The importance of an early onset of migraine preventive disease control: A roundtable discussion

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Abstract

Background: Newly approved migraine preventive therapies have allowed for rapid control of migraine activity, offering potential to minimize the burden of migraine. This report summarizes a roundtable discussion convened to analyze evidence for early onset of prevention, ascertain its clinical relevance, and provide guidance for healthcare professionals in crafting goals and treatment expectations for patients with migraine initiating preventive therapy.

Methods: A virtual roundtable meeting of migraine clinicians, researchers, and patient advocates convened in October 2020. Participants reviewed and discussed data summarizing patient and healthcare professional perceptions of migraine prevention and evidence from the peer-reviewed and gray literature to develop corresponding recommendations.

Summary: Evidence from clinical studies of anti-calcitonin gene-related peptide monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab) and the chemodenervation agent onabotulinumtoxinA indicate that patients may experience reduction of migraine activity within 7 days of drug administration and early attainment of disease control is associated with improvements in clinically important outcomes. The roundtable of experts proposes that early onset be defined as demonstration of preventive benefits within 1 week of treatment initiation. We recommend focusing discussion with patients around “disease control” and potential benefits of early onset of prevention, so patients can set realistic preventive therapy goals and expectations.

Keywords
CGRP, early onset, migraine, prevention

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Introduction

Migraine is a common and disabling neurologic disorder that affects more than 1 billion individuals worldwide. It is the most disabling disease in people under the age of 50 years and was second only to low back pain as the leading cause of disability globally in 2016. Migraine affects multiple areas of functioning (e.g., family and other relationships, career trajectories, educational achievement, financial security), may limit participation in healthy lifestyle choices (e.g., moderate or vigorous physical activity), and imposes a significant economic burden on individuals and on society as a whole.

The negative impacts of migraine often persist despite treatment. Poorly controlled migraine not only extends the burdens described above, it is also associated with acute medication overuse (MO) and medication overuse headache (MOH), it may result in the transformation or chronification of migraine, the latter of which likely arises from neuroinflammation and central sensitization resulting from repeated and prolonged exposure to migraine activity in genetically susceptible individuals.

While some studies suggest that poorly controlled migraine may worsen or chronify, other studies suggest that the prevalence of daily headache may stabilize, with 69% of participants with migraine aged 19–20 manifesting the same predominant headache subtype over a 30-year period. Furthermore, in a longitudinal population-based study of 9,944 participants, remission from chronic headache was observed in 58.2% and was associated with female sex, and no medication overuse compared to participants with persistent chronic headache.

The impact of migraine increases with increasing monthly headache day frequency. It has long been recognized that patients diagnosed with chronic migraine (CM) carry much higher levels of disability than those diagnosed with episodic migraine (EM); however, recent investigations have shown that patients with high-frequency episodic migraine, defined as 8–14 or 10–14 headache days per month, have levels of disability similar to CM, prompting a proposal to lower the threshold for CM diagnosis.

The American Headache Society consensus statement recommends that preventive treatment be offered to patients who experience 6 or more headache days per month regardless of the degree of associated disability. It further advises that preventive treatment (both pharmacologic and nonpharmacologic) be offered to/considered for patients with less frequent attacks that significantly interfere with daily life (associated disability) as well as for patients who cannot use, do not use, or use more than the recommended dosage of acute therapies. The goals of preventive therapy for patients with migraine are not only to reduce headache frequency and duration, but also to reduce attack severity; improve response to acute treatment/avoid escalation of use and reliance on poorly tolerated, ineffective, or unwanted acute treatments; reduce associated disability and costs; improve functioning; and to reduce headache-associated psychological distress, enable patients to self-manage migraine, and improve quality of life.

The introduction of migraine-specific preventives with demonstrated early onset of preventive disease control has the potential to vastly improve the lives of patients with migraine, who in the past may have had to wait 2 to 6 months to recognize the benefits of available preventive therapies.

The objective of this report is to summarize discussions and recommendations from a roundtable of experts convened to analyze available evidence related to early onset of preventive disease control, ascertain its clinical relevance, and provide guidance for healthcare professionals in crafting goals and treatment expectations for patients with migraine initiating preventive therapy.

Methods

A virtual roundtable meeting attended by migraine clinicians, researchers, and patient advocates was convened and hosted by H. Lundbeck A/S and Lundbeck Seattle BioPharmaceuticals, Inc. on October 8, 2020. The objective of the meeting was to discuss migraine preventive therapies, with a specific focus on the early onset of migraine prevention. Participants (the authors of this report) reviewed and discussed data summarizing patient and physician perceptions of migraine preventive disease control and evidence from the peer-reviewed, gray (i.e., from government, academic, business, and industry sources), and consumer literature on the benefits of an early onset in migraine preventive disease control, with an emphasis on issues relevant to prevention in clinical practice (Table 1). Identified data were reviewed in order of scientific merit and integrity, as well as relevance. Recommendations were then developed by the authors, based on their knowledge of identified literature as well as clinical expertise. These recommendations are described in this report, highlighted in italics. All authors contributed to this meeting summary.

Results/discussion

Appropriately defining “early onset of prevention”:

Disease control

The authors recommend that migraine prevention should be broadly defined as “the control of disease activity, including benefits beyond reductions in attacks/days per month frequency, such as reductions in acute medication use or in non-pain symptoms present during and between attacks as well as improvements in patient functionality, satisfaction, and quality of life. Early onset denotes demonstration of preventive benefits within one week of treatment initiation.”
Table 1. Relevant questions raised during roundtable discussion for migraine preventive disease control in clinical practice.

- What impact would the early onset of prevention be expected to have on the patient’s quality of life?
- Does a preventive therapy that offers a rapid reduction in migraine severity have clinical benefits?
- How would early prevention impact a patient’s ability to work/return to work?
- What benefits on overall patient outcomes would you expect to see with an early onset of prevention?
- How would the early onset of prevention be expected to impact acute medication use?
- Can an early preventive effect reverse disease chronification?
- How is the effect of early prevention different from the overall reduction in migraine frequency?
- What clinical outcomes (apart from monthly migraine days) could be utilized to evaluate the benefits of early prevention?
- How important is an early preventive effect in the goal of preventing disease chronification?
- How meaningful is it that the migraine preventive agent has an impact on the current attack?
- Would an impact on medication overuse headache be an indicator of early prevention?
- How would an early onset of prevention impact personal and overall healthcare costs?
- How would a patient’s personal relationships be affected by an early onset of prevention?
- Would an early onset of preventive effect be expected to have an impact on non-migraine comorbidities?

Impact on migraine and headache attack/day per month frequency

We believe that the term “prevention” may be potentially misleading, since many patients would naturally, if unconsciously, infer that the goal of preventive intervention is to eliminate the chance of having a migraine. For this reason, we recommend that prevention be more broadly defined as “disease control”; that is, its goal is not necessarily to eliminate all migraine attacks (an unrealistic expectation for a chronic disease), but rather to reduce overall migraine frequency, attack duration and severity, migraine-related disability, and disease-related psychological distress. When disease control is achieved, patients often experience enhanced response to acute treatment and improved functioning in key domains and in overall health-related quality of life. These goals are consistent with those enumerated by the American Headache Society in their 2021 consensus statement.\(^{33}\)

The onset of preventive benefits with traditional oral migraine preventive therapies is typically expressed in months, if not longer. Based on trial design and the resulting clinical data for these agents, current guidelines and the American Headache Society consensus statement recommend that patients who are prescribed oral preventive therapies should continue treatment for at least 8 weeks “after achieving the target or usual effective dose.”\(^{33}\) Further, the guidelines recommend that patients who are experiencing a partial response at that 8-week timepoint be advised that the medication(s) may take 6 to 12 months to achieve a full preventive effect.\(^ {33}\) In contrast, evidence from studies of the anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs; erenumab, fremanezumab, galcanezumab, and eptinezumab) and the chemodenervation agent onabotulinumtoxinA indicate that patients receiving these newer injectable agents may experience clinically relevant preventive benefits much sooner—as early as Day 1 and consistently by Day 7 post-administration.\(^ {38-60}\) As such, based on the availability of clinical evidence, we propose that early onset be defined as the demonstration of preventive benefits within 1 week of treatment initiation. In the following discussion, we describe outcomes supportive of this definition.
OnabotulinumtoxinA has also demonstrated an early onset of preventive efficacy, significantly reducing headache frequency as early as Week 1 after first dose (–0.9 days/week [onabotulinumtoxinA] vs –0.7 days/week [placebo] compared with the week before treatment; \( p = 0.046 \) vs placebo).

**Reduced acute medication use**

We agree that “a rapid reduction in migraine and headache frequency can reduce reliance upon acute medications (including over-the-counter and prescription) and result in fewer medication trials in the quest to find one that works, less medication overuse, less frequent development of medication overuse headache, and fewer side effects and drug interactions.”

The side effects of acute medications—wooziness/dizziness, fatigue, chest and throat pressure, chest pain, impaired concentration, and upset stomach, among others—have likely negatively impacted the quality of life of thousands of patients over the past 50 years, and can be especially detrimental in patients with comorbid conditions. The potential for gastrointestinal side effects, including gastric ulceration, may preclude acute non-steroidal anti-inflammatory drug (NSAID) use for acute migraine in some patients, particularly those with peptic ulcer, bowel diseases, or hemorrhagic stroke. Caffeine-containing combinations may permit reduced NSAID doses but can also lead to gastrointestinal disturbances as well as anxiety and motor unrest. Triptans have been associated with many central nervous system, gastrointestinal, and skin-related side effects, as well as chest tightness and pain. Among patients with EM, acute opioid or barbiturate use increases the risk for transformation to CM. Opioids may also increase the risk for comorbidities. In the population-based American Migraine Prevalence and Prevention (AMPP) study, depression, anxiety, and cardiovascular disease risk factors were higher among opioid users than among nonusers, as was headache-related healthcare resource utilization. And, as is always the case with opioids, the potential for abuse and dependence is an obvious concern. While migraine treatment utilizing acute medications may lead to the side effects described above, it is important to emphasize that not treating migraine may result in worsening in disease symptoms and overall functioning.

Acute medication overuse is common and may contribute to transformation from EM to CM. In the Migraine in America Symptoms and Treatment (MAST) study, a longitudinal cross-sectional survey of adults with migraine in the United States, 2107/13,649 participants (15.4%) reported acute medication use that met the definition for overuse; that is, they were using a triptan, opioid, barbiturate, isometheptene, ergot alkaloid, or combination analgesic \( \geq 10 \) days/month or an NSAID or simple analgesic \( \geq 15 \) days/month. A similar proportion of patients in the Chronic Migraine Epidemiology and Outcomes (CaMEO) study met the criteria for acute medication overuse (2975/16,789 [17.7%]). Although the factors contributing to transformation are likely complex, reports indicate that patients with MOH are up to 19.4 times more likely than non-overusers to experience migraine transformation.

To this end, data from erenumab, eptinezumab, and fremanezumab clinical studies have demonstrated reductions in acute medication use that were consistent with rapid reductions in migraine frequency. In the ARISE study, which was conducted in patients with EM, erenumab significantly reduced acute migraine—specific medication treatment days as early as Month 1 \( (p < 0.05) \) with further reductions at Week 12 \( (–1.2 \) days vs –0.6 days from baseline in the erenumab and placebo groups, respectively \( [p = 0.002]) \); Week 12 reductions were of even greater magnitude when only patients with baseline acute migraine—specific medication use were considered \( (–2.1 \) days vs –1.2 days, respectively \( [p = 0.002]) \). In a CM study, patients who received erenumab experienced greater reductions in acute migraine—specific medication treatment days than did patients who received placebo, whether or not they had acute medication overuse at baseline. This effect was present at Month 1, with differences achieving statistical significance by Month 3 (without overuse, \( –0.9 \) days \( [p < 0.05] \) to \( –2.4 \) days \( [p < 0.001] \) vs placebo; with overuse, \( –2.8 \) days \( [p < 0.001] \) to \( –3.3 \) days \( [p < 0.001] \) vs placebo).

Similarly, eptinezumab reduced acute medication use (ergots, triptans, and analogesics) more than placebo as early as Month 1 after treatment and across 6 months of treatment in patients with EM in the PROMISE-1 study, with greater reductions by Month 6 observed in patients with \( \geq 10 \) days/month baseline use \( (\geq 10 \) days/month) baseline use (eptinezumab 100 mg, \( –4.0 \) days; eptinezumab 300 mg, \( –7.4 \) days; placebo, \( –4.1 \) days). For those with CM and \( \geq 10 \) days of acute headache medication use during PROMISE-2 at baseline, reductions at Month 1 were \( –8.7 \) (100 mg) and \( –9.4 \) (300 mg) days with eptinezumab versus \( –5.1 \) days with placebo, which was sustained out to Month 6 (eptinezumab 100 mg, \( –8.9 \) days; eptinezumab 300 mg, \( –11.1 \) days; placebo, \( –7.9 \) days). Additionally, a recent post hoc analysis of patients in PROMISE-2 who were prospectively diagnosed with MOH found that eptinezumab reduced total days/month of acute medication use from 20.6 (100 mg) and 20.7 (300 mg) at baseline to 10.8 (100 mg) and 12.2 (300 mg) over the first dosing interval (Weeks 1–12) versus from 19.8 to 14.8 with placebo. These reductions were sustained or further improved with eptinezumab over the second dosing interval. In fact, 50.5% (100 mg) and 49.5% (300 mg) of eptinezumab-treated patients, versus 27.1% of those receiving placebo, consistently used acute headache medication at frequencies that were below the diagnostic thresholds for MOH for all 6 months of treatment.

Further, when preventive treatment with eptinezumab was initiated during a migraine attack in patients with
migraine (in the RELIEF study), the likelihood of acute medication use for that ongoing attack was reduced within the first 24 hours after the start of infusion.63

Among patients who overused acute medications at baseline in the fremanezumab HALO studies (13% of patients with EM and 54% of patients with CM), significant proportions reverted to no acute medication overuse at Month 6 (EM, 61% to 85%; CM, 59% to 65%); this benefit was maintained through Month 12 (EM 77% to 86%; CM 66% to 68%).74,75 In both HALO studies, reductions in migraine frequency were evident by Week 4,51,74 as was reversion from medication overuse to no medication overuse in the CM study.76

**Increased functionality/decreased disability and improved quality of life**

The authors agree that “available data indicate that the CGRP inhibitors and onabotulinumtoxinA increase function, reduce disability, and improve quality of life.”

For patients with migraine, we believe that waiting 4 to 12 weeks for medications to work, let alone longer, can have serious negative implications. For many patients, the inability to work for extended periods can adversely impact job, school, and financial opportunities and success and place additional strain on relationships, all of which can lead to loss of self-efficacy and hope. Thus, medications that quickly address the effects of migraine on the ability to function have the potential to significantly improve the lives of these patients. Patients may be able to confidently return to work or school sooner and be more productive while there. They may be better able to cope with attacks, care for their children, make healthy lifestyle choices (e.g., increase level of physical activity), and plan and consider opportunities at work or in social settings. It seems reasonable to expect that increases in days free from headaches could translate into improvements in one or more of these parameters. In the non-interventional National Health and Wellness Survey,77 each incremental increase in headache-free days was associated with a 5% reduction in work days missed and days of household activities missed. Further, if not managed appropriately, i.e., quickly, migraine may have long-term clinical and pathophysiological implications for patients, such as worsening of headache/migraine day frequency, increased acute medication use, and structural brain changes.78–84

Tools to directly assess impact of migraine and treatment on functionality/disability and quality of life are sometimes included in clinical trials of preventive migraine treatments;85 many are also useful in clinical practice.86 A variety of both general health and migraine-specific patient-reported outcome measures (PROMs) have been utilized for these purposes,86,87 such as the 36-item Short-Form Health Survey (SF-36) and Migraine-Treatment Optimization Questionnaire. These PROMs vary in parameters covered, response categories, and recall time frames, making selection and interpretation challenging based on context.87 We believe that standardized use of PROMs in future clinical trials will be invaluable in evaluating the benefits of an early onset of prevention in patients with migraine.

Available data indicate that the CGRP inhibitors increase function, reduce disability, and improve quality of life (reviewed in Gottschalk et al.88). These achievements would be expected to provide patients with even more benefits—those that are not easily captured with available measures. For example, increased functionality would be expected to provide patients with more time to spend on healthy lifestyle activities (vs having to rest), which could further improve their disease control. They could also potentially aid relationships by giving patients greater ability to make and fulfill familial and social commitments and by reducing their reliance upon others for support. Additional studies are needed to examine these potential effects as well as to determine how quickly these benefits manifest and whether or not they extend to the periods between attacks.

The PREEMPT trials—randomized, double-blind, placebo-controlled studies of onabotulinumtoxinA for the treatment of CM—indicated functional improvement as well. In one report, 44.1% of patients who received onabotulinumtoxinA versus 25.4% of patients who received placebo had a ≥5-point reduction from baseline in the 6-item Headache Impact Test (HIT-689,90) total score at Week 24 (difference vs placebo, p < 0.001).43 Similarly, all role function domains of the Migraine-Specific Quality-of-life Instrument (MSQ91,92) were improved more with onabotulinumtoxinA than with placebo at Week 24 (all p < 0.001).43 For both measures, improvements continued through Week 56, but differences between the groups that received onabotulinumtoxinA and placebo in the double-blind phase (both followed by open-label onabotulinumtoxinA) were no longer statistically significant.43

**Reduced anxiety and depression (comorbidities)**

The authors agree that “data from fremanezumab and onabotulinumtoxinA studies suggest that these preventive agents may reduce the symptoms of anxiety and depression in patients with migraine; however, additional studies are needed to clarify the impact of the early onset of prevention on these comorbidities.”

Because anxiety and depression are likely related to headache pain frequency and intensity,93 early control of migraine activity would be expected to reduce the severity of these comorbidities. Comorbidities of migraine increase as headache day frequency increases.77,93 Few studies have, however, assessed this potential benefit. In the HALO-CM trial,76 fremanezumab improved MSQ–Emotional Function domain scores 19.7 to 22.4 points from baseline to Month 12 (vs 16.7 to 17.3 points in the placebo groups) and reduced 9-item Patient Health Questionnaire...
(PHQ-9) scores 2.3 to 2.8 points from baseline to Month 12 (vs 1.6 to 2.4 points in the placebo groups). Patients also self-reported improvements in anxiety in a long-term free-
manezumab extension study.94 In a pilot study conducted
in patients with comorbid depression, onabotulinumtoxinA
significant improved symptoms of depression and anxiety
as early as Week 12.95 In the larger open-label COM-
PHEL trial,96 onabotulinumtoxinA treatment was associated
with improvements in symptoms of depression (PHQ-9;
3.7- to 6.3-point reductions) and anxiety (Generalized
Anxiety Disorder [GAD-7]; 5.2- to 8.0-point reductions)
over a 2-year period.96 The speed of onset of these effects
likely varies from patient to patient and is an area requiring
further study.

Increased patient satisfaction and persistence
with therapy

The authors highlight that the “early control of migraine
activity provides patients with more timely validation that
the preventive treatment is working, improving persistence
with therapy.”

Patients who fail to experience benefits of preventive
therapies early and patients who experience side effects
(sometimes before benefits) are likely to be dissatisfied
with the treatment and may fail to give the therapy an
adequate trial. This was demonstrated in the Second Inter-
national Burden of Migraine Study (IBMS-II), in which
24.0% of patients with EM and 40.8% of patients with
CM discontinued traditional preventive therapy (i.e., anti-
depressants, anti-epileptics, beta blockers, and calcium
channel blockers), 36.8% to 48.2% (EM and CM, respec-
tively) because they believed the medications were not
working, and 34.2% to 53.2% because of side effects.97
A 2017 retrospective analysis of inpatient, outpatient, and
pharmacy claims for patients with CM indicated that many
patients make the decision to discontinue or switch oral
preventives early—with 50% doing so within 60 days of
initiation.98 There is a real benefit in feeling rapid improve-
ment, as it provides the patients with more timely valida-
tion that the preventive is working. This may help explain
why dropouts in the primary study periods of CGRP-
targeted therapy trials were low (≤18%).42,49–
51,53,55,57,75,98–101

Reduced healthcare utilization/direct costs

The authors agree that “the effects on healthcare resource
utilization and direct costs have yet to be examined in
clinical studies of the newer preventive therapies for
patients with migraine.”

Patients who experience early control of migraine are
likely to use less acute medication than are patients who
must wait for their preventive treatment to start working.
This could also mean fewer emergency department and
urgent care visits, acute intravenous infusions, neuroimaging
studies, and hospitalizations during this time period and
overall. Because patients often seek medical help not only
for headaches, but also for other migraine-related features,
there is a need for studies to explore relationships between
onset of effect with respect to the full range of disease
variables (e.g., attack frequency, disability, and associated
symptoms and comorbidities) and healthcare resource uti-
lization and costs.

Effects on healthcare resource utilization and direct
costs have yet to be examined in clinical studies of newer
preventive therapies; however, the costs of these preventive
medications, particularly for patients with chronic
migraine, can be high.102 It is interesting to note that in
an analysis of data from the non-interventional US National
Health and Wellness Survey, there was no significant rela-
tionship between headache-free days and direct costs
observed.77 This finding underscores the need to examine
the impact of the full range of treatment effects on these
outcomes in future preventive medication trials.

Reduced non-medical costs

The authors similarly agree that “the effects of an early
onset of preventive benefits on non-medical costs have yet
to be examined in clinical studies of patients with
migraine.”

Likewise, effects on non-medical costs have yet to be
examined in clinical studies of newer preventive therapies.
Data from the US National Health and Wellness Survey
indicated that greater freedom from headache (headache-
free days) was associated with lower non-medical costs.
Specifically, each headache-free day was associated with
a 4% reduction in non-medical costs related to reduced
work productivity; annualized non-medical costs were
$16,975, $12,564, and $6,919 when stratified by 0–10,
11–20, and 21–26 headache-free days per month,
respectively.77

Reduced risk of transition/chronification

The authors highlight that “the ability to rapidly control
migraine activity with CGRP-targeted agents would be
expected to reduce migraine transformation; however, this
potential benefit has not yet been evaluated in clinical
studies of patients with migraine.”

There are several identified risk factors associated with
increased rates of progression from EM to CM.19,22–24,103
Sociodemographic characteristics (e.g., female sex and low
family socioeconomic status), lifestyle factors (e.g., caf-
faine consumption, major/stressful life events), comorbid-
ities (e.g., obesity, depression, asthma, noncephalic pain,
head and neck injury), headache day frequency, non-
optimized acute treatment, and overuse/increasing use of
acute migraine medications are all associated with an
increased risk of transformation. Although the effects of
modification of risk factors on the new onset of CM have
not been established, we believe that it remains good clinical practice to do so. Thus, education and lifestyle modifications remain an important aspect of migraine management, as do interventions to treat comorbidities, minimize migraine frequency and duration, and optimize acute medication use.

Whereas the ability to rapidly control migraine activity with CGRP-targeted agents would be expected to reduce migraine transformation, this potential benefit has not yet been evaluated in clinical studies. It is notable that persistent reversion from CM to EM was reported in post hoc analysis of data from a long-term erenumab clinical study in which patients receiving erenumab were more than twice as likely as patients receiving placebo to revert to EM during the initial 12-week double-blind phase of the study, and nearly 96.9% of those experiencing early reversion maintained this benefit throughout the subsequent 52-week open-label study period.\(^\text{104}\)

**Additional benefits**

We anticipate that there may be additional clinical benefits of an early onset of migraine preventive disease control, including reductions in the intensity of average headache pain, interictal allodynia and neck pain and cognitive impairment, migraine symptom frequency and duration (during and between attacks), and prodromal symptoms, as well as prolongation of the duration of interictal periods. Outcomes assessing these potential benefits should be included in future migraine prevention studies.

**Discussing the benefits of an early onset of prevention with patients**

We strongly recommend that “clinicians take time to ensure that patients with migraine have a clear understanding of realistic rates of improvements to expect with preventive therapy and when they may expect to see the benefits from treatment.”

We believe that clinicians should take time to ensure that migraine patients have a realistic understanding of the rates and amount of benefits they may experience with preventive therapy and the estimated timing. We recommend focusing discussion with patients around “disease control”; that is, not necessarily curing or eliminating all migraine attacks (an unrealistic expectation for a chronic disease), rather describing the benefits of an early onset of migraine prevention as described above. Clinicians should also help patients establish realistic expectations for treatment efficacy and disease control. For example, with traditional preventives, many patients experience some benefits early and then continue to improve over the first 3 to 6 months of treatment. Thus, they should be advised that this might be the case. Education about time to benefit with respect to other migraine symptoms—particularly the patient’s most bothersome symptom—or with a comorbidity, such as anxiety, is also important. Satisfaction and compliance with therapy may be enhanced when a patient recognizes that the time to improvement with respect to these benefits may differ from time to improvement in headache.

**Conclusion**

The goals of migraine management have long focused on the control of attacks and associated functional impairment using both acute abortive and preventive therapies. Despite the potential burden that migraine has on the individual patient, limited guidance has been provided regarding the importance of the clinical benefits that patients are provided with the earliest onset of preventive disease control. Based on the available evidence with the anti-CGRP mAbs (erenumab, fremanezumab, galcanezumab, and eptinezumab) and chemodenervation agents (onabotulinumtoxinA), we suggest that a broader approach regarding the goal of early control of migraine activity be undertaken in managing patients with migraine—one that encompasses effects on clinically important outcomes, such as acute medication use, patient function, satisfaction, quality of life, and comorbidity.

Attainment of disease control early in the process can reduce both the impact on daily life and potential for transformation that arises from repeated migraine attacks. We anticipate that these benefits will translate into improved adherence and persistence with therapy as well as reduced acute medication use, healthcare resource utilization, and associated costs. Additional studies are needed to fully elucidate the extent of these effects.

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**Author contributions**

CG, AB, AB, BT, MJM, JMP, PKD, NL, and DCB contributed to the conception and design of the manuscript. All authors reviewed and provided critical revision of all manuscript drafts for important intellectual content, as well as read and approved the final manuscript for submission.

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Lundbeck selected the chairperson, Dr. Christopher Gottschalk, who steered the content development, moderated the roundtable, and served as lead author for this manuscript.

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References

1. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018; 17(11): 954–976.
2. Steiner TJ, Stovner LJ, Vos T, et al. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain 2018; 19(1): 17.
3. Buse DC, Fanning KM, Reed ML, et al. Life with migraine: effects on relationships, career, and finances from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache 2019; 59(8): 1286–1299.
4. Bond DS, Thomas JG, O’Leary KC, et al. Objectively measured physical activity in obese women with and without migraine. Cephalalgia 2015; 35(10): 886–893.
5. Farris SG, Thomas JG, Abrantes AM, et al. Anxiety sensitivity and intentional avoidance of physical activity in women with probable migraine. Cephalalgia 2019; 39(11): 1465–1469.
6. Messali A, Sanderson JC, Blumenfeld AM, et al. Direct and indirect costs of chronic and episodic migraine in the United States: a web-based survey. Headache 2016; 56(2): 306–322.
7. Bonafe de M, Sapra S, Shah N, et al. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. Headache 2018; 58(S): 700–714.
8. Foster SA, Chen CC, Ding Y, et al. Economic burden and risk factors of migraine disease progression in the US: a retrospective analysis of a commercial payer database. J Med Econ 2020; 23(11): 1356–1364.
9. Law HZ, Chung MH, Nissan G, et al. Hospital burden of migraine in United States adults: a 15-year national inpatient sample analysis. Plast Reconstr Surg Glob Open 2020; 8(4): e2790.
10. Buse DC, Yurgrah MS, Lee JK, et al. Burden of illness among people with migraine and ≥ 4 monthly headache days while using acute and/or preventive prescription medications for migraine. J Manag Care Spec Pharm 2020; 26(10): 1334–1343.
11. Lipton RB, Munjal S, Buse DC, et al. Unmet acute treatment needs from the 2017 Migraine in America Symptoms and Treatment Study. Headache 2019; 59(8): 1310–1323.
12. Bonafe de M, McMorrow D, Noxon V, et al. Care among migraine patients in a commercially insured population. Neurol Ther 2020; 9(1): 93–103.
13. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia 2018; 38(1): 1–211.
14. Mose LS, Pedersen SS, Debrabant B, et al. The role of personality, disability and physical activity in the development of medication-overuse headache: a prospective observational study. J Headache Pain 2018; 19(1): 39.
15. Schwedt TJ, Alam A, Reed ML, et al. Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America Symptoms and Treatment (MAST) study. J Headache Pain 2018; 19(1): 38.
16. Thorlund K, Sun-Edelstein C, Druys E, et al. Risk of medication overuse headache across classes of treatments for acute migraine. J Headache Pain 2016; 17(1): 107.
17. Bernstein C and Burstein R. Sensitization of the trigemino-vascular pathway: perspective and implications to migraine pathophysiology. J Clin Neurol 2012; 8(2): 89–99.
18. Boyer N, Dallel R, Artola A, et al. General trigemino-spinal central sensitization and impaired descending pain inhibitory controls contribute to migraine progression. Pain 2014; 155(7): 1196–1205.
19. Buse DC, Greisman JD, Baigi K, et al. Migraine progression: a systematic review. Headache 2019; 59(3): 306–338.
20. Lipton RB, Fanning KM, Serrano D, et al. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology 2015; 84(7): 688–695.
21. Torres-Ferrus M, Ursitti F, Alpuente A, et al. From transformation to chronicization of migraine: pathophysiological and clinical aspects. J Headache Pain 2020; 21(1): 42.
22. Xu J, Kong F and Buse DC. Predictors of episodic migraine transformation to chronic migraine: a systematic review and meta-analysis of observational cohort studies. Cephalalgia 2020; 40(5): 503–516.
23. Andreou AP and Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. J Headache Pain 2019; 20(1): 117.
24. Su M and Yu S. Chronic migraine: a process of dysmodulation with sensitization. Mol Pain 2018; 14: 141744806918767967.
25. Merikangas KR, Cui L, Richardson AK, et al. Magnitude, impact, and stability of primary headache subtypes: 30 year prospective Swiss cohort study. BMJ 2011; 343: d5076.
26. Henning V, Katsarava Z, Obermann M, et al. Remission of chronic headache: rates, potential predictors and the role of medication, follow-up results of the German Headache Consortium (GHC) Study. Cephalalgia 2018; 38(3): 551–560.
27. Buse DC, Reed ML, Fanning KM, et al. Demographics, headache features, and comorbidity profiles in relation to headache frequency in people with migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache 2020; 60(10): 2340–2356.
28. Torres-Ferrús M, Quintana M, Fernandez-Morales J, et al. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. Cephalalgia 2017; 37(2): 104–113.
29. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia 2011; 31(3): 301–315.
30. Silberstein SD, Lee L, Gandhi K, et al. Health care resource utilization and migraine disability along the migraine continuum among patients treated for migraine. Headache 2018; 58(10): 1579–1592.
31. Chalmer MA, Hansen TF, Lebedeva ER, et al. Proposed new diagnostic criteria for chronic migraine. Cephalalgia 2020; 40(4): 399–406.
32. Ishii R, Schwedt TJ, Dumkrieger G, et al. Chronic versus episodic migraine: the 15-day threshold does not adequately reflect substantial differences in disability across the full spectrum of headache frequency. Headache 2021; 61(7): 992–1003.
33. Ailani J, Burch RC, Robbins MS, et al. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021; 61(7): 1021–1039.
34. Silberstein SD, Holland S, Freitag F, et al. 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.
35. Silberstein SD. Preventive migraine treatment. Continuum (Minneapolis, Minn) 2015; 21(4 Headache): 973–989.
36. Kumar A and Kadian R. Headache, migraine prophylaxis. StatPearls. Treasure Island, FL: StatPearls Publishing, 2018.
37. Paez A. Grey literature: an important resource in systematic reviews. J Evid Based Med 2017; 10(3): 233–240.
38. Bendtsen L, Sacco S, Ashina M, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. J Headache Pain 2018; 19(1): 91.
39. Simpson DM, Hallett M, Ashman EI, 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.
40. Herd CP, Tomlinson CL, Rick C, et al. Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine. BMJ Open 2019; 9(7): e027953.
41. Dodick DW, Silberstein SD, Lipton RB, et al. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: analysis of PREEMPT data. Cephalalgia 2019; 39(8): 945–956.
42. 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.
43. Aurora SK, Dodick DW, Diener HC, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta Neurol Scand 2014; 129(1): 61–70.
44. Bigal ME, Dodick DW, Krymchantowski AV, et al. TEV-48125 for the preventive treatment of chronic migraine: efficacy at early time points. Neurology 2016; 87(1): 41–48.
45. Brandes J, Yeung PP, Aycardi E, et al. Early onset of action with fremanezumab versus placebo for the preventive treatment of episodic migraine (P4.107). Neurology 2018; 90(15 Supplement): P4.107.
46. 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.
placebo-controlled REGAIN study. Neurology 2018; 91(24): e2211–e2221.

48. Detke HC, Millen BA, Zhang Q, et al. Rapid onset of effect of galcanezumab for the prevention of episodic migraine: analysis of the EVOLVE studies. Headache 2020; 60(2): 348–359.

49. 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.

50. 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.

51. 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.

52. Forderreuther S, Zhang Q, Stauffer VL, et al. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. J Headache Pain 2018; 19(1): 121.

53. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017; 377(22): 2123–2132.

54. Goadsby PJ, Dodick DW, Martinez JM, et al. Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis. J Neurol Neurosurg Psychiatry 2019; 90(8): 939–944.

55. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of erenumab in patients with chronic migraine. PROMISE-2. Neurology 2020; 94(13): e1365–e1377.

56. Schwedt T, Reuter U, Tepper S, et al. Early onset of efficacy with erenumab in patients with episodic and chronic migraine. J Headache Pain 2018; 19(1): 92.

57. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the prevention of chronic migraine. N Engl J Med 2017; 377(22): 2113–2122.

58. Silberstein SD, Rapoport AM, Loupe PS, et al. The effect of beginning treatment with fremanezumab on headache and associated symptoms in the randomized phase 2 study of high frequency episodic migraine: post-hoc analyses on the first 3 weeks of treatment. Headache 2019; 59(3): 383–393.

59. Yeung PP, Ayacori E, Bigal M, et al. Early onset of action with fremanezumab versus placebo for the preventive treatment of chronic migraine (P4.102). Neurology 2018; 90(15 Supplement): P4.102.

60. Winner PK, Spierings ELH, Yeung PP, et al. Early onset of efficacy with fremanezumab for the preventive treatment of chronic migraine. Headache 2019; 59(10): 1743–1752.

61. Tassorelli C, Diener HC, 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.

62. Schwedt TJ, Kuruppu DK, Dong Y, et al. Early onset of effect following galcanezumab treatment in patients with previous preventive medication failures. J Headache Pain 2021; 22(1): 15.

63. Winner PK, McAllister P, Chakhava G, et al. Effects of intravenous erenumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. JAMA 2021; 325(23): 2348–2356.

64. Tajti J, Majláth Z, Szok D, et al. Drug safety in acute migraine treatment. Expert Opin Drug Saf 2015; 14(6): 891–909.

65. Thorlund K, Toor K, Wu P, et al. Comparative tolerability of treatments for acute migraine: a network meta-analysis. Cephalalgia 2017; 37(10): 965–978.

66. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 2008; 48(8): 1157–1168.

67. Buse DC, Pearlman SH, Reed ML, et al. Opioid use and dependence among persons with migraine: results of the AMPP study. Headache 2012; 52(1): 18–36.

68. Schwedt TJ, Buse DC, Argoft CE, et al. Medication overuse and headache burden: results from the CaMEO study. Neurol Clin Pract 2021; 11(3): 216–226.

69. Tepper SJ, Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. Neurology 2019; 92(20): e2309–e2320.

70. Smith TR, Janelidze M, Chakhava G, et al. Corrigendum to “Eptinezumab for the prevention of episodic migraine: sustained effect through 1 year of treatment in the PROMISE-1 study” [Clin Ther 2020; 42(12): 2254–2265]. Clin Ther 2021; 43(4): 791.

71. Tepper SJ, Smith T, Kassel E, et al. Eptinezumab reduces the frequency of acute medication usage in patients with episodic or chronic migraine. Headache 2019; 59(Suppl 1): 162–163.

72. Marmura MJ, Diener H-C, Cowan RP, et al. Preventive migraine treatment with erenumab reduced acute headache medication and headache frequency to below diagnostic thresholds in patients with chronic migraine and medication-overuse headache. Headache 2021; 61(9): 1421–1431.

73. Diener HC, Marmura MJ, Tepper SJ, et al. Efficacy, tolerability, and safety of erenumab in patients with a dual diagnosis of chronic migraine and medication-overuse headache: subgroup analysis of PROMISE-2. Headache 2021; 61(1): 125–136.

74. Friedman DI and Cohen JM. Fremanezumab: a disease-specific option for the preventive treatment of migraine, including difficult-to-treat migraine. Emerg Top Life Sci 2020; 4(2): 179–190.

75. Bigal ME, Edvinsson L, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 2015; 14(11): 1091–1100.
76. Silberstein SD, Cohen JM, Seminero MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. J Headache Pain 2020; 21(1): 114.

77. Lipton RB, Lee L, Saikali NP, et al. Effect of headache-free days on disability, productivity, quality of life, and costs among individuals with migraine. J Manag Care Spec Pharm 2020; 26(10): 1344–1352.

78. Bigal ME and Lipton RB. Migraine chronification. Curr Neurol Neurosci Rep 2011; 11(2): 139–148.

79. Negro A, Curto M, Lionetto L, et al. A critical evaluation on MOH current treatments. Curr Treat Options Neurol 2017; 19(9): 32.

80. Diener HC and Limbroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol 2004; 3(8): 475–483.

81. Houts CR, McGinley JS, Nishida TK, et al. Systematic review of outcomes and endpoints in acute migraine clinical trials. Headache 2021; 61(2): 96–111.

82. 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.

83. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. J Neurol Neurosurg Psychiatry 2019; 90(3): 353–360.

84. Lipton RB, Fanning KM, Buse DC, et al. Migraine progression in subgroups of migraine based on comorbidities: results from the second International Burden of Migraine Study (IBMS-II). Headache 2013; 53(4): 644–655.

85. Gottschalk et al. Cephalalgia 2017; 37(5): 470–485.

86. 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.

87. Buse DC, Gandhi SK, Cohen JM, et al. Improvements across a range of patient-reported domains with fremanezumab treatment: results from a patient survey study. J Headache Pain 2020; 21(1): 109.

88. Boudreau GP, Grosberg BM, McAllister PJ, et al. Prophylactic onabotulinumtoxinA in patients with chronic migraine and comorbid depression: an open-label, multicenter, pilot study of efficacy, safety and effect on headache-related disability, depression, and anxiety. Int J Gen Med 2015; 8: 79–86.

89. Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. JAMA Neurology 2018; 75(9): 1080–1088.

90. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 2018; 38(8): 1442–1454.

91. 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.

92. 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 (MASH) study. J Headache Pain 2020; 21(1): 23.

93. Bouse 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 (MASH) study. J Headache Pain 2020; 21(1): 23.

94. Bouse 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 (MASH) study. J Headache Pain 2020; 21(1): 23.

95. Bouse 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 (MASH) study. J Headache Pain 2020; 21(1): 23.