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Setting higher standards for migraine prevention: a position statement of the international headache society

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Citation

Sacco, S., Ashina, M., Diener, H. C., Haghdoost, F., Lee, M. J., Monteith, T. S., ... Tassorelli, C. (2025). Setting higher standards for migraine prevention: a position statement of the international headache society. *Cephalalgia*, 45(2), 1-11. doi:10.1177/03331024251320608

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

Setting higher standards for migraine prevention: A position statement of the International Headache Society

Cephalalgia

2025, Vol. 45(2) 1–11

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DOI: 10.1177/03331024251320608

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Abstract

Migraine is one of the most prevalent and disabling neurological diseases, significantly affecting quality of life and productivity, as well as contributing to substantial societal costs. Recent innovations, including calcitonin gene-related peptide (CGRP) pathway inhibitors and onabotulinumtoxinA, have transformed migraine prevention by offering high efficacy and excellent tolerability, thus improving adherence. Clinical trials and real-world studies show that significant reductions in migraine frequency and, in some cases, complete migraine freedom is achievable. In this Position Statement, we advocate for raising the standards of migraine prevention by setting ambitious treatment goals aimed at optimal outcomes,

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Correction (September 2025): Figure 2 amended: Definition of migraine control now matches the text.



such as migraine freedom or very low number of days with migraine or moderate/severe headache. We emphasize the importance of addressing residual migraine burden, highlighting that achieving a $\geq 50\%$ reduction in monthly migraine days, although often considered a successful response, may not fully restore quality of life. Relying solely on percentage-based improvements can obscure the persisting impact of residual burden. This Position Statement does not want to change the standards for clinical trials but aims primarily at real-world clinical practice and proposes a shift from percentage-based measures of success to absolute goals while on treatment. We outline a framework that categorizes outcomes into four tiers: migraine freedom (no days with migraine or moderate-to-severe headache), optimal control (less than four days with migraine or moderate-to-severe headache), modest control (four to six days with migraine or moderate-to-severe headache) and insufficient control (more than six days with migraine or moderate-to-severe headache). Focusing on residual burden while on treatment aims to further improve patient quality of life and drive innovation in preventive therapies and non-pharmacological approaches. By advocating for higher standards, this Position Statement, is not aimed primarily to drive reimbursement policies for migraine preventive treatments, but seeks to inspire clinicians, researchers and policy-makers to prioritize ambitious goals in migraine prevention, ultimately enhancing patient outcomes and reducing the broader societal and economic impact of this debilitating condition.

Keywords

CGRP, chronic migraine, gepant, monoclonal antibodies, migraine, prevention

Date received: 19 January 2025; accepted: 20 January 2025

Introduction

Migraine is one of the most prevalent diseases worldwide (1). It predominantly affects adults but also occurs in children, adolescents and the elderly (1). For many individuals, migraine is a deeply disabling condition that affects multiple aspects of life well beyond physical pain, having an impact on overall well-being and health. In addition to headache, migraine attacks include disabling non-pain symptoms, such as nausea, vomiting, phonophobia and photophobia (2). In migraine with aura, the focal neurological disturbances of aura can play a major role in producing disability, even if there is absence of migraine headache. The recurrent and unpredictable nature of migraine disrupt emotional health, social connections and overall quality of life. Migraine often imposes significant limitations on daily activities and functions, contributing to considerable disability (3). The impact of migraine can extend to substantial loss in work productivity and missed opportunities for social engagement and family responsibilities (4). As a result, migraine is associated with significant economic challenges, including high healthcare costs, reduced workplace productivity (4–6) and high costs for society. Notably, quality of life is affected not only by the direct disability associated with headache days, but also by symptoms experienced on non-headache days, such as anticipatory anxiety and difficulty in making plans, which further undermine daily well-being (7). Furthermore, subjects with chronic migraine (CM) endure ≥ 15 headache days per month of which eight or more are migraine days, with heightened disability and a more pronounced reduction in quality of life than those with less frequent attacks (8,9).

Recent advances in preventive therapies, including calcitonin gene-related peptide (CGRP) pathway inhibitors,

have proved effective and better tolerated than previously available treatments (10,11), providing new hope for more effective and sustained migraine relief (12). Trials of onabotulinumtoxinA and the new classes of migraine preventive medications have yielded monthly migraine headache day reduction rates of $\geq 50\%$, $\geq 75\%$ and, in smaller portions of subjects, even 100% from baseline, with marked improvements in functioning across studies (13,14). The consistency of these results across multiple clinical trials and real-world studies (15,16) indicates that meaningful reductions, and even the elimination of disability as a result of migraine, are now a real possibility for some individuals with migraine. Indeed, as our understanding of migraine and its subtypes continues to grow, advancements in current and future treatments could bring us closer to effectively controlling the disease and ultimately striving for migraine freedom. While the complete elimination of migraine attacks or migraine-related disability has been considered an unrealistic goal for migraine treatment, such a high standard is not a novelty in other areas of neurology. The goal of anti-seizure medications in patients with epilepsy is seizure freedom (17), whereas the treatment goal of relapsing-remitting multiple sclerosis is “no evidence of disease activity” (18). For epilepsy or multiple sclerosis, the basic knowledge of mechanisms implied in the pathogenesis of the disease led to the development of disease-specific drugs. A similar evolution, toward complete control of diseases, has occurred in other fields of medicine, such as for arterial hypertension (19), diabetes mellitus (20), depression (21) and HIV/AIDS (22).

Historically, migraine lacked specific preventive therapies, but now migraine-specific CGRP pathway inhibitors have revolutionized prevention strategies. Drugs targeting CGRP or its receptor, including monoclonal antibodies

and small molecules (gepants), can result in a substantial improvement in migraine prevention. It is now essential to set ambitious goals for migraine prevention to drive further advancements. This includes the combination of available strategies (pharmacological and non-pharmacological), expanding the repertoire of migraine-specific preventive drugs, exploring additional non-pharmacological treatment options and conducting research to uncover additional disease mechanisms. Such efforts are crucial to addressing the complexity of migraine, a disorder that involves multiple neural structures and mediators and has complex mechanisms underlying pain and its maintenance over time (23).

This Position Statement seeks to raise the standard of care in migraine management by advocating for ambitious but achievable treatment goals. Rather than settling for what might be considered an “acceptable” response, this approach encourages researchers and clinicians to aim for what are ideal outcomes whenever possible, striving to deliver maximum relief from both pain and additional migraine-related symptoms, including aura. By shifting the focus to residual migraine burden while on treatment, this Position Statement emphasizes the importance of addressing the impact of remaining symptoms on patients’ lives. Through patient-centered, aspirational goals that move beyond minimum thresholds, it inspires the migraine care community to pursue the best achievable outcomes.

The ultimate aim is to ensure that every person living with migraine can experience the greatest possible improvement in their condition and quality of life, and this in turn will have a positive impact on society and health-related costs. Furthermore, setting ambitious goals might encourage research on new treatments that are also particularly needed for individuals not showing a satisfactory response to the current available ones.

Migraine prevention

Migraine prevention aims to reduce the frequency, severity, duration and overall burden of migraine attacks, improving quality of life (24,25). It should be considered in adults, children and adolescents, as well as in the elderly where appropriate. The Practice Recommendations of the International Headache Society consider four components to identify candidates for preventive therapy (26) with the presence of at least one of them being sufficient to start treatment. The components to be considered are:

1) *Frequency of migraine days.* Prevention is typically recommended for individuals experiencing four or more monthly migraine days (MMDs), particularly when these days are severe, prolonged, or do not respond to acute therapy. However, even individuals with two or more debilitating migraine days per month may benefit from preventive therapy to enhance their daily functioning and quality of life (24,25). The number of MMDs is

usually counted with the help of a migraine diary but may be documented by subjective report.

2) *Substantial disability or functional impairment* affecting work, education or family responsibilities. In such cases, the goal of prevention is to restore function and minimize the impact of migraine on daily activities and to reduce the interictal burden (26). Disability and impairment can be measured via validated questionnaires such as the Migraine Disability Assessment Scale (MIDAS) (27), the six-item Headache Impact Test and the Migraine Specific Quality of Life Questionnaire (MSQ) on a daily basis with a headache diary (28).

3) *Frequent use of acute medications.* Individuals who frequently resort to acute medications require preventive therapy because it can reduce their dependency on these medications and help prevent medication overuse headache. As migraine frequency increases, individuals increase the use of acute migraine treatments and are at risk of overusing analgesics and triptans which paradoxically can exacerbate migraine. Instead, the use of prevention has demonstrated an improved control of migraine frequency patterns (29), making preventive options essential in these situations (26). The quantification of acute medication use can be ascertained encouraging the use of headache diaries.

4) *Inadequate relief or intolerable side effects from acute treatments.* For those subjects, preventive therapy can be instrumental (26). By reducing the frequency, intensity and duration of migraine attacks, as well as attack recurrence, prevention minimizes the need for acute interventions and supports a more consistent symptom control. The adequacy of acute treatments can be tested via tools such as the Migraine Treatment Optimization Questionnaire (MTOQ), by assessment on a daily basis with e-diaries or by patient report when other data is not available (30).

When initiating preventive therapy, it is crucial to set realistic expectations from both patient and clinician perspectives. Traditional oral pharmacological preventive treatments often require titration and might take several weeks or months to demonstrate full effectiveness, requiring patience and commitment for an accurate evaluation of efficacy (24,31,32). Preventive treatments may not only reduce the frequency of attacks, but also reduce pain severity, duration of attacks and improve the response to acute treatments. Individuals should be encouraged to continue therapy despite early perceptions of inefficacy and possible adverse events to allow time for a true therapeutic effect.

The advent of CGRP pathway inhibitors has ushered in a new era of efficiency, tolerability, safety and adherence in migraine prevention (33). Unlike previously used therapies, CGRP pathway inhibitors often reduce migraine frequency and severity within days or weeks, with very few adverse events, which favors the observed high compliance and

persistence rates (34,35). Many individuals report noticeable improvements after the first week of treatment, marking a significant advancement for those previously frustrated by lengthy efficacy onset delays. Although the initial effects of CGRP-targeting treatments appear quickly, additional benefits may continue to accrue with ongoing use. These treatments, along with onabotulinumtoxinA for chronic migraine, have transformed migraine care, leading to greater adherence, less medication overuse and higher overall patient satisfaction. It is worth noting that some gepants may serve not only for prevention, but also to treat the acute migraine attack, and they do not appear to be associated with an increased risk of medication overuse.

Efficacy in migraine prevention: the clinical trials criteria

In the field of migraine prevention, specific criteria have been established by health agencies (e.g. Food and Drug Administration, European Medicine Agency) and scientific societies to assess treatment efficacy in clinical trials and to identify participants as “responders”. The responder rate is defined as the percent change from baseline in the number of MMDs or number of moderate/severe headache days in each dosing interval.

According to the Guidelines of the International Headache Society for controlled trials of preventive treatment in episodic and chronic migraine in adults, achieving a $\geq 50\%$ reduction in MMDs qualifies a participant as a responder (36,37). However, for individuals with chronic or refractory types of migraine, a $\geq 30\%$ reduction has also been considered acceptable as a meaningful response, especially when considering traditional preventive drugs (38). This lower threshold of response reflects the complex nature of chronic migraine and refractory migraine, recognizing that in participants with difficult-to-treat migraine, any improvement may be significant. The 30% threshold represents a balance between realistic expectations and the challenges of managing patients with relatively treatment-refractory migraine, where complete relief is often difficult to achieve. In clinical trials and in real-world settings, this benchmark offers a practical measure for evaluating treatment impact on the disease (39). Regulatory and insurance agencies have also used those criteria to ensure continued reimbursement for ongoing treatments, although only for patients classified as responders to the current medications.

From clinical trials to clinical practice: understanding the impact of percentage reductions

When transitioning from clinical trials to clinical practice, it is essential to recognize the limitations of using percentage reductions in migraine frequency as the primary measure of

treatment success. The commonly accepted benchmark of a $\geq 50\%$ reduction in MMDs – or their proxy moderate-to-severe headache days – is widely used in research to indicate improvement, yet this metric can mask important aspects of the residual migraine burden in many individuals. The true impact of a $\geq 50\%$ reduction in MMDs varies greatly depending on each individual’s baseline frequency, and this variability directly influences their quality of life (Figure 1). For example, a person with migraine with a baseline of eight MMDs achieving a $\geq 50\%$ reduction would still experience around four MMDs. On the other hand, a person with an initial baseline of 14 MMDs would see their migraine days reduced to around seven with a 50% response. Although both of these individuals gained precious migraine-free days each month, their disease will still have substantial impact, limiting their quality of life despite the improvement. Individuals with migraine with higher baseline MMDs may experience even less satisfactory outcomes. A subject with 20 MMDs achieving a 50% reduction will still experience around 10 MMDs, which, although transformative, continue to impose a significant burden. For individuals with 30 MMDs, a $\geq 50\%$ reduction leaves them with approximately 15 MMDs each month and still with a diagnosis of CM. While this represents a dramatic shift from daily migraine, the patient remains in a highly disabling situation, experiencing migraine days for about half of each month. Furthermore, outcomes measuring MMDs and moderate-to-severe headache days do not account for days with milder headaches that can also have meaningful negative impacts on patient comfort, functioning and quality of life (40).

These differences highlight the need of changing how we measure treatment success in clinical practice. Simply focusing on percentage reduction can lead to an incomplete understanding of each person’s status, as the same reduction rate can result in widely varying degrees of functional improvement based on baseline frequency.

The ESTEEMen study illustrates the limitations of relying solely on percentage reductions, showing that this approach can obscure the true burden of migraine for certain subjects (41). In particular, individuals with CM receiving a prevention therapy who achieve high percentage reductions in MMDs may still experience a substantial number of residual MMDs, which can continue to impair quality of life and daily functioning, potentially warranting additional preventive measures. According to the study, most subjects with a $\geq 75\%$ response achieved an optimal outcome with zero to three residual MMDs. However, five out of six patients with a 50–74% response still had over four residual MMDs per month, with 62.0% of these individuals meeting the criteria for high-frequency EM and 23.9% for CM. Furthermore, participants with a 30–49% response had residual MMDs close to those observed in individuals with a 0–29% response, underscoring the persisting burden of the disease.

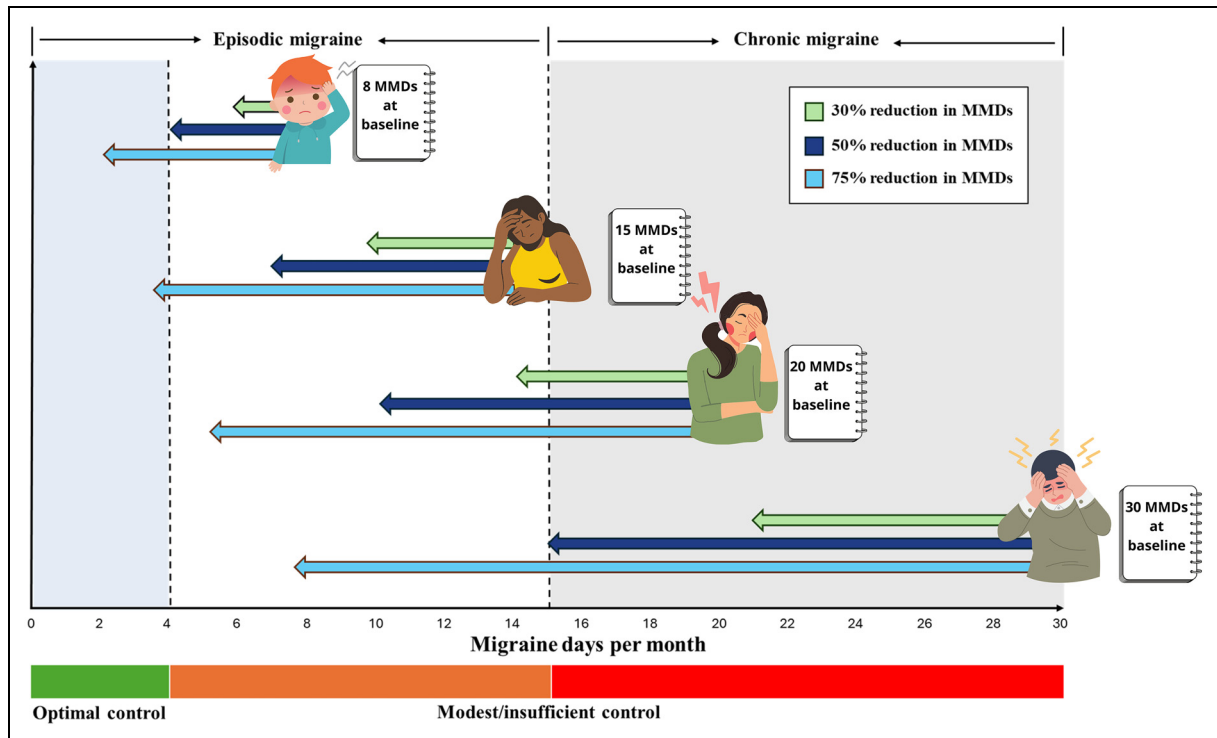


Figure 1. The impact of a 50% reduction in monthly migraine days (MMDs) varies greatly depending on baseline frequency. This variability is highly likely to influence differently the patients' quality of life.

Implementing a focus on migraine burden while on treatment in clinical practice

The above reported information highlights the need to shift, in clinical practice, from percentage reductions, as the primary measure of success of a treatment, to migraine burden while on treatment (residual migraine burden). Instead of solely considering reaching a $\geq 50\%$ response to define treatment success, clinicians should consider the number of migraine days, or, as a proxy, with moderate-to-severe headache, as well as each individual's quality of life. This approach allows treatment strategies to be tailored more precisely, to achieve meaningful, life-enhancing outcomes that align with individual needs.

In clinical practice, there are no universally defined criteria for what constitutes an "ideal" outcome for migraine prevention. Unlike the structured benchmarks used in clinical trials, real-world treatment success is highly individualized. Measures of individuals' satisfaction with treatments can help overcome the complexities of evaluating treatment effectiveness in clinical practice; nevertheless, they are not standardized and rely on subjective considerations. Patient satisfaction with a treatment depends on factors such as the baseline migraine burden, personal goals and values, and specific quality-of-life concerns. Tools to assess individuals' satisfaction with treatments might be useful to add elements to evaluate treatment effectiveness especially in

individuals not achieving "ideal" outcomes. For many individuals, partial therapeutic successes might be satisfactory and lead to treatment continuation, while other patients might expect/require more improvement and opt for a treatment switch.

Despite the complexity of migraine symptoms and the challenges to have unique metrics to detect the residual burden while on treatment, there is the need to have simple metrics to be used in clinical practice. Days with migraine or moderate-to-severe headache is an accessible metric that is easy to monitor and correlates closely with other quality-of-life parameters. When migraine frequency remains high, it is likely that related symptoms and functional limitations are also elevated. Conversely, when frequency is low, there is a high probability that many aspects of an individual's life, including productivity and emotional health, improve as well, even if some residual issues persist. Research consistently shows that individuals with EM and CM experience functional gains (as measured by the MSQ, version 2.1) when migraine days decrease (42). The most significant improvements appear in role function, particularly for subjects with a response rate $\geq 75\%$. Item-level analysis also reveals that higher response rates correlate with greater positive changes in quality-of-life metrics, underscoring that reducing migraine frequency has a direct, positive impact on daily functioning across multiple domains. Another important parameter

associated with the reduction of migraine days is the Patients' Global Impression of Change (PGIC) score (43).

By using migraine frequency as a foundational metric and supplementing it with personalized goals and patient-reported outcome measures, clinicians can adopt a straightforward, adaptable approach to improve migraine management and the quality of life of individuals who suffer from the disease. This strategy balances simplicity with comprehensiveness, making its application feasible in any clinical setting at the same time as maximizing positive outcomes.

Setting goals of migraine burden while on treatment

The Author Panel of this Position Statement set the following goals as the targets of migraine prevention:

Migraine Freedom. This is defined as the complete elimination of days with migraine or moderate-to-severe headache, ideally over a period of three months. This is the ideal outcome, where the individual is mostly free of disease (44). Migraine freedom includes freedom from interictal burden. Achieving migraine freedom represents the highest standard of treatment success, leading to a life almost free from migraine-related disability and from the need for acute medications. This includes freedom to live, without substantial fear of migraine triggers. Although it may be rarely attainable, migraine freedom remains the aspirational goal in preventive therapy.

Optimal Control. This is defined as less than four days with migraine or moderate-to-severe headache per month for three months, with a satisfactory response to acute treatment, defined as pain-freedom within two hours from the intake. This level of control is a compromise between the aspirational goal of migraine freedom with the generally more realistic expectation for the effectiveness of migraine prevention. Achieving this goal is also consistent with falling below the commonly used threshold of four or more migraine days per month that is used as an indication for recommending migraine preventive treatment.

Modest Control. This is defined as four to six days with migraine or moderate-to-severe headache per month. In this case, disability may persist, but this level of control may represent a meaningful improvement especially for those with high frequency episodic migraine (10–14 headache days per month) or CM (>14 headache days per month) before treatment. While migraine attacks still occur, they are likely to disrupt the individuals' life to a lesser extent. Furthermore, this migraine frequency is not associated with a high risk of migraine progression to CM. For many patients, particularly those with CM before treatment, this reduction allows for a more active daily life, decreased acute medication use, and improved overall functionality.

Insufficient Control. This is defined as more than six days with migraine or moderate-to-severe headache per

month. At this level, migraine imposes a substantial burden and may require frequent use of acute medications. This outcome suggests that the current preventive approach is not adequately managing the migraine burden and the risk of progressing toward CM or medication overuse headache is high, such that clinicians should consider adjusting treatment by making changes in the ongoing preventive drug, switch to another drug or combining approaches to improve control. In some cases, insufficient control may be present when there are less than six MMDs, especially when attacks are associated with very high levels of disabling symptoms such as severe and repeated vomiting, hemiplegia or long-lasting aura, which may be associated with increased healthcare utilization (Figure 2).

The assessment of the above goals requires a clear definition of migraine day. The panel decided to adopt the following three definitions of a migraine day, as modified from van der Arend et al. (45), in subjects with a diagnosis of migraine:

1. A day with headache satisfying criteria (a) + (b)
 - (a) matching more than two of four characteristics: unilateral, pulsating, moderate-to-severe pain, aggravated by or causing avoidance of routine physical activity;
 - (b) during headache, more than one of the following: nausea and/or vomiting, photophobia and phonophobia.
2. A day with a (visual) aura lasting 5–60 minutes.
3. A day with headache for which a migraine-specific acute migraine medication or a usually effective acute migraine medication is taken.

We included in our definitions of treatment goals also moderate-to-severe headache days as a proxy of migraine days to account for days with a headache sufficiently severe to impair daily activities but not associated with migraine symptoms. This decision is justified by the fact that an effective acute medication can prevent the progression to a full-blown migraine attack and inadequate acute attack treatment is a risk factor for chronic migraine (46).

Clinical implications and possible limitations

The proposed approach has several important clinical implications, as well as limitations, that must be considered. The primary clinical implication and the core objective is to foster a more ambitious perspective in migraine management, striving to provide individuals with migraine a normal or near-normal quality of life despite the presence of the disease. This represents a substantial shift from the current mindset, where the primary goal of preventive treatment focuses on achieving relative improvement. By

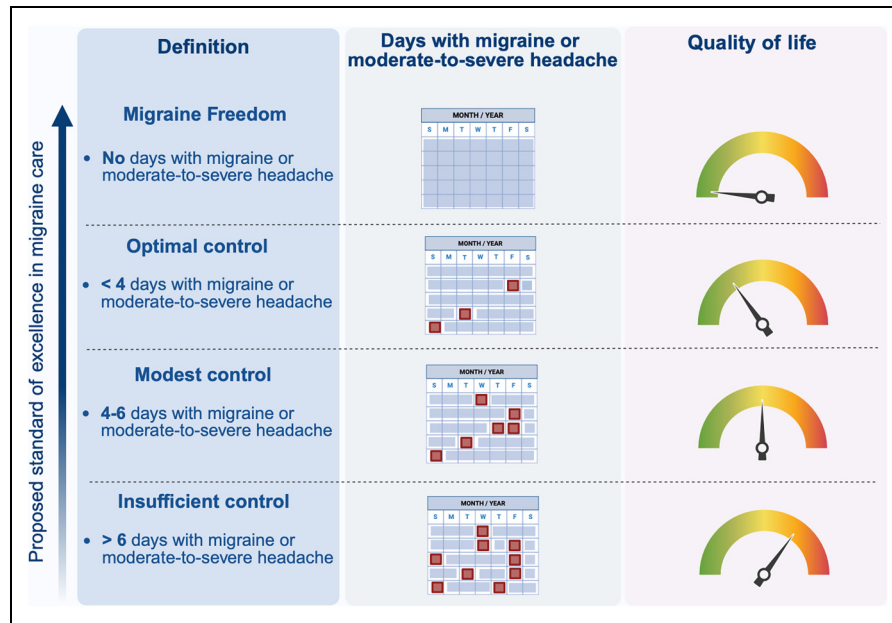


Figure 2. Aspirational goals of migraine prevention according to the position statement of the International Headache Society.

adopting this new definition, greater emphasis will be placed on addressing the residual burden of migraine, ultimately promoting better overall health and quality of life for individuals with migraine. We anticipate that this paradigm shift will stimulate innovative research, driving the development of more effective treatment options by optimizing existing therapies and fostering the development of novel options.

It is important to note that the definitions elaborated in this consensus document and the newly proposed goals are instrumental to advocate for an improvement in the clinical standards of migraine prevention (37) for the benefit of patients in a landscape characterized by an increased availability of effective treatment options. It is however extremely important to maintain the standard criteria of efficacy when considering drug reimbursement and approval of new drugs. These standard criteria, requiring a $\geq 50\%$ reduction in MMDs or moderate-to-severe headache days, with a $\geq 30\%$ reduction being acceptable when no superior alternative exists, remain valid to ensure an equitable access to treatment for individuals with migraine. Altering these well-established thresholds could inadvertently restrict access to preventive therapies, disproportionately affecting patients who achieve partial, yet clinically meaningful, responses. Such thresholds have been carefully designed to reflect achievable and meaningful improvements, balancing the realities of therapeutic efficacy with the need to ensure treatment accessibility. Maintaining the current reimbursement framework is crucial for preserving fairness in healthcare delivery, minimizing barriers for patients who rely on these

therapies to manage their migraine and avoid compromising the foundational principles of patient access and equity. Ultimately, separating aspirational goals aimed at optimizing patient outcomes from the pragmatic requirements governing reimbursement criteria ensures that advancements in migraine care can progress without jeopardizing existing pathways to treatment. We recognize the unmet needs associated with refractory and resistant forms of chronic migraine, which are typically excluded from migraine clinical trials (38). We call for research to better classify this population, and to evaluate treatment paradigms that improve clinical outcomes. This may include novel patient-centered metrics and region-specific, multidisciplinary interventions. Taken together, wholistic evaluations to assess clinically meaningful improvements including physician attestation for reimbursement remain important for highly disabled populations.

It is also important to point out that, in clinical practice, the evaluation of MMDs should be coupled with patient-reported outcomes (PROs), and in particular PGIC, that provide an account of patients' satisfaction with treatment and other important migraine-related outcomes. Medication side effects need to be considered and the optimal balance between side effects and migraine improvement must be sought. We intentionally did not include PROs in our definitions because we wanted to focus attention on easy-to-track and objective goals that can be reliably associated with residual disability. However, in individuals with moderate response to migraine prevention, PROs, as well as migraine diaries, are very important to quantify disability and its improvement with treatments.

We focused our definitions on the response to migraine prevention. Nevertheless, we would like to remark that the optimization of acute treatment is key for migraine management together with that of migraine prevention. The advent of effective acute migraine treatments that can also be used for migraine prevention, such as gepants (13,47), holds the potential to provide further improvements and flexibility avoiding medication overuse headache in migraine management.

The role of the International Headache Society is to provide a powerful and credible voice to champion best practice approaches globally. The criteria proposed in the present paper have the purpose of setting higher standards of treatment goals that can encourage research for more effective treatment strategies for migraine – both pharmacological and non-pharmacological – and for new migraine-specific treatment targets. Our proposed approach also encourages the combination of preventive treatments, including non-pharmacological treatments, and the assessment and treatment of comorbidities in individuals without full control of their migraine (44). This approach ultimately promotes an individualized and dynamic treatment strategy for patients who reach moderate goals that can be further improved. Notably, this strategy is not intended to encourage frequent treatment changes associated with increased opportunity costs (48), but rather to address unmet needs and enhance the individuals' quality of life where feasible.

Because the International Headache Society is a global society, we acknowledge that different regions of the globe will achieve these aspirational goals at different rates considering the different availability of facilities and drugs (49). With this in mind, we have prioritized the guidance on both essential and optimal treatments for migraine (26) to provide a management framework that fosters the adoption and implementation of the essential level of migraine management in all the countries worldwide, and, once achieved, it points to the adaptations required to achieve the optimal approach. Positive changes along the continuum will require regional and global efforts in terms of advocacy, education and resources not only to integrate the proposed approach in low- and medium-income countries, but also in high-income countries, where it is estimated that about half of people with migraine may benefit from prevention, but only 13% are currently taking preventive medications (50).

A potential limitation is that current treatment success is defined primarily by reductions in MMDs or days with moderate-to-severe headache, which, while useful, may not capture the full spectrum of improvement. As explained above, currently used PROs should be used to integrate the information collected with headache diaries for deciding whether the response to migraine

treatment is acceptable. We note, however, that those outcomes may not be designed to pursue ambitious treatment goals. Further research is warranted to explore comprehensive indices of substantial treatment effectiveness ensuring they are both clinically relevant and straightforward for routine use.

Conclusions

While acknowledging that response criteria for clinical trials that drive approval of new treatments should not be changed, this Position Statement aims to raise the bar in migraine prevention and management, encouraging clinicians, healthcare providers and patients to strive for the highest possible outcomes with migraine preventive treatments. While a reduction in migraine or headache days is often deemed as a success, this Position Statement advocates for a mindset of continual improvement, striving for ideal, rather than merely acceptable results. It encourages a shift towards setting ambitious goals in real-world clinical practice, aiming to achieve complete migraine freedom. This approach promotes ongoing reassessment and innovation in treatment strategies, aiming for excellence in care and support. The Position Statement calls for a commitment to surpass current conventional targets, transforming migraine management so that patients gain not only relief, but the opportunity for a more fulfilling, migraine-free life, with a potential impact on society as a whole.

Declaration of conflicting interests

Simona Sacco has received personal fees as speaker or advisor from Abbott, Allergan-Abbvie, AstraZeneca, Bayer, Boehringer, Eli Lilly, Lundbeck, Novartis, NovoNordisk, Pfizer and Teva, as well as research grants from Novartis, Uriach. She is president elect European Stroke Organisation, editor-in-chief of *Cephalalgia* and *Cephalalgia Reports*, and assistant editor for *Stroke*.

Messoud Ashina reports receiving personal fees as speaker or consultant from AbbVie, Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Novartis, Pfizer and Teva. MA reports research support from Lundbeck Foundation, Novo Nordisk Foundation, Novartis and Lundbeck (all to institution). MA also reports serving as an Associate Editor of *Brain* and *The Journal of Headache and Pain*.

Hans-Christoph Diener received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: AbbVie, Lundbeck, Teva and WebMD. The German Research Council (DFG) supports headache research by HCD. HCD serves on the editorial boards of *Cephalalgia*, *Lancet Neurology* and *Drugs*.

Faraidoon Haghdooost declares no conflict of interest.

Mi Ji Lee has received personal fees as speaker or advisor from Abbvie, Eli Lilly, Lundbeck, Pfizer, Teva, Organon, CKD, SK Chemical, YuYu and NuEyne; research support

from Abbvie, Pfizer, Eli Lilly, Pfizer, Lundbeck, Novartis, Teva, Otsuka, BioHaven, Ildong, Yuhan, NuEyne, Teva and YuYu; as well as research grants from National Research Foundation of Korea (NRF), Medical Device Development Fund grant funded by the Korea government, Korean Headache Society and Seoul National University. She is an associate editor for *Cephalalgia* and *Headache and Pain Reports*.

Teshamae S. Monteith has the following disclosures over the past three years: clinical trial site principal investigator for studies sponsored by Eli Lilly and AbbVie (all paid to the institution); participation in an advisory board/consultancy for AbbVie, Teva, Linpharma, e-Neura, Novartis, Merz, Lundbeck and Pfizer; Educational grant from Amgen and AbbVie; personal fees from Medscape, Massachusetts Medical Society, American Headache Society, American Academy of Neurology, Neurodiem, Academic CME, AbbVie and Novartis; and unpaid co-author for research funded by AbbVie, Pfizer/Biohaven and Theranica. She is an associate editor for *Cephalalgia* and *Continuum Audio*, deputy editor for *Neurology Minute*, and is on the editorial board for *Neurology*, *American Migraine Foundation* and *Brain and Life Magazine*. TSM has provided unpaid service on the board of directors for the International Headache Society (2021–2023) and is currently on the executive board for the Florida Society of Neurology.

Bronwyn Jenkins has received personal fees as speaker, advisor or to attend a conference from Allergan-Abbvie, Care Pharmacy, Eli Lilly, Lundbeck, Novartis, Pfizer and Teva. She is immediate past president of the Australian and New Zealand Headache Society, an associate editor of *Cephalalgia* and is on the subcommittees for education and ethics of the International Headache Society.

Mario F. P. Peres has received honoraria as a consultant and speaker from Ache, Allergan-AbbVie, Eli-Lilly, Eurofarma, Libbs, Lundbeck, Novartis, Pfizer, Sanofi and Teva. He is President-Elect of the International Headache Society.

Patricia Pozo-Rosich, within the prior 36 months, has received honoraria as a consultant and speaker from AbbVie, Dr Reddy's, Eli Lilly, Lundbeck, Medscape, Novartis, Organon, Pfizer and Teva Pharmaceuticals. Her research group has received research grants from AbbVie, AGAUR, EraNet Neuron, FEDER RIS3CAT, Instituto Investigación Carlos III, MICINN, Novartis and Teva Pharmaceuticals, and has received funding for clinical trials from AbbVie, Amgen, Biohaven, Eli Lilly, Lundbeck, Novartis, Pfizer and Teva Pharmaceuticals. She is the Honorary Secretary of the International Headache Society, is on the editorial board of *Revista de Neurologia*, is an associate editor for *Cephalalgia*, *Headache*, *Neurologia* and *Frontiers of Neurology*, and is an advisor of the Scientific Committee of the Editorial Board of *The Journal of Headache and Pain*. She is a member of the Clinical Trials Guidelines Committee and Scientific Committee of the International Headache Society. She has edited the Guidelines for the Diagnosis and Treatment of Headache of the Spanish Neurological Society. She is the founder of www.midolordecabeza.org.

Raffaele Ornello reports personal fees and non-financial support from AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer and Teva. He has received research funding from the Italian Ministry of Health. He is Editorial Board Member for *The*

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Francesca Puledra has received speaker honoraria from TEVA and Abbvie and serves on the editorial boards of *Cephalalgia* and *The Journal of Headache and Pain*.

Fumihiko Sakai has received honoraria as a consultant and speaker from AbbVie, Eli Lilly, Otsuka, Amgen and Daiichi-Sankyo Pharmaceuticals.

Todd Schwedt, within the prior 24 months, has received consulting fees from AbbVie, Allergna, Amgen, Linpharma, Lundbeck, Salvia BioElectronics and Scilex, as well as royalties from UpToDate. He holds/held stock options in Aural Analytics and Nocira. He has received research funding from the American Heart Association, Flinn Foundation, Henry Jackson Foundation, National Headache Foundation, National Institutes of Health, Patient Centered Outcomes Research Institute, Pfizer, Spark Neuro and United States Department of Defense.

Gisela Terwindt reports consultancy or industry support from Novartis, Lilly and Teva, Allergan/Abbvie, Lundbeck, Pfizer and Interactive Studios, as well as independent support from the European Community, Dutch Heart Foundation, Dutch Research Council, Dutch Brain Foundation and Dioraphte.

Gloria Vaghi has received personal fees for participating in speaking at scientific events from Lundbeck.

Shuu-Jiun Wang has served on the advisory boards of Taiwan Pfizer, AbbVie and Hava-Biopharma; has received honoraria as a moderator from AbbVie, Pfizer and Biogen; and has been the principal investigator in clinical trials sponsored by AbbVie, Novartis, Lundbeck and Pfizer. He has received research grants from the National Council of Technology and Science of Taiwan, Brain Research Center, National Yang Ming Chiao Tung University from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan, Taipei Veterans General Hospital, and Taiwan branches of Eli Lilly and Novartis.

Fayyaz Ahmed received honoraria for being on the advisory board of Abbvie Novartis Lundbeck Eli Lilly Teva organon Dr Reddy and Pfizer. Recipient of service improvement grant from Pfizer.

Cristina Tassorelli received personal fees for participating in advisory boards or for lecturing at sponsored symposia for AbbVie, Dompé, Eli Lilly, Ipsen, Lundbeck, Medscape, Pfizer and Teva. She is principal investigator or collaborator in clinical trials sponsored by AbbVie, Eli Lilly, Ipsen, Lundbeck, Pfizer and Teva. She has received research grants from the European Commission, the Italian Ministry of Health, the Italian Ministry of University, the Migraine Research Foundation and the Italian Multiple Sclerosis Foundation.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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Public health relevance

- Innovations in preventive treatments for migraine, such as treatments targeting the calcitonin gene-related peptide (CGRP) pathway and onabotulinumtoxinA, have demonstrated substantial efficacy and safety in reducing migraine frequency and severity, encouraging clinicians to set ambitious goals for migraine prevention.
- This position statement by the International Headache Society (IHS) calls for a paradigm shift in migraine prevention by proposing the following treatment outcomes: (1) Migraine Freedom (complete elimination of migraine or moderate-to-severe headache days); (2) Optimal Control (less than four days of moderate-to-severe headaches per month); (3) Modest Control (four to six days per month); and (4) Insufficient Control (more than six days per month).
- These metrics focus on addressing absolute migraine frequency instead of proportional decrease in headache days compared to baseline, aiming to capture the real burden of migraine.
- While recognizing that current outcomes and thresholds for drug reimbursement remain essential to ensure equitable access, the IHS aims at setting aspirational goals to maximize patient outcomes and societal benefits.

References

1. Peres MFP, Sacco S, Pozo-Rosich P, et al. Migraine is the most disabling neurological disease among children and adolescents, and second after stroke among adults: a call to action. *Cephalalgia* 2024; 44: 3331024241267309.
2. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
3. Freitag FG. The cycle of migraine: patients' quality of life during and between migraine attacks. *Clin Ther* 2007; 29: 939–949.
4. Leonardi M and Raggi A. A narrative review on the burden of migraine: when the burden is the impact on people's life. *J Headache Pain* 2019; 20: 41.
5. 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: 301–315.
6. Peles I, Sharvit S, Zlotnik Y, et al. Migraine and work - beyond absenteeism: migraine severity and occupational burnout - A cohort study. *Cephalalgia* 2024; 44: 3331024241289930.
7. Brandes JL. The migraine cycle: patient burden of migraine during and between migraine attacks. *Headache J Head Face Pain* 2008; 48: 430–441.
8. Bigal ME, Rapoport AM, Lipton RB, et al. Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. *Headache J Head Face Pain* 2003; 43: 336–342.
9. Guitera V, Muñoz P, Castillo J, et al. Quality of life in chronic daily headache. *Neurology* 2002; 58: 1062–1065.
10. Pozo-Rosich P, Dolezil D, Paemeleire K, et al. Early use of erenumab vs nonspecific oral migraine preventives. *JAMA Neurol* 2024; 81: 461–470.
11. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia* 2022; 42: 108–118.
12. Lampl C, MaassenVanDenBrink A, Deligianni CI, et al. The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis. *J Headache Pain* 2023; 24: 56.
13. Haghdoost F, Puledda F, Garcia-Azorin D, et al. Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: a systematic review and network meta-analysis of phase 3 randomised controlled trials. *Cephalalgia* 2023; 43: 3331024231159366.
14. Charles A and Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. *Lancet* 2019; 394: 1765–1774.
15. Ornello R, Baraldi C, Ahmed F, et al. Excellent response to OnabotulinumtoxinA: different definitions, different predictors. *Int J Environ Res Public Health* 2022; 19: 10975.
16. Wang YF, Yang FC, Chen LA, et al. Comparative effectiveness and tolerability of calcitonin gene-related peptide (CGRP) monoclonal antibodies and onabotulinumtoxinA in chronic migraine: a multicenter, real-world study in Taiwan. *Eur J Neurol* 2024; 31: e16372.
17. Kanner AM and Bicchi MM. Antiseizure medications for adults with epilepsy. *JAMA* 2022; 327: 1269–1281.
18. Lu G, Beadnall HN, Barton J, et al. The evolution of “No evidence of disease activity” in multiple sclerosis. *Mult Scler Relat Disord* 2018; 20: 231–238.
19. Geldsetzer P, Manne-Goehler J, Marcus ME, et al. The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet* 2019; 394: 652–662.
20. Jacobsen LM, Sherr JL, Considine E, et al. Utility and precision evidence of technology in the treatment of type 1 diabetes: a systematic review. *Commun Med* 2023; 3: 132.
21. Namiot ED, Smirnovová D, Sokolov AV, et al. Depression clinical trials worldwide: a systematic analysis of the ICTRP and comparison with ClinicalTrials.gov. *Transl Psychiatry* 2024; 14: 315.
22. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay

- couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multi-centre, prospective, observational study. *Lancet* 2019; 393: 2428–2438.
23. Burstein R, Noseda R and Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci* 2015; 35: 6619–6629.
 24. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. *Nat Rev Neurol* 2021; 17: 501–514.
 25. Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition): on behalf of the European headache federation and lifting the burden: the global campaign against headache. *J Headache Pain* 2019; 20: 57.
 26. Puledda F, Sacco S, Diener HC, et al. International headache society global practice recommendations for preventive pharmacological treatment of migraine. *Cephalalgia* 2024; 44: 3331024241269735.
 27. Stewart WF, Lipton RB, Dowson AJ, et al. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache-related disability. *Neurology* 2001; 56: S20–S28.
 28. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003; 12: 963–974.
 29. Gallardo VJ, Alpuente A and Pozo-Rosich P. Association of a cyclical migraine phenotype with disease progression: a 1-year time series analysis. *Neurology* 2022; 99: e1326–e1e34.
 30. Lipton RB, Kolodner K, Bigal ME, et al. Validity and reliability of the migraine-treatment optimization questionnaire. *Cephalalgia* 2009; 29: 751–759.
 31. Ornello R, Ahmed F, Negro A, et al. Early management of OnabotulinumtoxinA treatment in chronic migraine: insights from a real-life European multicenter study. *Pain Ther* 2021; 10: 637–650.
 32. Sacco S, Russo A, Geppetti P, et al. What is changing in chronic migraine treatment? An algorithm for onabotulinumtoxinA treatment by the Italian chronic migraine group. *Expert Rev Neurother* 2020; 20: 1275–1286.
 33. Sacco S, Amin FM, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *J Headache Pain* 2022; 23: 67.
 34. Pozo-Rosich P, Ailani J, Ashina M, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023; 402: 775–785.
 35. Tassorelli C, Nagy K, Pozo-Rosich P, et al. Safety and efficacy of atogepant for the preventive treatment of episodic migraine in adults for whom conventional oral preventive treatments have failed (ELEVATE): a randomised, placebo-controlled, phase 3b trial. *Lancet Neurol* 2024; 23: 382–392.
 36. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the international headache society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. *Cephalalgia* 2020; 40: 1026–1044.
 37. 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: 815–832.
 38. Ornello R, Andreou AP, De Matteis E, et al. Resistant and refractory migraine: clinical presentation, pathophysiology, and management. *EBioMedicine* 2024; 99: 104943.
 39. de Vries Lentsch S, Verhagen IE, van den Hoek TC, et al. Treatment with the monoclonal calcitonin gene-related peptide receptor antibody erenumab: a real-life study. *Eur J Neurol* 2021; 28: 4194–4203.
 40. Whitaker DJ, Dumkrieger GM, Hentz JG, et al. Physical impairment during and between migraine attacks: a daily diary study of patients with chronic migraine. *Cephalalgia* 2024; 44: 3331024241249747.
 41. Ornello R, Baraldi C, Guerzoni S, et al. Comparing the relative and absolute effect of erenumab: is a 50% response enough? Results from the ESTEEMen study. *J Headache Pain* 2022; 23: 38.
 42. Ford JH, Kurth T, Starling AJ, et al. Migraine headache day response rates and the implications to patient functioning: an evaluation of 3 randomized phase 3 clinical trials of galcanezumab in patients with migraine. *Headache J Head Face Pain* 2020; 60: 2304–2319.
 43. Belvis R, Irimia P, Pozo-Rosich P, et al. MAB-MIG: registry of the spanish neurological society of erenumab for migraine prevention. *J Headache Pain* 2021; 22: 74.
 44. Blumenfeld AM, Lipton RB, Silberstein S, et al. Multimodal migraine management and the pursuit of migraine freedom: a narrative review. *Neurol Ther* 2023; 12: 1533–1551.
 45. van der Arend BWH, Verhagen IE, van Leeuwen M, et al. Defining migraine days, based on longitudinal E-diary data. *Cephalalgia* 2023; 43: 3331024231166625.
 46. Lipton RB, Fanning KM, Serrano D, et al. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology* 2015; 84: 688–695.
 47. Messina R, Huessler EM, Puledda F, et al. Safety and tolerability of monoclonal antibodies targeting the CGRP pathway and gepants in migraine prevention: a systematic review and network meta-analysis. *Cephalalgia* 2023; 43: 3331024231152169.
 48. Steiner TJ. Headache in the world: public health and research priorities. *Expert Rev Pharmacoecon Outcomes Res* 2013; 13: 51–57.
 49. Puledda F, de Boer I, Messina R, et al. Worldwide availability of medications for migraine and tension-type headache: a survey of the international headache society. *Cephalalgia* 2024; 44: 3331024241297688.
 50. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68: 343–349.