recaptured even after restarting a treatment that was once effective.

Maximize Adherence.—The long-term adherence to oral preventive treatment is poor, mainly due to suboptimal efficacy and poor tolerability.[28] A study of adherence to 14 oral migraine preventive medications used to treat patients with chronic migraine (N = 8688) found adherence rates between 26 to 29% at 6 months and 17 to 20% at 12 months.[38] Patient education about dose adjustments, treatment expectations, and AEs may improve adherence. Patient preference is important in treatment decisions and shared decision making leads to improved outcomes. Potential treatment-emergent AEs need to be considered.

Developing Treatment Plans for Injectable Preventive Therapies.—As of this writing, there are 4 injectable preventive therapies for migraine marketed in the United States: onabotulinumtoxinA and 3 monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) (fremanezumab, galcanezumab) or the CGRP receptor (erenumab).[39-43] OnabotulinumtoxinA is approved for chronic migraine, and erenumab, fremanezumab, and galcanezumab are approved for episodic and chronic migraine. While the principles of preventive therapy for oral preventives generally apply to injectable preventives, there are several notable points of contrast. First, there is no need for gradual dose escalation. The optimal dose of onabotulinumtoxinA is 155 units, and it is given as the initial dose. Erenumab is available in 2 doses (70 mg and 140 mg), either of which can be used as a starting dose. Fremanezumab is supplied in 2 doses, 225 mg and 675 mg, to support monthly and quarterly dose regimens, respectively,[44] and galcanezumab is provided in a 120 mg dose intended for monthly use following an

initial loading dose of 240 mg.[45] The lack of need for slow dose escalation, the rapid onset of therapeutic benefits, and the favorable tolerability profiles are advantages that injectable therapies have in common. In the section on emerging therapies, we will discuss the use of these approved injectable therapies and the likely role of emerging treatments, including CGRP-targeted therapies.

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 (eg, 50%) in MHDs is a useful benchmark in both clinical trials and practice.[46] However, efficacy is variable 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 A.

EMERGING PREVENTIVE OPTIONS

While erenumab targets the CGRP receptor, 3 other mAbs (fremanezumab, galcanezumab, eptinezumab) target the CGRP ligand. These biologic agents have demonstrated efficacy, safety, and tolerability for the preventive treatment of episodic and chronic migraine in phase 2 and phase 3 randomized, placebo-controlled trials,[43,44,47-55] and they represent the first mechanism-based and disease-specific class of preventive treatment that was designed, developed, and made available for migraine since methysergide was Food and Drug Administration approved in 1962.[56] At the time of this writing, erenumab, fremanezumab, and galcanezumab are available for use in migraine prevention, and filing is expected for eptinezumab in 2019.[57] These agents can be administered every 4 weeks (fremanezumab, galcanezumab) by subcutaneous (SC) injection or every 12 weeks by SC (fremanezumab) or intravenous (IV) (eptinezumab) infusion. None of these agents requires dose titration. All may achieve rapid treatment effects over days to weeks, and are effective in patients who have failed prior preventive treatment, as well as in those on concurrent oral preventive treatments. The lack of hepatic metabolism or renal clearance avoids interactions with concomitant drugs and these biologics may be added to or used in conjunction with other oral or injectable preventive treatments for migraine. In addition, tolerability profiles are similar to placebo, with injection site reactions being the most common.[43,44,47-55] Conclusions about long-term safety will require real-world clinical experience from use in large, heterogeneous patient populations.

These biologics will almost certainly be a higher cost to health insurance plans and patients than currently available oral generic preventive drugs. Therefore, to achieve cost-effective care while ensuring access to those most appropriate for these treatments, it is important that the indications for initiating treatment with anti-CGRP mAbs are widely understood and followed closely (Table 5). Clinical judgment may result in an emerging treatment being added to 1 or more established treatments. If initiating treatment with an anti-CGRP mAb in a patient already on a preventive treatment, since the risk of drug-mAb interactions is minimal or nonexistent, it is appropriate to add the mAb to the existing regimen and make no other changes until the effectiveness of the mAb is determined. Outcomes as outlined below should be assessed and shared decision-making between patient and provider should guide decisions on the appropriate use of polytherapy or monotherapy.

CGRP small-molecule receptor antagonists are also being studied as preventive treatments for migraine, though published data are not yet available.

Measuring Response to Emerging Preventive Options.—Measuring the response to anti-CGRP mAbs will be patient- and healthcare professional-dependent and will be guided by the same outcome metrics described previously for preventive treatments, with emphasis on migraine/headache days, migraine-related disability, impact, and functional impairment. Measuring outcomes for patients on mAbs and making a decision regarding continuation requires 3 months of outcome data for

Table 5.—Indications for Initiating Treatment With Monoclonal Antibodies to Calcitonin Gene-Related Peptide or Its Receptor

Use is approved when ALL of the following are met:
A. Prescribed by a licensed medical provider[†]
B. Patient is at least 18 years of age
C. Diagnosis of ICHD-3 migraine with or without aura[‡] (4–7 monthly headache days) and both of the following:
a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 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-AHS guideline
b. At least moderate disability (MIDAS>11, HIT-6>50)
D. Diagnosis of ICHD-3 migraine with or without aura[‡] (8–14 monthly headache days) and inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 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-AHS guideline
E. Diagnosis of ICHD-3 chronic migraine[‡] and EITHER a or b:
a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 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-AHS guideline
b. Inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA

AAN-AHS, American Academy of Neurology-American Headache Society; HIT, Headache Impact Test; ICHD, International Classification of Headache Disorders; MHDs, monthly headache days; MIDAS, Migraine Disability Assessment.
[†]Doctor of medicine, doctor of osteopathy, advanced practice provider (DDS [Doctor of Dental Surgery] or DMD [Doctor of Medicine in Dentistry or Doctor of Dental Medicine]).
[‡]Patient can only meet criteria for C, D, or E.
[§]Not for use in women of childbearing potential who lack an appropriate method of birth control.[34,35]

patients receiving monthly injections or 6 months of follow-up for a treatment designed for quarterly injection or infusion.

Based on emerging evidence, 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 may achieve a response in the 4 weeks after a second dose. Similarly, a smaller yet significant proportion of patients will respond in 4 to 8 weeks after a third consecutive SC dose. Therefore, it is recommended that the benefits of anti-CGRP mAbs be assessed after 3 months of treatment for those administered monthly and 6 months after the start of quarterly treatments. After 3 or 6 months of treatment, clinicians and patients should reassess the benefits of mAbs and continue treatment only if treatment benefits can be documented (Table 6). Evidence of treatment benefits may be provided by at least 1 of the following:

1. A reduction in mean monthly headache days of 50% or more relative to the pretreatment

Table 6.—Criteria for Continuation of Monoclonal Antibodies to Calcitonin Gene-Related Peptide or Its Receptor or Neuromodulation Therapy[†]

Reauthorization after initial use[‡] is approved when EITHER of the following criteria are met:
1. Reduction in mean monthly headache days of ≥50% relative to the pretreatment baseline (Diary documentation or healthcare provider attestation)
2. 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 scores >20
b. MPFID
i. Reduction of ≥5 points
c. HIT-6
i. Reduction of ≥5 points

HIT, Headache Impact Test; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MPFID, Migraine Physical Function Impact Diary.
Reauthorization duration: Indefinite; guided by patient response and healthcare provider attestation.
[†]Exceptions to these criteria may be made under circumstances when deemed medically indicated by the prescribing licensed healthcare provider.
[‡]Initial authorization: 3 months for treatments administered monthly; for treatments delivered quarterly (every 3 months), 2 cycles of treatment (6 months).

baseline (Diary documentation is recommended but not required).

2. A clinically meaningful improvement in a validated migraine-specific patient-reported outcome measure, including but not limited to:
   - o A reduction of at least 5 points or more in Migraine Disability Assessment (MIDAS) score for those whose baseline score was between 11 and 20
   - o A 30% reduction in MIDAS score for those with baseline scores above 20
   - o Reduction of 5 or more points on the Migraine Physical Function Impact Diary (MPFID)
   - o Reduction in scores on the 6-item Headache Impact Test (HIT-6) of at least 5 points[58]
   - o Other documented benefits reported by clinician and patient

ACUTE TREATMENT

The following are goals of acute migraine treatment:[22]

- Rapid and consistent freedom from pain and associated symptoms without recurrence
- Restored ability to function
- Minimal need for repeat dosing or rescue medications
- Optimal self-care and reduced subsequent use of resources (eg, emergency room visits, diagnostic imaging, healthcare provider and ambulatory infusion center visits)
- Minimal or no AEs

Effective acute treatment can reduce the pain, associated symptoms, and disability associated with attacks. Suboptimal acute treatment leads to an increase in migraine-related disability and disease progression.[59]

Indications for Acute Treatment.—All patients with migraine should be offered a trial of acute treatment. The following principles may help to improve outcomes in patients with migraine.[22]

Developing Treatment Plans.—*Use Evidence-Based Treatments*.—Use NSAIDs (including aspirin), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (eg, aspirin + acetaminophen + caffeine) for mild-to-moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE]) for moderate or severe attacks and mild-to-moderate attacks that respond poorly to NSAIDs or caffeinated combinations. Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability. Acute treatments considered effective or

probably effective based on a 2015 American Headache Society expert review of evidence from controlled trials[18] are presented in Table 7.

Choose a Nonoral Route of Administration for Severe Nausea or Vomiting.—Use a nonoral formulation in patients whose attacks are associated with severe nausea or vomiting or who have trouble swallowing orally administered medications. This includes sumatriptan 3, 4, or 6 mg SC and intranasal and inhaled powder formulations and ketorolac in intranasal and intramuscular (IM) formulations.[60-64] Dihydroergotamine SC and intranasal spray are alternatives. Consider IV DHE and an antiemetic for especially refractory headaches. In addition, antiemetics, such as prochlorperazine suppositories (for both headache and nausea), may be useful. 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.

Account for Tolerability and Safety Issues.—The tolerability and safety of certain acute treatments may preclude usage in sensitive patients and those with certain coexistent or comorbid illnesses. For instance, NSAIDs can cause serious gastrointestinal and cardiovascular side effects; triptans and ergotamine 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. Failure to account for tolerability and safety issues in prescribing may cause patients to limit, delay, or forego acute treatment altogether.[65]

Consider Self-Administered Rescue.—When first-line acute treatment does not bring relief, patients may require rescue medication. Depending on the initial treatment, options for outpatient rescue include SC sumatriptan, DHE injection or intranasal spray, or corticosteroids (eg, dexamethasone, IM ketorolac); inpatient options may include parenteral formulations of triptans, DHE, antiemetics, NSAIDs (eg, ketorolac), anticonvulsants (eg, valproate sodium and topiramate [not in women of childbearing potential who are not using an appropriate method of birth control[34,35]]), corticosteroids, and magnesium sulfate. 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.

Avoid Medication Overuse.—Migraine patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 headache days per week, and patients observed to be exceeding this limit should be offered preventive treatment.[18] Patients who have medication overuse despite the use of preventive treatment may require an escalation in dose, a change in preventive therapy, or the addition of another preventive treatment including but not limited to established drugs, biologics, neuromodulation, and biobehavioral approaches.

Measuring Response to Acute Treatment.—Response to acute treatment of migraine can be

Table 7.—Assessment of Acute Treatments for Migraine[18]

Established efficacy[†]	Probably effective
Triptans	Ergotamine and other forms of DHE
Ergotamine derivatives	NSAIDs: ketoprofen, IV and IM ketorolac, flurbiprofen
NSAIDs: aspirin, diclofenac, ibuprofen, naproxen	IV magnesium[†]
Opioids: butorphanol[§]	Isometheptene-containing compounds
Combination medications	Combinations: codeine/acetaminophen, tramadol/acetaminophen[‡]
	Antiemetics: prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide

DHE, dihydroergotamine; IV, intravenous; IM, intramuscular; NSAID, nonsteroidal antiinflammatory drug.
[†]Consider single-pulse transcranial magnetic stimulation, noninvasive vagus nerve stimulation, or electrical trigeminal nerve stimulation in patients who prefer nondrug treatments or in whom drug treatment is ineffective, intolerable, or contraindicated.
[‡]In migraine with aura.
[§]Use is not recommended.

assessed in many ways, but the efficacy endpoints typically used in clinical trials may not fully reflect the outcomes valued by patients[66-68] or the need for ease of use in clinical practice. Failure to understand patient preferences may reduce adherence, discourage patients from continuing treatment, and limit the ability to match treatment with patient needs. As with preventive treatment, 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. For acute treatment, examples of these measures are listed in Appendix B.

EMERGING ACUTE TREATMENTS

Emerging agents with novel mechanisms of action that have demonstrated efficacy for the acute treatment of migraine include the small molecule CGRP receptor antagonists, ubrogepant[69-72] and rimegepant,[73-76] and lasmiditan,[77] a selective serotonin ($5\text{-}HT_{1F}$) receptor agonist. Unlike triptans and ergotamine derivatives, these novel treatment options do not result in constriction of blood vessels and may have a special role in patients with cardiovascular contraindications to triptans. These novel agents will almost certainly be more costly to health insurance plans and patients than currently available oral triptans for which generic options are available. Therefore, to achieve cost-effective care while ensuring access to those most appropriate for these treatments, it is important that the indications for initiating treatment with novel acute oral medications, including ubrogepant, rimegepant, and lasmiditan, are widely understood and followed closely.

Patients who have contraindications to the use of triptans or who have failed to respond to or tolerate at least 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire (eg, Migraine Treatment Optimization Questionnaire [mTOQ], Migraine Assessment of Current Therapy [Migraine-ACT], Patient Perception of Migraine Questionnaire-Revised [PPMQ-R], Functional Impairment Scale [FIS], Patient Global Impression of Change [PGIC]) or healthcare provider attestation, are eligible for ubrogepant, rimegepant, lasmiditan, or a neuromodulation device. Coverage should be provided until at least 2 attacks are treated to determine efficacy and tolerability. Continuation of coverage should be based on the frequency of migraine attacks in an average month and response to a validated acute treatment patient-reported outcome questionnaire or clinical assessment of improvement by the healthcare provider.

NEUROMODULATION AND BIOBEHAVIORAL THERAPIES

Neuromodulation.—Several noninvasive devices have been developed for the treatment of patients with migraine. These treatments modulate pain mechanisms involved in headache by stimulating the nervous system centrally or peripherally with an electric current or a magnetic field.[78] Based on results demonstrating efficacy and safety in clinical trials, the United States Food and Drug Administration has cleared:[79,80]

- Single-pulse transcranial magnetic stimulation for the acute and preventive treatment of migraine
- Electrical trigeminal nerve stimulation for the acute and preventive treatment of migraine
- Noninvasive vagus nerve stimulation for the acute treatment of migraine

Patients who prefer nondrug therapies and those who have failed to respond to, have contraindications to, or poor tolerability with pharmacotherapy may be candidates for neuromodulation.

Biobehavioral Therapies.—As with all chronic medical conditions, education and lifestyle modification is important in the management of migraine. Minimizing exposure and managing unavoidable trigger factors, appropriate and individualized nutrition advice, exercise, and adequate hydration should be implemented and personalized for each patient.

There is a large and growing body of published evidence examining the use of behavioral therapies for migraine (and other forms of headache) including meta-analytic studies and evidence-based reviews. Biobehavioral therapy, including cognitive behavioral therapy (CBT) and biofeedback, and relaxation therapies have been shown to be effective in the acute and preventive treatment of migraine and have Grade A evidence for their use preventively.[81-85] The US Headache

Consortium advised that nonpharmacologic treatments might be particularly well suited for patients who:[22]

- 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 as defined in the section on *Indications for Preventive Treatment*
- Exhibit significant stress or deficient stress-coping skills

They identified the following goals for behavioral interventions as preventive treatment for headache:

- 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 may be used alone or in conjunction with pharmacologic and interventional treatments. Evidence suggests that combining biobehavioral interventions with pharmacotherapy provides greater benefits than either modality alone.[82,83,86]

CONCLUSIONS

Patients with migraine featuring severe, disabling, or frequent attacks, as well as those who cannot tolerate or are nonresponsive to acute treatment, are candidates for preventive treatment. The decision to initiate preventive treatment should be based on the frequency of individual attacks, average number of days with migraine or moderate or severe headache, and degree of disability. The choice of treatment should be based on evidence of efficacy, provider experience, tolerability, patient preference, headache subtype, comorbid and coexistent disease, concomitant medications, and the potential for childbearing. The principles of preventive treatment with oral treatments include initiating treatment with evidence-based treatments at a low dose, titrating until clinical benefits are achieved, giving each treatment a trial of 2 to 3 months, avoiding overuse of acute treatments. Measuring the overall efficacy and tolerability of preventive treatment is a patient-driven decision made in partnership and after consultation with their healthcare provider. 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.

Many evidence-based acute treatments are available, including triptans, ergotamine derivatives, NSAIDs (including aspirin), nonopioid analgesics, and analgesic combinations. As with preventive pharmacologic treatment, to individualize the choice of medication(s), evidence of efficacy, potential medication side effects, patient-specific contraindications, and drug interactions should be considered. Noninvasive vagus nerve stimulation is approved for the acute treatment of migraine pain, and single-pulse transcranial magnetic stimulation, supraorbital nerve stimulation are nonpharmacologic options that may be effective for the acute and preventive treatment of migraine, especially in those for whom pharmacologic treatment is contraindicated, poorly tolerated, ineffective, or not preferred. Empirically validated behavioral treatments with Grade A evidence for the prevention of migraine, including CBT, biofeedback, and relaxation therapies, should be considered in the management of migraine. These modalities may also be used alone or in addition to pharmacologic treatment, particularly in those with a partial therapeutic response and are excellent options for pregnant/lactating women as well as people with contraindications to certain treatments. In addition, all people with migraine will benefit from education and migraine-related lifestyle guidance.

It is the intent of the American Headache Society that this position statement will be reviewed annually and updated, if appropriate, based on the emergence of new evidence.

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APPENDIX A
Validated Instruments that May Be Used to Measure Meaningful Change after a Therapeutic Intervention for Migraine Prevention

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)[87]
- 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[88]
- Migraine-Specific Quality of Life questionnaire (MSQ v2.1)[89]
- 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 hours[90]
- Headache Impact Test (HIT-6)[58]
- Migraine Disability Assessment (MIDAS)[29]
- Work Productivity and Activity Impairment (WPAI), a general instrument adapted for migraine that evaluates migraine-related disability and costs[91,92]
- Generic measures of health-related quality of life (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[93,94]

APPENDIX B
Validated Instruments That May Be Used to Measure Meaningful Change After a Therapeutic Intervention for Acute Treatment of Migraine

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 4 aspects of response to acute treatment[95]
- Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire, a 4-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[96]
- 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[97]
- Functional Impairment Scale (FIS), a 4-item assessment of function that has demonstrated sensitivity in clinical trials[98,99]

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