Chronic migraine—classification, characteristics and treatment

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Abstract | According to the revised 2nd Edition of the International Classification of Headache Disorders, primary headaches can be categorized as chronic or episodic; chronic migraine is defined as headaches in the absence of medication overuse, occurring on ≥15 days per month for ≥3 months, of which headaches on ≥8 days must fulfill the criteria for migraine without aura. Prevalence and incidence data for chronic migraine are still uncertain, owing to the heterogeneous definitions used to identify the condition in population-based studies over the past two decades. Chronic migraine is severely disabling and difficult to manage, as affected patients experience substantially more-frequent headaches, comorbid pain and affective disorders, and fewer pain-free intervals, than do those with episodic migraine. Data on the treatment of chronic migraine are scarce because most migraine-prevention trials excluded patients who had headaches for ≥15 days per month. Despite this lack of reliable data, a wealth of expert opinion and a few evidence-based treatment options are available for managing chronic migraine. Trial data are available for topiramate and botulinum toxin type A, and expert opinion suggests that conventional preventive therapy for episodic migraine may also be useful. This Review discusses the evolution of our understanding of chronic migraine, including its epidemiology, pathophysiology, clinical characteristics and treatment options.

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Introduction

Chronic migraine is a disabling illness that has a substantial effect on the patient's ability to perform routine daily activities and on their productivity in the workplace.[1–3] The burden of chronic migraine, (and its precursor chronic daily headache) has been evaluated using both quality of life measures[1,4–7] and disability questionnaires.[1,5,8,9] These studies indicate that chronic migraine has a considerable adverse effect on health-related quality of life and daily functioning, and exacts a substantially higher economic toll on both patients and health-care systems than does episodic migraine.[10,11]

Neurologists who identified the needs of patients at the severe end of the migraine spectrum almost 30 years ago[12,13] were only rediscovering conclusions arrived at more than a century ago.[14] Terms used in the diagnosis of this group of patients included chronic mixed headache, chronic daily headache[15] and transformed migraine.[16] Headache disorders were systematically classified and defined for the first time in 1988 in the 1st Edition of the International Classification of Headache Disorders (ICHD-1) by the Headache Classification Committee of the International Headache Society (IHS).[17] This framework enabled the implementation of meaningful and reliable epidemiological studies, which demonstrated a lifetime prevalence of 15–20% for migraine and >50% for tension-type headache.[18,19] The 2nd Edition of the International Classification of Headache Disorders (ICHD-2), which was published in a revised form (ICHD-2R) by the IHS in 2006, defines chronic migraine as headaches on ≥15 days per month for ≥3 months. Headaches on ≥8 days must fulfill the criteria for migraine without aura, which can be successfully treated with acute-care medications such as ergots or triptans (Box 1).[20] These criteria have only been in use for the past 6 years and, as such, this group of patients with severe migraine is still poorly recognized and undertreated by clinicians, as well as insufficiently studied.

This Review describes the evolution in nomenclature for chronic migraine and presents the literature on the epidemiology, pathophysiology and treatment of this condition. Since the ICHD-2R[20] definition has only been available for a short period of time, this Review will also draw on the literature regarding transformed migraine (Box 2) and/or chronic daily headache, because validation studies have identified these disease entities as relating to almost the same groups of patients as would now be diagnosed as having chronic migraine.[21]

Changing nomenclature and definitions

The term chronic is used to refer to a condition that has persisted for a long time, but can also imply a severe condition that is difficult to treat. In migraine and tension-type headache, the use of the term chronic incorporates all these elements. Before publication of the

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Key points

- Chronic migraine is defined as headache on ≥15 days per month for ≥3 months; headaches on ≥8 days per month must fulfill criteria for migraine without aura
- Treatment requires a multimodal and multidisciplinary approach, including education, behavioral therapy, regular exercise and preventive drug therapy
- Topiramate and botulinum toxin type A have shown modest but significant efficacy in placebo-controlled trials; other preventive drugs have not been adequately studied for use in chronic migraine
- Chronic migraine can occur with or without medication overuse; patients with medication overuse should receive advice and support on discontinuation, as well as multidisciplinary treatment for chronic migraine
- The full therapeutic armamentarium for chronic migraine is best offered in headache referral centers

Box 1 | Current chronic migraine criteria

ICHD-2 criteria (2004)[26]

1.5 Complications of migraine

1.5.1 Chronic migraine

Description:

Migraine headache occurring on ≥15 days per month for >3 months in the absence of medication overuse

Diagnostic criteria:

A. Headache fulfilling criteria C and D for 1.1 Migraine without aura on ≥15 days per month for >3 months

B. Not attributed to another disorder*

Revised International Headache Society criteria for chronic migraine, ICHD-2R (2006)[20]

Appendix 1.5.1 Chronic migraine

A. Headache (tension-type and/or migraine) on ≥15 days per month for ≥3 months*

B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 Migraine without aura

C. On ≥8 days per month for ≥3 months headache has fulfilled C1 and/or C2 below (that is, has fulfilled criteria for pain and associated symptoms of migraine without aura):

1. Has at least two of a–d:
   (a) Unilateral location
   (b) Pulsating quality
   (c) Moderate or severe pain intensity
   (d) Aggravation by or causing avoidance of routine physical activity (for example, walking or climbing stairs) and at least one of i or ii:
   (i) Nausea and/or vomiting
   (ii) Photophobia and phonophobia
2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above

D. No medication overuse and not attributed to another causative disorder*

*Additional notes relating to these criteria can be found in the original publications.

Abbreviation: ICHD, International Classification of Headache Disorders. ICHD-2 criteria from Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd Edition. *Cephalagia* **24** (Suppl. 1), 24–136 © 2004 by International Headache Society. Reprinted by permission of SAGE. Reproduced with permission of International Headache Society. ICHD-2R criteria from Olesen, J. *et al. Cephalagia* **26**(6), 742–746 © 2006 Blackwell Publishing Ltd. Reprinted by permission of SAGE.

IHS classification in 1988, some countries were using the term chronic mixed headache for patients at the severe end of the migraine spectrum.[22] Neurologists also recognized that some patients who start with episodic migraine attacks can gradually get increasingly frequent headaches, which then to some extent lose their migraine characteristics. This presentation was called transformed migraine; however, the diagnosis could not be applied universally as only a small subgroup of patients showed this course.

According to the 1988 IHS classification committee, the problem caused by earlier nomenclature, in which these headache subtypes were grouped together under the term chronic mixed headache,[23] could be solved by providing a separate diagnosis for each recognized subtype of headache.[17] With the establishment of the ICHD-1, a patient at the severe end of the migraine spectrum could receive a diagnosis of migraine with or without aura, chronic tension-type headache or headache attributed to medication overuse. However, the system was criticized because distinguishing between severe migraine and severe tension-type headache remained difficult, as both groups of patients tend to have daily headaches, sometimes with migraine characteristics and sometimes with tension-type headache characteristics. In addition, patients at the severe end of the migraine spectrum often exhibit high use or overuse of acute medications.

An extremely important requirement in the development of new drugs is to test candidate agents in patients with a definite diagnosis. For this reason, until the inclusion of chronic migraine in the ICHD-2R in 2006, all drug trials for migraine focused on patients with fewer than six to eight episodes of migraine per month, leaving the severe end of the migraine spectrum unstudied. In 1997, Silberstein and Lipton published a paper that redefined the term chronic daily headache.[24] Although this paper made it clear that this term was not actually a diagnosis, but rather a collective term for severe chronic headaches (which included the severe end of the migraine spectrum), the unintended consequence was that chronic daily headache was used as a diagnosis in many patients.[25]

In 2004, ICHD-2 was published and the diagnostic category chronic migraine was introduced, for which unambiguous diagnostic criteria were provided (Box 1).[26] However, these criteria turned out to be more restrictive than anticipated, which resulted in substantial confusion. Multiple diagnostic terms and criteria were used variably in different countries and clinical settings. Realizing that an internationally accepted term and set of diagnostic criteria were needed for patients at the severe end of the migraine spectrum, the IHS classification committee reassembled and a consensus was reached that the diagnostic term chronic migraine should replace the problematic terms chronic mixed headache, transformed migraine and chronic daily headache. New, more-inclusive, but still explicit, diagnostic criteria for chronic migraine were also agreed on and included in the appendix of the ICHD-2R, published in 2006 (Box 1).[20] Subsequently, the criteria were validated in Europe and the USA,[27–29] and will be incorporated into the 3rd Edition of the ICHD (ICHD-3), which is being prepared. Although the criterion that a patient must have headaches on ≥15 days per month to fulfill the definition of chronic migraine is certainly arbitrary, the general

principle that patients with a high number of headache days have increased disability seems intuitive, and this group of patients should, therefore, be singled out for aggressive therapy.

According to the ICHD-2R, the diagnosis of chronic migraine should not be made in a patient who demonstrates medication overuse—the most common reversible cause of headaches resembling chronic migraine. After detoxification, at least half of such patients no longer show features of chronic migraine, but instead revert to episodic migraine; the remainder, in whom medication overuse has been ruled out as the cause, can be diagnosed with chronic migraine.

Epidemiology

The gradual evolution of the definition of chronic migraine over time has resulted in varying conclusions being drawn in studies of its prevalence. Two reviews that defined chronic headache as being present on ≥15 days per month estimated its global prevalence to be 3–4%.[18,19] A systematic review from 2010 focused on 12 worldwide, population-based incidence and prevalence studies that determined rates of chronic migraine using either the Silberstein–Lipton criteria for transformed migraine (Box 2),[24,30,31] or the current ICHD-2R criteria for chronic migraine.[32] The prevalence of chronic migraine in these studies ranged from 0.0% to 5.1% (initial estimates for these rates were typically in the range of 1.4–2.2%), and varied by WHO-defined geographical regions as well as sex.[32] These estimates are imperfect owing to the heterogeneity of definitions applied across studies, and the lack of data from certain regions. Nevertheless, the target population is equally well-defined by both the Silberstein–Lipton transformed migraine criteria and the ICHD-2R term chronic migraine, so the data presented are likely to give a reasonably accurate global perspective. The prevalence of chronic migraine in this systematic review also suggests that this condition represents approximately half of all cases of chronic primary headache. In further population-based studies—HUNT 2 and HUNT 3, published in 2011—the age-adjusted prevalence of chronic migraine was consistently 0.5% throughout an 11-year follow-up period.[33]

A cross-sectional study and a cohort analysis were conducted to identify risk factors that predict onset or remission of chronic daily headache in a US adult population.[34] This study revealed an annual incidence rate of 3% for chronic daily headache, and identified several demographic factors associated with a high prevalence of this condition, including female sex, white European heritage, obesity, physician-diagnosed diabetes mellitus or arthritis, low educational level, and divorce. A high baseline frequency of headache and acute medication overuse were also significant risk factors for the progression from a diagnosis of episodic migraine to a chronic headache disorder. The critical headache frequency was defined as ≥10 days per month; patients who experienced headaches at this frequency were at significant risk of developing chronic daily headache.

Box 2 | Previous chronic migraine criteria

Proposed 1995 criteria for transformed migraine[31]

A. Daily or almost daily (>15 days per month) head pain for >1 month

B. Average headache duration of >4 h daily (if untreated)

C. At least one of the following:
   1. History of episodic migraine meeting any IHS criteria 1.1 to 1.6*
   2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months
   3. Current headache meets IHS criteria for migraine 1.1 to 1.6* other than duration

D. At least one of the following:
   1. There is no suggestion of one of the disorders listed in groups 5–11‡
   2. Such a disorder is suggested, but it is ruled out by appropriate investigations
   3. Such a disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder

*IHS criteria 1.1–1.6 from the ICHD-1.‡Groups 5–11 from the ICHD-1. Abbreviations: ICHD, International Classification of Headache Disorders; IHS, International Headache Society. Permission obtained from Wolters Kluwer Health © Silberstein, S. D. *et al.* Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology* **47**(4), 871–875 (1996).

Another population-based US study also confirmed overuse of acute headache medications as an important risk factor for developing chronic migraine.[35,36] Opioid and barbiturate intakes, in particular, are correlated with a transition from episodic to chronic migraine owing to medication overuse.[37,38]

Although data on the natural history of patients with chronic migraine is not available (owing to the 10–15-year timescale that would be required for a population-based study of this condition), information from the American Migraine Prevalence and Prevention study on the clinical evolution of this condition was published in 2011.[39] Longitudinal data over 3 years were analyzed to determine rates of chronic migraine remission, and to assess predictors of remission using logistic regression models. 383 individuals were identified who had chronic migraine in 2005 and were followed up in 2006 and 2007. Among individuals with chronic migraine at baseline, 52.7% continued to report this condition for at least 1 year of follow-up. The study also found that 34% had persistent chronic migraine (defined as chronic migraine across all 3 years), while only 26% had remission of chronic migraine (defined as fewer than 10 headache days per month).[39] Over 2 years, the individuals with persistent chronic migraine demonstrated increased disability, while those with remission showed decreased disability. Predictors of remission included a lower baseline headache frequency (15–19 headache days per month versus 25–31 headache days per month; OR 0.29, 95% CI 0.11–0.75) and the absence of allodynia (OR 0.45, 95% CI 0.23–0.89).

Pathophysiology

The pathophysiology of chronic migraine is unclear, but is likely to be multifactorial and to involve more than

one level of the CNS. The brainstem contains descending circuitry that can modulate nociceptive processing in the trigeminocervical complex.[40] Activity-independent sensitization of central trigeminothalamic pathways is considered to be a possible cause of the development of chronic migraine.[41] Such sensitization might occur during repeated migraine attacks through impaired descending inhibition and/or enhanced descending facilitation of nociception.[42] Moreover, some experimental data suggest that the ventral posteromedial thalamic nucleus, which receives direct projections from trigeminovascular nociceptive neurons,[43] can be modulated by standard migraine-preventive drugs, such as propranolol[44] and sodium valproate.[45]

Several functional imaging studies have demonstrated abnormal brainstem activation in cases of both episodic and chronic migraine,[46–49] suggesting that dysfunction of descending inhibitory pathways might facilitate migraine attacks. The underlying basis of this dysfunction is not clear, but repeated episodes of hypoxia during migraine attacks, leading to abnormal deposition of nonheme iron and iron-catalyzed free-radical injury, have been proposed.[50] Functional imaging studies have also demonstrated interictal hypofunction of lateral descending pain modulatory circuits in patients with migraine.[51] Specifically, these individuals had decreased activation of the nucleus cuneiformis, which might account for either descending facilitation of nociception or impairment of descending inhibitory pathways in migraine. The nucleus cuneiformis is responsible for sensory modulation in animals and humans; it sends dense neural projections to the rostral ventral medulla, thereby modulating nociceptive transmission neurons in the spinal cord and medullary dorsal horn.[51,52] The hyperexcitability of nociceptive circuitry downstream of the nucleus cuneiformis might contribute to central sensitization, and is speculated to lead to progressive changes in the spinal trigeminal nucleus (localized allodynia) and/or the thalamus and spinal cord (generalized allodynia).[51] Enhanced cortical excitability, exceeding that in patients with episodic migraine or in migraine-free controls, has also been demonstrated in individuals with chronic migraine.[53,54] Whether this finding is due to intrinsically increased excitability or to impaired intracortical inhibitory mechanisms is unclear.

As previously discussed, overuse of acute pain medications has a major role in the development of headaches resembling chronic migraine.[28,36,55,56] Experiments in animal models have revealed persistent pronociceptive adaptations following exposure to opioids and triptans, resulting in enhanced sensitivity to stimuli that trigger migraine in humans.[57,58] These findings could provide insight into the adaptive changes that occur in patients who have chronic migraine associated with medication overuse, and thus further elucidate the pathophysiology of chronic migraine.

Treatment

Until 2007, evidence on the efficacy and safety of preventive medications used in the treatment of chronic migraine had been limited to case studies and open-label trials. The paucity of randomized controlled trials in this field can be attributed to the lack of consistent diagnostic criteria and clinical trial guidelines for chronic migraine, as well as an unfounded view that this condition is highly refractory to treatment. Furthermore, there is a notable dearth of new chemical entities progressing to randomized controlled trials for the prevention and/or treatment of migraine of any sort, which necessarily limits the pool of studies in chronic migraine. However, some randomized controlled trials for medications and devices have now been conducted in the chronic migraine population, and are discussed below. The evidence of efficacy for therapeutic regimens used to treat chronic migraine is still of variable quality, and while it is important to consider the strength of evidence presented, some weight must also be given to clinical experience with the use of migraine preventive agents.

Correct diagnosis is essential to devise an appropriate treatment strategy. Patients who present with chronic migraine and acute medication overuse need advice and support to enable them to discontinue the drug. Once chronic migraine has been diagnosed, management of the condition requires an interdisciplinary approach,[59] including identification and management of risk factors, establishment of limits on acute pain medications to minimize the effects of overuse, initiation of nonpharmacological treatment, and treatment of neuropsychiatric disorders (such as depression and anxiety) and other comorbid conditions (such as obesity) that might contribute to increased attack frequency. These therapeutic approaches are all based on clinical experience rather than the results of randomized, placebo-controlled trials.

The primary goals of preventive therapy in patients with chronic migraine are to reduce the frequency and severity of attacks, to reduce reliance on acute medications, and to improve the quality of life. In addition to education, behavioral therapy and exercise, migraine prevention by drug treatment has to be considered, as in patients with episodic migraine.[60–65] A treatment strategy that incorporates an effective prophylactic regimen should be initiated. An effective prophylactic agent reduces the need for acute medication use, yet only 33% of patients with chronic migraine are currently using preventive drugs.[35] However, given the degree of nociceptive bombardment of the nervous system, causing peripheral and central sensitization, and the ensuing tendency to overuse acute symptomatic relief medications, chronic migraine represents a therapeutic challenge for many clinicians.

Pharmacological treatment

Sodium valproate

The efficacy of sodium valproate in the treatment of chronic daily headache (that is, both chronic migraine and chronic tension-type headache) was assessed in a study of 70 patients.[66] The study showed that sodium valproate was superior to placebo for a number of outcome parameters, such as general and maximum pain levels, and pain frequency (Table 1). Larger randomized, placebo-controlled

Table 1 | Studies of treatment with sodium valproate and topiramate in patients with chronic migraine

Study	Study design	Population and treatment	Results
Sodium valproate			
Yurekli *et al.* (2008)[66]*	Prospective, double-blind, randomized, placebo-controlled trial	70 patients with chronic daily headache (29 with chronic migraine, 41 with chronic tension-type headache) Treatment (500 mg twice daily) or placebo for 3 months	All chronic daily headache patients: decreased maximum pain levels and pain frequency, no change in general pain levels Chronic migraine subgroup: significant improvement in general and maximum pain levels, and pain frequency
Topiramate			
Silvestrini *et al.* (2003)[67]	Double-blind, randomized, placebo-controlled, parallel-group trial	28 patients with chronic migraine and medication overuse 9-week, low-dose treatment phase (50 mg daily)	Baseline headache frequency: 20.8 days per month Mean 28-day headache frequency: topiramate 8.1±8.1 vs placebo 20.6±3.4 (P<0.0007)
Silberstein *et al.* (2007)[69]	Double-blind, randomized, placebo-controlled, parallel-group, multicenter trial	306 patients (intent-to-treat population) with chronic migraine‡ and without medication overuse 153 in treatment group and 153 given placebo, 16 weeks' treatment (100 mg daily; 4-week titration period, 12-week maintenance phase)	Significant reduction in mean number of migraine days per month (P=0.01): topiramate 6.4±5.8 days (baseline frequency 17.1 days) vs placebo 4.7±6.1 days (baseline frequency 17.0 days)
Diener *et al.* (2007)[68]	Double-blind, randomized, placebo-controlled, parallel-group, multicenter trial	59 patients (intent-to-treat population) with chronic migraine§ most of whom had medication overuse (namely, triptans) 32 in treatment group and 27 given placebo, 16 weeks' treatment (100 mg daily, range 50–200 mg daily)‖	Significant reduction from baseline in the mean number of migraine days per month (P=0.02): topiramate 3.5±6.3 days (baseline frequency 15.5±4.6) vs placebo 0.2±4.7 days (baseline frequency 16.4±4.4)

*Pain levels were assessed using a visual analog scale. ‡Defined as ≥15 headache days per 28-day period, of which at least 50% were migraine headaches. §Defined as ≥15 monthly migraine days for ≥3 months before trial entry, regardless of acute medication overuse. ‖Patients included if they had ≥12 migraine days during the 28-day baseline phase.

trials are required for further evaluation of chronic migraine treatment with sodium valproate.

Topiramate

The encouraging results from a small placebo-controlled trial[67] of topiramate in patients with chronic migraine prompted further investigation into the efficacy of this drug in large, rigorously controlled studies (Table 1). Two separate studies in Europe and the USA showed that topiramate at a dose of 100 mg daily was effective as a preventive therapy for chronic migraine.[68,69] The key difference between the two studies was that patients were allowed to take acute rescue medication as usual in the European trial,[68] but not in the US trial.[69] Remarkably, the benefits of topiramate extended to the subgroup of patients who were overusing acute medications, as demonstrated by the significant reductions in mean monthly migraine days in this group compared with the placebo group (Table 1).[68] Topiramate use was also associated with a decreased number of days per month that patients were taking acute medication (reductions of 3 days per month in the topiramate group versus 0.7 days per month in the placebo group); however, this difference was not statistically significant.[68] An interesting finding in the European study was the lack of a placebo response, perhaps attributable to the fact that patients continued to overuse acute headache medications throughout the study.[68]

Adverse effects observed in the European study were mild to moderate in severity, and consistent with those noted in previous clinical trials of topiramate: paresthesia (53% in the treatment group versus 7% in the placebo group) and nausea (9% in the treatment group versus 0% in the placebo group) were both reported.[68] In the US study, commonly reported adverse effects in the topiramate group included paresthesia, upper respiratory tract infection and fatigue.[69] No serious adverse effects were reported in the treatment or placebo groups of either study.[68,69] Both trials demonstrated that topiramate was effective and safe in populations of patients with chronic migraine, and efficacy seemed to be maintained regardless of the presence or absence of acute medication overuse.[70]

Botulinum toxin type A

Botulinum toxin type A has been reported to relieve the pain associated with a variety of conditions,[71–74] and this agent is currently approved for use as a prophylactic therapy in patients with chronic migraine in more than 40 countries, including the UK and the USA. Unlike its well-known ability to block signaling at the neuromuscular junction, the mechanism of action of botulinum toxin type A in migraine relief is not at all understood. This drug is thought to inhibit sensitization of peripheral trigeminal sensory fibers, which in turn modulates the activity of central trigeminal neurons and thus indirectly leads to inhibition of migraine headache.[75,76] None of the work done to support this contention has been conducted in patients with migraine, but instead has been carried out in established experimental models of trigeminovascular and peripheral nociception.[77]

A number of placebo-controlled trials in patients with episodic migraine or chronic daily headache failed to show efficacy of botulinum toxin type A.[78–83] *Post hoc* analyses, however, indicated that patients with frequent migraine headaches might benefit from this treatment.[84] Accordingly, the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT 1 and 2) multicenter randomized clinical trials were conducted to evaluate the efficacy and safety of botulinum toxin type A as a prophylactic treatment for adults with chronic migraine. A total

Table 2 | Results from phase III trials of botulinum toxin type A*

Study details	End points	Results
PREEMPT 1[85] (56 sites in the USA)	Primary: change in frequency of headache episodes at week 24 compared with baseline Secondary: change in frequency of headache days at week 24 compared with baseline	No significant improvement in frequency of headache episodes Significant reduction in frequency of headache days ($P=0.006$)
PREEMPT 2[86] (50 sites in the USA and 16 sites in Europe)	Primary: change in frequency of headache days at week 24 compared with baseline Secondary: change in frequency of headache episodes at week 24 compared with baseline	Significant reduction in frequency of headache days ($P<0.001$) Significant improvement in frequency of headache episodes ($P=0.003$)
Pooled analysis of results from PREEMPT 1 and 2[87]	Not applicable	Significant reduction in headache days after 6 months in treatment groups vs placebo groups ($P<0.001$), therapeutic gain of 11%: treatment, 8.4 days (baseline frequency 19.9 days) vs placebo 6.6 days (baseline frequency 19.8 days) Significant improvements in treated patients vs placebo groups in other efficacy variables: frequency of migraine episodes ($P=0.004$), migraine days ($P<0.001$), severe headache days ($P<0.001$); cumulative hours of headache per day ($P<0.001$); proportion of patients with severe disability ($P<0.001$) Intake of medications to treat acute migraine attacks was not different between placebo and treatment groups (however, in *post hoc* analysis, intake of triptans was significantly reduced in the treatment group)

*Similar study designs were used in both trials: 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase. Abbreviation: PREEMPT, Phase III Research Evaluating Migraine Prophylaxis Therapy.

of 1,384 patients with chronic migraine were enrolled across both trials (Table 2).[85–87] Patients were stratified into groups according to whether they were overusing acute headache medications at baseline, and were randomly assigned in a 1:1 ratio to either botulinum toxin type A or placebo injections. A total dose of botulinum toxin type A of 155 U was administered to 31 sites in seven head and neck muscles.[85–87] The studies incorporated a double-blind phase and an open-label phase, although the efficacy of blinding was not evaluated. The PREEMPT study results demonstrated significant improvements at the population level in multiple measures of headache symptoms, as well as improvements in patients' functioning, vitality, psychological distress, and overall health-related quality of life, in response to treatment with botulinum toxin type A.

Botulinum toxin type A versus topiramate

Although the indirect comparison of drugs across trials has many limitations, comparing the effect size of different therapies is of importance to both the clinician and the patient. We have compared the findings from the largest available randomized, placebo-controlled trial evaluating the efficacy and safety of topiramate in the treatment of chronic migraine[69] with the pooled results from the two PREEMPT studies evaluating botulinum toxin type A.[87] These studies were not directly comparable, and the end points differed between the studies; hence, some adjustment is necessary to compare their results. The primary end point in the topiramate study—the change from baseline in the mean monthly number of migraine and/or migrainous headache days (evaluated at week 16)—is similar to a secondary end point used in an analysis of the pooled PREEMPT data—the change from baseline in frequency of migraine or probable migraine days (evaluated at week 24). These end points can, therefore, be used for the purpose of comparing the two treatments: a reduction of 8.8 migraine or probable migraine days with botulinum toxin type A is compared with a reduction of 6.4 migraine or migrainous headache days after treatment with topiramate. Both botulinum toxin type A and topiramate studies demonstrated a significant between-group difference in the number of headache days, favoring treatment over placebo. The mean between-group differences (treatment minus placebo) in change from baseline of the number of headache days are comparable for botulinum toxin A and topiramate (2.3, $P<0.001$ versus 1.8, $P=0.010$, respectively) suggesting similar efficacy of both drugs.

For topiramate, the number of patients needed to treat (NNT) to achieve a significant reduction in the rate of migraine or probable migraine days was 12.5 versus an NNT of 8.0 for botulinum toxin type A. However, the topiramate dataset was much smaller than the pooled PREEMPT data, which might influence the results as the NNT is more reliable with large datasets.

Fewer treatment-related adverse effects occurred with botulinum toxin type A in the PREEMPT studies (29.4% treatment group versus 12.7% placebo) than in the topiramate study (65.0% treatment group versus 42.9% placebo). Likewise, fewer patients discontinued treatment owing to adverse effects in the PREEMPT studies (3.8% treatment group versus 1.2% placebo) than in the topiramate trial (10.9% treatment group versus 6.1% placebo). Topiramate is arguably a poor choice of comparison therapy owing to its frequent systemic adverse effects; however, other preventive treatments, such as β-blockers and tricyclic antidepressants, have not been sufficiently studied for use in patients with chronic migraine, and randomized controlled trials of these agents would be of value.

Most patients are referred to tertiary headache centers because they cannot achieve migraine prevention with β-blockers, flunarizine or amitriptyline. Preventative therapy with topiramate or botulinum toxin type A

should be offered to these patients. Owing to cost considerations, prevention should be initiated with topiramate, and botulinum toxin type A should be offered to patients in whom topiramate is ineffective, not tolerated, or contraindicated. Interestingly, studies involving patients with chronic migraine who have coexisting acute medication overuse suggest that these patients also benefit from either topiramate[68] or botulinum toxin type A (approximately 65% of patients in the PREEMPT studies overused acute medication).[85–87] At present, we are not aware of any randomized trials that have investigated whether topiramate or botulinum toxin type A is as effective as detoxification in patients with medication overuse, or whether some subgroups of individuals with chronic migraine might do better with one or other of these strategies.

Treatment with limited supporting evidence

Levetiracetam was studied in a multicenter, randomized, placebo-controlled, crossover study that included patients with either chronic migraine or chronic tension-type headache.[88] The primary end point was the highly desirable—but somewhat stringent—outcome of freedom from headache. Of 96 patients recruited to the study, 73 had chronic migraine. The study failed to meet its primary efficacy end point, although levetiracetam was associated with a nonsignificant 3.9% increase in the headache-free rate versus placebo. Nevertheless, some secondary end points were achieved, including a reduction in the number of headache days per month ($P = 0.0325$), reduced disability ($P = 0.0487$), and reduced pain severity ($P = 0.0162$).[88] The use of levetiracetam in patients with chronic migraine cannot currently be recommended on the basis of these data.

Nonpharmacological treatment

Occipital nerve stimulation

Two studies have evaluated the safety and efficacy of occipital nerve stimulation for the treatment of chronic migraine. In a multicenter, prospective, randomized, single-blind, sham-treatment-controlled feasibility study, published in 2011, 66 patients who met the ICHD-2 criteria for chronic migraine received an occipital nerve block, and those with a positive response to this test (a ≥50% reduction in migraine pain within 24 h of the injection of bupivacaine into each greater occipital nerve distribution) underwent simulator implantation and were randomly allocated to one of three treatment groups: adjustable stimulation (28 patients), preset stimulation (16 patients), or medical management (17 patients).[89] An ancillary group of five patients who did not respond to the nerve block test also underwent implantation and were managed with adjustable stimulation. Responder rates at 3 months (defined as a ≥50% reduction in migraine days per month, or a ≥3-point reduction in average pain intensity from baseline) for these treatment groups were 39% (adjustable stimulation), 6% (preset stimulation), 0% (medical management) and 40% (ancillary group on adjustable stimulation). Lead migration occurred in 12 of 51 patients (24%).

In the second study, which also defined chronic migraine according to the ICHD-2 criteria, 125 patients from 13 US centers participated in a prospective, randomized, blinded, 12-week feasibility study using a different stimulation system.[90] These patients were randomly allocated in a 1:1 ratio to either sham stimulation (10 μs pulses, 2 Hz, <1 mA; 1 s on-simulation and 90 min off-stimulation cycle) or active intermittent occipital nerve stimulation (250 μs pulses, 60 Hz, 0.0–12.7 mA) The primary end point was the decrease from baseline in the number of migraine days per month, which was evaluated 12 weeks after device implantation. This parameter did not differ significantly between the active-treatment and sham-treatment groups, which demonstrated reductions of 5.5 and 3.9 migraine days per month, respectively. Interestingly, when the two groups were stratified for medication overuse, the difference between treatment arms increased only in patients without overuse (but was still not statistically significant); reductions of 5.9 and 2.6 migraine days per month in the active-treatment and sham-treatment groups, respectively. The most frequent device-related adverse effects and complications included non-target-area sensory symptoms (18%), implant-site pain (17.3%), infection (15.1%), residual incision-site pain (7.9%), and lead migration (6.8%).

On the basis of the results from these two studies, occipital nerve stimulation could potentially be an effective treatment for patients with drug-refractory chronic migraine and, in fact, this treatment has already been approved in the USA. Two randomized, sham-controlled phase III studies were planned to begin in 2011.

Acupuncture and behavioral sleep modification

Our literature search yielded only three randomized controlled trials that investigated nonpharmacological treatment in patients with chronic daily headache or transformed migraine. All other such studies recruited patients with episodic migraine.[91] In a study of 74 patients with chronic daily headache who were randomly allocated to either medical management alone or medical management and acupuncture, only the combination therapy was associated with improved clinical outcome.[92]

A pilot trial investigated the efficacy of safflower (*Carthamus tinctorius*) seed extract.[93] Injections of either normal saline or safflower seed extract were administered into a series of acupuncture points in 40 patients with chronic daily headache. Compared with normal saline injections, safflower seed extract injections resulted in a significantly higher reduction in scores on the Headache Impact Test-6, which is used to assess headache-related quality of life.

In another study, 43 women with transformed migraine were randomly assigned to either behavioral sleep modification—consisting of scheduled bedtimes that allowed 8 h of time in bed; elimination of television, reading and listening to music while in bed; visualization techniques to shorten the time to sleep onset; moving consumption of food and liquids to >4 h and >2 h before bedtime, respectively; and eliminating

naps—or placebo.[94] The intervention was associated with a significant reduction in headache frequency. Owing to their small sample sizes, these studies are, at best, hypothesis-generating.

Conclusions

Chronic migraine is a disabling, poorly recognized and undertreated disorder. Only 20% of patients who fulfill the IHS criteria for chronic migraine are diagnosed with the condition,[10,35] highlighting the need for improved recognition. Full support and universal use of the ICHD-2R diagnostic criteria will help to identify patients with chronic migraine who would benefit from preventive treatment. With the very few existing randomized controlled trials of treatments for chronic migraine, a great need remains for further studies of existing drugs to be conducted, as well as for the development of new chemical agents and nonpharmacological therapies.

Review criteria

A MEDLINE search was conducted for articles published in 2008–2011 using the search terms "chronic migraine", "transformed migraine", "chronic daily headache" and "medication overuse headache". The personal literature collection of the authors was also searched for relevant publications. In addition, the authors reviewed the results of a MEDLINE search conducted by Imprint Publication Science for Allergan, which had been included in a document submitted to the FDA before approval of botulinum toxin type A in patients with chronic migraine. Allergan also provided copies of articles listed therein that could not be accessed by the authors' university library.

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Author contributions
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