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FEATURE ARTICLE

Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update

Andrew C. Charles MD[1] | Kathleen B. Digre MD[2] | Peter J. Goadsby MD, PhD[1,3] | Matthew S. Robbins MD[4] | Andrew Hershey MD, PhD[5,6] | on behalf of The American Headache Society

[1]Department of Neurology, UCLA Goldberg Migraine Program, Los Angeles, California, USA

[2]Departments of Neurology and Ophthalmology, University of Utah, Salt Lake City, Utah, USA

[3]King's College London, London, UK

[4]Department of Neurology, Weill Cornell Medical College, New York, New York, USA

[5]Department of Pediatrics and Neurology, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[6]Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Correspondence
Andrew C. Charles, Neurology, UCLA Goldberg Migraine Program, Los Angeles, CA, USA.
Email: acharles@ucla.edu

Abstract

Objective: To provide a position statement update from The American Headache Society specifically regarding therapies targeting calcitonin gene-related peptide (CGRP) for the prevention of migraine.

Background: All migraine preventive therapies previously considered to be first-line treatments were developed for other indications and adopted later for migraine. Adherence to these therapies is often poor due to issues with efficacy and tolerability. Multiple new migraine-specific therapies have been developed based on a broad foundation of pre-clinical and clinical evidence showing that CGRP plays a key role in the pathogenesis of migraine. These CGRP-targeting therapies have had a transformational impact on the management of migraine but are still not widely considered to be first-line approaches.

Methods: Evidence regarding migraine preventive therapies including primary and secondary endpoints from randomized placebo-controlled clinical trials, post hoc analyses and open-label extensions of these trials, and prospective and retrospective observational studies were collected from a variety of sources including PubMed, Google Scholar, and ClinicalTrials.gov. The results and conclusions based upon these results were reviewed and discussed by the Board of Directors of The American Headache Society to confirm consistency with clinical experience and to achieve consensus.

Results: The evidence for the efficacy, tolerability, and safety of CGRP-targeting migraine preventive therapies (the monoclonal antibodies: erenumab, fremanezumab, galcanezumab, and eptinezumab, and the gepants: rimegepant and atogepant) is substantial, and vastly exceeds that for any other preventive treatment approach. The evidence remains consistent across different individual CGRP-targeting treatments and is corroborated by extensive "real-world" clinical experience. The data indicates that the efficacy and tolerability of CGRP-targeting therapies are equal to or greater than those of previous first-line therapies and that serious adverse events associated with CGRP-targeting therapies are rare.

Abbreviations: AHS, American Headache Society; CGRP, calcitonin gene-related peptide; FDA, US Food and Drug Administration; mAbs, monoclonal antibodies; RCT, randomized controlled trial.

Conclusion: The CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments without a requirement for prior failure of other classes of migraine preventive treatment.

KEYWORDS
calcitonin gene-related peptide-targeting therapies, CGRP, migraine, position statement, prevention

INTRODUCTION

Preventive therapy is a core principle in the treatment of migraine and its use is a measure of high-quality care. Preventive treatment is defined as an intervention to reduce migraine attack frequency, intensity, duration, and disability. Successful preventive therapy should also improve responsiveness to acute treatments, reduce overall costs attributed to migraine and its treatment, and improve quality of life. Preventive therapy is indicated in ~40% of patients with migraine, although only a minority of such patients are using such treatments, in part because of limitations with efficacy and tolerability for more longstanding, established therapies.[1,2]

The simple definition of a first-line treatment is one that is considered appropriate as an initial treatment for a specific indication. The practical definition includes comparison with other available treatments and the recommendation that certain treatments should be prioritized, and tried first before newer and potentially superior treatments are considered (often referred to as step care).

The medications previously considered to be first-line approaches for the prevention of migraine include some medicines from the classes of antihypertensives, antiseizure medications, antidepressants, and onabotulinumtoxinA specifically for chronic migraine (Table 1). In the revised recommendations in the present statement (Table 2), candesartan is listed specifically as a first-line agent because of clinical trial evidence and "real-world" experience with this therapy.[3]

The available evidence and a wealth of clinical experience indicate that legacy first-line treatments, particularly orally administered medications, may not be consistently effective, have concerns with tolerability and safety, and lack clear predictors of treatment response that guide clinical decisions about which to try first. As these medications were all developed for indications other than migraine, the choice of which of these preventive treatments to implement is often based upon comorbidities, such as hypertension, insomnia, depression, and obesity, that may make a given treatment either indicated or contraindicated. Multiple studies show that adherence to these therapies is poor, based in part on unsatisfactory tolerability, and, in part, on lack of efficacy.[4–6] Further, it is not uncommon for individuals to give up on preventive therapy rather than switch to a different treatment after a first treatment has failed.[5,7]

The advent of migraine-specific preventive treatments over the last several years has led to multiple new therapeutic options. For migraine prevention, calcitonin gene-related peptide (CGRP)-targeting therapies include the monoclonal antibodies (mAbs): erenumab, fremanezumab, galcanezumab, and eptinezumab, and the small-molecule CGRP receptor antagonists (gepants): rimegepant and atogepant. As such, The American Headache Society (AHS) has provided iterative guidance for integrating these treatments into clinical practice based on the contemporaneous evidence and burgeoning clinical experience at the time.[8,9]

The previous AHS consensus statements on migraine treatments recommended, based on the available evidence and clinical experience at the time, that an individual try at least two classes of previous first-line migraine medications for ≥8 weeks before being considered for CGRP-targeting therapy.[8] In the case of chronic migraine, the recommendation was that a trial of onabotulinumtoxinA could be an alternative to a trial of two classes of medications.

Since the time of that statement, substantial new evidence has been published regarding the efficacy, safety, and tolerability of CGRP-targeting therapies for migraine prevention, adding to an already large body of evidence. These therapies include the mAbs erenumab, eptinezumab, fremanezumab, and galcanezumab, and the small molecules ("gepants") rimegepant and atogepant. In addition, there has been extensive "real-world" experience with these CGRP-targeting therapies, some of which have been documented in publications and much that has amassed from clinical experience. As the stated goal of the prior AHS consensus statements was to provide iterative updates as evidence and experience accumulated, this updated position statement accounts for this evolution in the approach to migraine preventive therapy.

METHODS

The AHS Board of Directors recognized the need for this specific guidance based on the pre-specified criteria in prior AHS consensus statements for iterative updates addressing the integration of newer migraine treatments. After a series of discussions at AHS Town Halls and Membership meetings over 2022 to 2023, and discussions at Board of Directors meetings in September and November 2023, a task force of authors working on behalf of AHS was identified by the Executive Committee. Conflicts of interest for individual authors and the organization based upon its interactions with industry and role as an advocate for patients and clinicians were all considered. This update reviewed data about the efficacy, safety, and use of migraine treatments since the previous AHS Consensus Statement was undertaken. A literature search included sources from PubMed, Google Scholar, and ClinicalTrials.gov. Evidence regarding migraine-preventive therapies

TABLE 1 Indications for initiation of calcitonin gene-related peptide-targeting therapies for migraine in previous American Headache Society consensus statement.[8]

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[a] 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[10]
- b. At least moderate disability (MIDAS score ≥11 or HIT-6 score >50

D Diagnosis of ICHD-3 migraine with or without aura (8–14 MMDs) and inability to tolerate (due to side-effects) or inadequate response to an 8-week trial of two or more[a] 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

E Diagnosis of ICHD-3 chronic migraine 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[a] 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 two quarterly injections (6 months) of onabotulinumtoxinA

Abbreviations: AAN, American Academy of Neurology; HIT-6, six-item Headache Impact Test; ICHD-3, International Classification of Headache Disorders, third edition; MHDs, monthly headache days; MIDAS, Migraine Disability Assessment.

Source: Ailani et al. [8].

[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.

including primary and secondary endpoints from randomized placebo-controlled clinical trials, post hoc analysis and open-label extensions of these trials, and prospective and retrospective observational studies

TABLE 2 Updated recommendations for migraine prevention.

A Diagnosis of episodic migraine with or without aura (4–14 MMDs) based upon ICHD-3 with at least moderate disability (MIDAS score ≥11 or HIT-6 score >50). Treatments to consider include:
1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
9. Small-molecules targeting the CGRP receptor ("gepants") including atogepant and rimegepant

B Diagnosis of chronic migraine with or without aura (≥15 MHDs) based upon ICHD-3. Treatments to consider include:
1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. OnabotulinumtoxinA
9. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
10. Small-molecules targeting the CGRP receptor ("gepants") including atogepant

Abbreviations: AAN, American Academy of Neurology; CGRP, calcitonin gene-related peptide; HIT-6, six-item Headache Impact Test; ICHD-3, International Classification of Headache Disorders, third edition; MMDs/MHDs, monthly migraine/headache days; MIDAS, Migraine Disability Assessment.

were collected with summarized results. These data and clinical experiences were incorporated into a proposed update, followed by review and commentary by the AHS Board of Directors with final integration into this focused consensus statement update.

RESULTS

Development of CGRP-targeting therapies

There is a strong foundation of basic, preclinical, and clinical evidence to support a key role of the neuropeptide CGRP in migraine. After having been identified in pre-clinical models as a potential mediator of migraine, seminal studies found that blood levels of CGRP are elevated during both migraine and cluster headache attacks, and that these elevated blood levels return toward baseline levels upon

effective treatment of the attacks.[11] These findings led to the development of small-molecule CGRP receptor antagonists (gepants) that were found to be effective in the acute treatment of migraine. Subsequent studies found that administration of CGRP could trigger migraine in susceptible individuals, further evidence for a causative role of CGRP in migraine pathophysiology.[12,13]

Clinical trial evidence regarding CGRP-targeting treatments

Pivotal clinical trials of CGRP-targeting preventive therapies have all shown statistically significant improvement in migraine (or headache) days for both episodic and chronic migraine in nearly all agents as summarized in our previous consensus statements. This evidence led to a US Food and Drug Administration (FDA) indication for the prevention of both episodic and chronic migraine for all agents. Rimegepant is only FDA approved for episodic migraine prevention because its pivotal prevention study excluded participants with >18 monthly headache days, and no chronic migraine-specific preventive pivotal trial has been reported to date. These indications for *both* episodic *and* chronic migraine are unique to the class of CGRP-targeting migraine preventive therapies and are important in clinical practice where patients may spontaneously transition back and forth along the continuum of episodic and chronic migraine.[14] Grading of Recommendations, Assessment Development and Evaluation (GRADE) analysis of the pivotal trials substantiates that all mAbs targeting CGRP were superior to placebo for the primary endpoint of these trials; that is, the reduction in monthly migraine days for participants with episodic and chronic migraine.[15]

The trial endpoint of mean monthly migraine days, while an obvious standard as a primary endpoint for trials of preventive therapies, provides an incomplete picture of the potential benefit of these therapies. One issue with this endpoint is that because it averages over all participants in a trial, it may fail to identify exceptional responses in individual patients. Responder rates have therefore emerged as an important secondary efficacy endpoint that indicate the magnitude of efficacy in individual patients.[13] Although this outcome has been examined in some clinical trials,[16,17] responder rates as a *specified endpoint* do not exist for many of the previous first-line migraine therapies. Other key secondary endpoints of the trials include reduced acute medication use[18] and multiple patient-reported outcomes.[19] All pivotal studies found the CGRP-targeting therapies to be well tolerated and safe, with very few serious adverse events reported. A prospective randomized head-to-head study of galcanezumab and rimegepant also showed that both were effective, safe, and well tolerated.[20] These results have been borne out by long-term open-label extension studies (see below). Multiple meta-analyses[7,21–25] have been performed to evaluate the CGRP-targeting migraine preventive therapies. All confirm their efficacy, and some also confirm their safety and tolerability. There have been several trials that have examined the efficacy and tolerability of CGRP-targeting preventive therapies in individuals for whom multiple previous therapies have failed.[26–30] All of these studies, which have been corroborated by post hoc analysis in multiple other studies, have met their primary efficacy endpoint in this population which is considered "difficult to treat". Post hoc analysis of randomized controlled trial (RCT) data has also led to several other important observations. One such observation is that the CGRP-targeting therapies are effective for migraine prevention in individuals who have pre-existing acute medication overuse and may therefore be particularly useful in this clinical setting.[25,31–34] Open-label extensions of RCTs of CGRP-targeting migraine preventive therapies have shown good adherence to therapy, persistent efficacy and tolerability over time, and no emergent serious adverse effects across the class of medications.[35–38] Finally, such studies also show no differences in efficacy or adverse effects among individuals with migraine with aura who may have a slightly higher inherent risk for vascular events.

Of all the previous first-line migraine preventive therapies, the greatest amount of evidence for efficacy exists for topiramate. Indirect comparison of results of studies for topiramate with those of CGRP-targeting therapies suggested similar efficacy.[7] A head-to-head study of erenumab vs. topiramate found that adherence to erenumab was significantly better than adherence to topiramate (primary endpoint), and found as a secondary endpoint that the efficacy of erenumab was statistically superior to that of topiramate.[39]

"Real-world" studies

A remarkable number of studies have been performed whose aim is to describe "real-world" experience with the CGRP-targeting therapies.[40] These include both prospective and retrospective studies in centers around the world. Although the evidence provided by these studies is not considered to be of the same quality as RCTs, they are very useful in that they generally confirm the results of the RCTs regarding efficacy, tolerability, and safety, and they do so within a wide variety of international cohorts, often over longer time periods.[40] Although not consistently identified as significant issues within the clinical trials,[35,41] safety issues that have been identified based on "real-world" experience include constipation and hypertension (both primarily for erenumab) and Raynaud's phenomenon;[42–46] however, it appears very uncommon for these or other adverse events to necessitate discontinuation of therapy. Given the active surveillance for adverse events internationally, there is a high level of confidence that any adverse events that emerge with long-term use will be identified rapidly.

Experience of the AHS

The published clinical trial and observational studies described above are consistent with the substantial unpublished clinical experience of the authors and the Board of Directors of the AHS. The consensus of this group on behalf of the AHS is that the CGRP-targeting therapies for prevention of migraine have had a transformational effect

on our ability to improve the lives of those with migraine, a primary mission of the AHS.

DISCUSSION

The evidence supporting the efficacy, tolerability, and safety of CGRP-targeting therapies for migraine prevention is substantial in its volume, scope, and quality. In addition to the standard endpoint of migraine or headache days, the efficacy and tolerability of these therapies is substantiated by several other important endpoints including responder rates, acute medication use, persistence with treatment, disability measures, patient global impression of change, and others. After >10 years of experience with these treatments in clinical trials, and experience in clinical practice since 2018, it is clear that these therapies are generally well tolerated with uncommon serious adverse events. Many "real-world" studies confirm the results of the RCTs in a variety of international populations. Based on this evidence and extensive clinical experience, CGRP-targeting therapies have rapidly become an indispensable option for the prevention of migraine.

Practical issues

Comorbid conditions

Comorbid conditions such as hypertension, tachycardia, insomnia, obesity, anxiety, depression, and epilepsy are obvious considerations in initiation or continuation of preventive therapies, particularly for individuals with these conditions for whom treatment with previous first-line therapies that also treat these comorbid conditions may be the most efficient approach. Conversely, these and other comorbid conditions or normal phenotypic variations (e.g., hypotension, bradycardia, daytime somnolence) may predispose to adverse effects from preventive therapies. These issues are not typically considered in RCTs or even observational studies but are fundamentally important issues in clinical practice. In many migraine clinical trials, participants with comorbid conditions are excluded,[47] such that "real-world" data and experience is essential to guide decision-making regarding patients with comorbid health issues. CGRP-targeting therapies represent a generally well-tolerated option that does not have the same contraindications as those associated with other established preventive treatments.

Medication switching

When a migraine preventive medication of any class is deemed to be effective and well tolerated by provider and patient, it is inappropriate to switch a patient from one agent to another except in situations where there are issues with safety. Even switching from one medication that is effective to another in the same class is associated with the risk of reduced efficacy or new adverse effects, so this practice is strongly discouraged.

Adherence

A consistent finding across all the studies of CGRP-targeting therapies for migraine prevention has been a very low drop-out rate. This finding is an indicator of adherence, which in turn is an indicator of both efficacy and tolerability.[48,49] There are potential significant consequences to step therapy that delays initiation of the most appropriate treatment for an individual patient. Lack of efficacy and tolerability of treatments initially tried with a step care approach may cause individuals to "give up" and not try other appropriate preventive treatments due to frustration and nihilism. In addition, if patients are overusing acute medication, this pattern may become further entrenched, resulting in long-term changes in brain structure and function that may make effective treatment more challenging.[31]

Long-term safety

As with any new class of therapy, it is important to be vigilant about the emergence of long-term adverse effects that were not identified in initial clinical trials. Although the CGRP-targeting therapies have been in clinical use for 5 years, and studied in trials for several years before approval, ongoing attention to adverse effects is clearly warranted. The increasing use of these therapies worldwide, and the intense scrutiny that these therapies have received in "real-world" studies, increases the confidence that any adverse effects that might emerge will be identified rapidly, allowing them to be assessed and addressed appropriately.

Additional populations

When newer treatments are developed, clinical trials commonly restrict the population that is evaluated. This restriction is then used to limit the use of the medications in populations that were excluded. Common reasons for exclusion include incomplete alignment with rigid diagnostic requirements, age limitations, headache frequency limitations, use of concomitant treatments, the presence of comorbid conditions, women who are pregnant or nursing, and limited inclusion of under-represented individuals. Limiting the availability of effective treatments by classifying them as second or third line, or in some cases excluding them completely, has the potential to exacerbate migraine in individuals already subject to care inequity, prolonging disability, and reducing therapeutic outcomes. As migraine is a disease of all ages it is important to address issues of therapy for children and adolescents, a population that is commonly excluded in clinical trials. There is no reason to believe that CGRP-targeting therapies are less effective in youth based on what is known about the developmental physiology of the CGRP-signaling system.[50] While

clinical experience with off-label use of these therapies in children and adolescents indicates that they are effective, at this stage there is limited clinical trial evidence or "real-world" evidence regarding the efficacy, tolerability, and safety of CGRP-targeting therapies in children and adolescents. Multiple studies in this population are ongoing. While awaiting the results of these studies, moving therapies that are effective and well-tolerated to a position that is earlier in the therapeutic hierarchy has the potential for expanded "real-world" experience in youth and other populations that are not well represented in clinical trials.

Access to treatment

When a treatment is not first line and may require trials of alternate treatments before initiation, there is an increased burden to both patients and providers. This may include elevated costs (burdening the patient) and prior authorization (burdening the prescriber). Additionally, delays or denials of approval can be expected to reduce response and outcome. There is evidence that suggests that a delay in effective preventive treatment may result in the disorder becoming more refractory.[49] Furthermore, this limitation of access has increased the burden on those patients with reduced resources who are the most at-risk patients, including under-represented medical minorities. Moving the CGRP-targeting preventive treatments to the first line should be expected to reduce these barriers to treatment and have overall improved outcomes.

Cost

As with any therapy for any disorder, economic considerations are an obvious factor in clinical decision-making regarding migraine treatment. Determining the "cost/benefit" relationship of a new treatment for migraine relative to established treatments may be particularly challenging for a variety of reasons. The cost per dose of a preventive medication is only one element of the cost of managing migraine in a given individual.[51] Other costs to insurers and health systems include those associated with acute treatment, overall healthcare utilization, and the potential expense of complications including medication overuse. For patients, the personal and socioeconomic costs of migraine can be devastating in terms of lost education, productivity, income, and interpersonal relationships. Although not commonly considered in economic analysis, adverse effects can also be viewed as a significant cost for the patient. There is a paucity of data regarding these costs for previous first-line treatments, which makes comparison difficult.[52] For example, there is evidence that CGRP-targeting preventive therapies reduce acute medication use that may represent a significant cost savings[18,53]; similar evidence does not exist for previous first-line preventive therapies. Apart from savings related to acute medication use, CGRP-targeting preventive therapies have been reported to generate several other types of health economic and socioeconomic benefits that may offset the direct costs of the treatments, and these benefits may accrue over time.[54–56]

Acknowledging these potential benefits, we recognize that the CGRP-targeting preventive therapies are significantly more expensive on a yearly basis than most of the previously established therapies, and some argue that this expense is a primary consideration in clinical decision-making. It is not our intention to justify the cost of the CGRP-targeting preventive therapies, and the AHS continues to encourage approaches to lowering costs of treatments of all kinds.[57] On the other hand, we argue that it is critically important to consider not only the direct cost of the treatment but also the substantial costs to the individual and society if effective treatment is delayed.

It is clear that if cost were not a primary consideration, there would be no controversy regarding the legitimate place for CGRP-targeting therapies as a first-line option for migraine prevention given their established safety, efficacy, and years of integration into practice. While some head-to-head evidence and substantial "real-world" experience indicates that CGRP-targeting therapies may be a superior option for a significant number of patients, further evidence and experience are needed to conclude that CGRP-targeting therapies are *the* first-line therapy, as opposed to *a* first-line therapy option, as is the position of this updated consensus statement from the AHS. This statement is consistent with guidelines published by other international organizations.[58]

SUMMARY

The basis for this focused AHS position statement is:

1. There is solid human evidence that establishes CGRP as a fundamental mechanism of migraine and therefore establishes CGRP-targeting therapies as "migraine-specific" in contrast to all the other established therapies.
2. The cumulative evidence for the efficacy, safety, and tolerability of CGRP-targeting therapies is significantly greater than that for any established migraine preventive therapy. The remarkable tolerability of the CGRP-targeting therapies is a particularly positive feature.
3. Nearly all CGRP-targeting therapies are FDA-approved for the preventive treatment of both episodic and chronic migraine, which simplifies decision-making in patients who may spontaneously transition back and forth between episodic and chronic migraine.
4. There are multiple categories of evidence supporting the use of CGRP-targeting therapies that do not exist for other migraine preventive therapies, including: responder rates, efficacy in patients with multiple prior treatment failures, efficacy in those with acute medication overuse, and those who do and do not have aura.
5. There is one head-to-head study demonstrating the superiority of a CGRP-targeting therapy (erenumab) over an established migraine preventive therapy (topiramate). In addition, multiple studies indicating the efficacy of CGRP-targeting migraine preventive

therapies in those who have previously failed multiple other established treatments provide indirect evidence of the superiority of CGRP-targeting therapies for some patients.
6. Acknowledging CGRP-targeting therapies as first-line approaches will increase the likelihood that their efficacy and safety will be more thoroughly evaluated in understudied populations, particularly youth.
7. Cost considerations regarding migraine therapies should include not only the direct cost of the treatments, but also the indirect costs of healthcare utilization and acute therapies, as well as socioeconomic costs for those who are disabled by the disease.

POSITION STATEMENT

The CGRP-targeting migraine therapies are a first-line option for migraine prevention. Initiation of these therapies should not require trial and failure of non-specific migraine preventive medication approaches.

AUTHOR CONTRIBUTIONS

Andrew C. Charles: Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Kathleen B. Digre:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Peter J. Goadsby:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Matthew S. Robbins:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Andrew Hershey:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The **American Headache Society** (AHS) is a non-profit organization that receives support from industry for educational programming, research, and advocacy. This includes support from multiple companies that are involved in the development, distribution, and marketing of therapies that are addressed in this statement, including (but not limited to) Abbvie, Amgen, Eli Lilly, Lundbeck, Pfizer, and Teva. These companies had no direct or indirect involvement in the development and writing of this consensus statement. **Andrew C. Charles** has served as a compensated consultant for Amgen, Eli Lilly, eNeura, and Lundbeck. He receives royalties from Oxford University Press. He is the current President of the AHS. **Kathleen B. Digre** has no relevant disclosures. **Peter J. Goadsby** reports, over the last 36 months, grants from Celgene and Kallyope, and personal fees from Eon Biopharma, Abbvie, Amgen, eNeura, CoolTech LLC, Dr Reddy's, Eli-Lilly and Company, Epalex, Linpharma, Lundbeck, Man&Science, Novartis, Pfizer, Sanofi, Satsuma, Shiratronics, and Teva Pharmaceuticals, and personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, Vector Metric, and fees for educational materials from CME Outfitters, and publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate and Wolters Kluwer, and a patent magnetic stimulation for headache (No. WO2016090333 A1) assigned to eNeura without fee. **Matthew S. Robbins** serves on the Board of Directors of the AHS as treasurer and the New York State Neurological Society, and in editorial capacities for Continuum and Current Pain and Headache Reports. He receives book royalties from Wiley. **Andrew Hershey** reports that his institution (University of Cincinnati) has received funds for his advising services, medical lead, and study support from AbbVie, Amgen, Eli Lilly, Lundbeck, Pfizer/Biohaven, Teva, Theranica, Upsher-Smith. He has received personal compensation from Scilex, Theranica and Up-To-Date. The members of the **AHS Board of Directors** and their disclosures are listed on the AHS website.

DISCLAIMER

This consensus statement published by The American Headache Society (AHS) is an assessment of current scientific and clinical information that is provided as an educational service. The information should not be considered inclusive of all appropriate treatments. New evidence may develop between the time this statement is submitted and when it is published or read. This statement addresses only the question that is specifically identified. It does not mandate any particular course of medical care and is not intended to substitute for the independent professional judgment of the treating provider. The AHS assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

ORCID

Andrew C. Charles https://orcid.org/0000-0003-3379-054X
Kathleen B. Digre https://orcid.org/0000-0003-2011-418X
Peter J. Goadsby https://orcid.org/0000-0003-3260-5904
Matthew S. Robbins https://orcid.org/0000-0002-5426-5333
Andrew Hershey https://orcid.org/0000-0002-1598-7536

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