

Review Articles

Epidemiology, Risk Factors, and Treatment of Chronic Migraine: A Focus on Topiramate

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The term chronic daily headache refers to a heterogeneous group of headache disorders characterized by a frequency of headaches on ≥ 15 days per month. Chronic migraine is a subtype of chronic daily headache. The prevalence of chronic migraine is $\sim 1\%$. Baseline attack frequency and acute medication overuse have been identified as potential risk factors for the progression of migraine from an episodic disorder to a chronic condition. There is an unmet patient need for effective and safe treatments for patients with chronic migraine, but data from rigorous controlled trials are limited. Previous studies have demonstrated that topiramate is an effective and safe preventive treatment for episodic migraine. In addition, pilot studies have suggested the utility of topiramate for the prevention of chronic migraine. Two randomized, double-blind, placebo-controlled, multicenter trials investigating the efficacy and safety of topiramate in the treatment of patients with chronic migraine have recently been completed. This review presents comparative data from these 2 clinical trials, which suggest that topiramate at a dose of 100 mg daily is effective and generally well tolerated in chronic migraine.

Key words: chronic migraine, topiramate

Abbreviations: AE adverse event, BMI body mass index, CDH chronic daily headache, CM chronic migraine, CM-R revised criteria, EM episodic migraine, ICHD International Classification of Headache Disorders, IHS International Headache Society, ITT intent-to-treat, OR odds ratio, 5-HT serotonin

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The primary objectives of this review are to highlight what is known about the risk factors contributing to the transformation of episodic to chronic migraine (CM) and to evaluate the efficacy and safety of topiramate, a migraine preventive medication, in the treatment of CM. In addition, this review will address the role of topiramate in the treatment of patients with episodic and CM with or without medication overuse.

The term chronic daily headache (CDH) refers to a heterogeneous group of headache disorders in which headaches occur on ≥ 15 days per month. Some patients with episodic migraine (EM) progress to have, while other patients de novo have, a high

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frequency of headache days (≥ 15 days per month) and frequent migraine attacks.¹⁻³ This condition has been termed CM and is a subset of CDH.^{4,5} It has been estimated that CM may affect 1.3% to 2% of the US population.⁶ CM has a substantial impact on patients' ability to perform routine daily activities and on productivity in the workplace.⁷⁻⁹

Definitions of CDH have been a subject of controversy.¹⁰ Currently, CDH is not defined by the International Headache Society (IHS). Silberstein et al proposed criteria for transformed migraine, a condition characterized as CDH with a link to migraine based on either current migraine features or a pattern of evolution from EM.¹¹ In its 2004 revision, the International Classification of Headache Disorders (ICHD) included operational diagnostic criteria for CM.¹² These criteria required the presence of migraine without aura on ≥ 15 days per month. Recently, these criteria were revised,⁴ since they failed to capture the majority of patients with frequent headache on the basis of migraine in clinical practice.¹³ The revised criteria (CM-R) require at least 15 headache days per month and that on at least 8 days, headaches either meet criteria for migraine without aura or respond to migraine-specific treatment. Field testing comparing the Silberstein-Lipton definition of transformed migraine with the CM-R definition showed that the revised criteria captured >90% of patients with frequent headache on the basis of migraine.¹⁴

In Scher et al's population-based study, 3% of subjects with episodic headache developed CDH over 1 year.¹⁵ In a clinic-based study that included individuals with low (0-4 days per month) intermediate (5-9 days per month), and critical-frequency migraine (10-14 days per month), 14% developed CDH over 1 year.¹⁶ Risk factors for transformation in both studies included high baseline frequency of episodic headache and acute medication overuse. Other modifiable risk factors for progression are reviewed in the next section. In the population-based study, remission occurred in some patients with CDH at baseline: 13% reported <52 headaches per year, 57% remitted to <180 headache days per year, and 44% continued to have ≥ 180 headaches per year.¹⁵ Remission was more likely in nonwhites, individuals with

higher levels of education, and those currently married. This study suggests that individuals with CDH represent a dynamic population characterized by individuals who may fluctuate between chronic and episodic headache patterns.

Ultimately, the effective management of CM involves gaining a more complete understanding of the risk factors that may be contributing to the development of this chronic disorder. Therapeutic regimens for the treatment of CM tailored to the needs of the individual patient have been suggested.¹⁷ Many factors need to be considered, including the level of evidence regarding therapeutic efficacy, potential side effects and contraindications, the presence or absence of coexisting or comorbid disease, and the patient's preferences regarding medications and other treatments.¹⁸⁻²⁰ An evidence-based approach to the treatment of CM, which incorporates empirical evidence into clinical practice and therapeutic treatment plans, has been advocated.²¹ Until recently, evidence regarding the efficacy and safety of migraine preventive medications for the treatment of CM has been mostly limited to case studies and open-label trials.

TRANSFORMATION OF EM TO CM: REVIEW OF RISK FACTORS

Identifying the known risk factors is an important priority as a possible way to prevent progression from occurring. Risk factors have been subdivided into nonmodifiable and modifiable categories.²²

Risk factors that may be associated with the development of CDH disorders and are not readily modifiable include female gender, age, low education/socioeconomic status, first-generation immigrant, and a history of head injury.²²⁻²⁵ In the above-mentioned population-based study, the prevalence of CDH decreased slightly with age and was more common in women and individuals of low socioeconomic status.¹⁵ Recent population-based studies in post-Soviet countries (ie, Georgia and Moldova) revealed a significantly higher prevalence of chronic headache than in Europe and the USA.^{26,27} The high prevalence of CDH in countries facing severe economic problems points to the importance of socioeconomic factors in the development of chronic headache. Similarly, high rates of CDH were observed in Florianopolis, Brazil.²⁸

Modifiable risk factors include stressful life events, sleep disturbances (ie, snoring/sleep apnea), obesity, and notably, baseline headache frequency and acute medication overuse.^{16,22,24,29} Scher et al found that overweight individuals (body mass index [BMI] 25-29) had a 3-fold higher risk of developing CDH, and those who were considered obese (BMI \geq 30) had a 5-fold higher risk for the development of CDH ($P < .05$).¹⁵ While it is believed that weight management may help to reduce the risk of transformation of episodic headache to CDH disorders, the evidence to support this is lacking. It has been suggested that a combination of cognitive-behavioral strategies, bio-feedback, and relaxation therapy to reduce stressful life events and improve sleep also may have an important role in helping to mitigate the progression of migraine to CDH;^{24,29} such approaches need systematic testing.

Attack frequency and acute medication overuse are also risk factors that contribute to the transformation of episodic to CM. In a clinic-based study, Katsarava et al found an association between high baseline headache frequency and the development of chronic headache in patients with EM who were observed for 1 year.¹⁶ Patients with a baseline headache frequency of 5-9 days per month had a substantially increased risk for progression to a chronic headache condition (odds ratio [OR] = 6.3, $P = .005$). This risk was further increased in patients with a "critical" headache frequency, defined as >10 days per month (OR = 20.1, $P = .001$). A 2003 population-based study followed individuals with episodic headache, including migraine, over the course of 1 year.¹⁵ In this study, the initial indication of an elevated risk of developing chronic headache was the occurrence of approximately 2-3 headache days per month at baseline, and the risk increased exponentially as the baseline headache frequency increased. These findings imply that reducing headache frequency might reduce the risk of developing CDH.

Acute medication overuse has also been suggested as an important risk factor leading to the development of CM.³⁰ Patients who overuse medications are 7 times more likely to develop CDH than those who do not,³¹ and between 30% and 50% of patients with CM in the general population overuse

acute headache medications.^{16,24} Medication overuse may lead to CM due to changes in pain modulatory systems, which include down-regulation of serotonin (5-HT) synthesis and/or receptor number and function,^{32,33} decreased pain thresholds,³⁴ and a facilitation of trigeminal pain processing.^{35,36} However, the hypothesis that acute medication overuse is a consequence rather than a potential cause or contributor to migraine progression has been suggested.^{15,37,38} For example, some subjects have reported that their increases in headache frequency clearly preceded acute medication overuse. The relative contribution of acute medication overuse to the development of CM remains an open debate.³⁸⁻⁴¹ Moreover, it has been suggested that medication overuse headache syndromes may be causally linked to migraine biology rather than be a separate entity.⁴²

The primary goals of preventive migraine therapies are to reduce the frequency and severity of attacks, to reduce reliance upon acute medications, and to improve patients' quality of life. Reducing the frequency of attacks and the reliance on acute medications may be particularly important in reducing the risk for CM. The following sections discuss the efficacy of topiramate as preventive treatment for EM and CM.

PREVENTIVE TREATMENT OF CM

Preventing the transition from episodic to CM has the highest priority. This includes the early initiation of nonmedical and medical prophylaxis and the identification of patients at risk. Integrated headache care in Germany provides a model for this approach. Patients with frequent prescriptions for headache medication or frequent work-loss days associated with a diagnosis of migraine are identified in the databases of insurance companies and referred to a local headache center.

Three large, randomized, placebo-controlled trials demonstrated that, compared with placebo-treated patients, topiramate 100 mg/day is effective for the prevention of migraine in adults.⁴³⁻⁴⁵ A later pooled analysis of these trials confirmed these results.⁴⁶ Another pooled analysis of the 3 aforementioned studies of topiramate for EM suggested that topiramate may reduce the risk of progression from

EM to chronic forms of headache.⁴⁷ Several open-label studies have also suggested that topiramate may be helpful in CM.⁴⁸⁻⁵⁰

A small-scale (N = 28) double-blind, placebo-controlled trial by Silvestrini et al demonstrated that low-dose topiramate (50 mg/day) may be effective in reducing headache frequency in patients experiencing CM with acute medication overuse.⁵¹ During the last 4 weeks of the 8-week maintenance phase, topiramate-treated patients reported significantly lower headache frequencies compared with patients treated with placebo (mean number of days with headache [\pm SD]: 8.1 ± 8.1 vs 20.6 ± 3.4 , $P < .0007$), and a higher proportion of topiramate-treated patients (71%) achieved a 50% response rate ($\geq 50\%$ improvement in monthly headache frequency) compared with placebo-treated patients (7%).

In the USA, a randomized, double-blind, placebo-controlled, parallel-group trial was conducted in 46 centers.⁵² The 16-week double-blind treatment phase consisted of a 4-week titration period and a 12-week maintenance phase. CM was operationally defined as the presence of ≥ 15 headache days per 28 days, of which at least 50% were migraine or migrainous headache (Silberstein-Lipton criteria for transformed migraine, with additional qualifications regarding the frequency of headaches possessing migraine features).¹¹ These diagnostic criteria are similar (but not identical) to those recently adopted by the ICHD-2 (CM-R) and represent what was under discussion by the IHS classification committee at the study's initiation. Although the diagnostic criteria did differ, Bigal et al showed in a diary study that there was almost 100% overlap between these criteria, transformed migraine, and the CM-R criteria if the overuse of medication was used as a separate diagnosis.¹⁴ The intent-to-treat (ITT) population in the US study consisted of a total of 306 patients (topiramate, n = 153; placebo, n = 153).

The key clinical efficacy results included a significant reduction in mean (\pm SD) monthly rate of migraine/migrainous days in patients receiving topiramate (6.4 ± 5.8 days) compared with placebo (4.7 ± 6.1 days, $P = .010$) and a mean reduction from baseline of 5.6 (± 6.0) migraine days per month, compared with 4.1 (± 6.1) days for the placebo group

($P = .032$). The total number of monthly headache days also decreased in the topiramate-treatment group more than in subjects receiving placebo (-5.8 ± 5.6 vs -4.7 ± 5.6 , $P = .067$). Although this difference between the 2 groups was not statistically significant, the percentage change in total headache days did show statistical significance (29.7% topiramate vs 23.1% placebo; $P = .037$). While the overall Migraine Disability Assessment (MIDAS) scores decreased, but did not separate statistically from baseline in both treatment groups (topiramate: 31.4; placebo: 21; $P = .123$), topiramate trended to improve the $>50\%$ improvement from baseline in MIDAS scores vs placebo (56% vs 45%, respectively; $P = .074$).⁵³ The most common topiramate-associated adverse events (AEs) were paresthesia (28.8% vs placebo 7.5%), upper respiratory tract infection (13.8% vs 12.4% placebo), and fatigue (11.9% vs placebo 9.9%). Treatment-emergent AEs were mild to moderate in severity and were consistent with those observed in previous topiramate clinical trials. No serious AEs were reported in either treatment group.⁵²

A European, randomized, double-blind, placebo-controlled, parallel-group, multicenter study was also conducted, consisting of 16 weeks of double-blind treatment.⁵⁴ CM was defined as ≥ 15 monthly migraine days for ≥ 3 months prior to trial entry, whether or not patients were overusing acute medications (ICHD-2 CM criteria). Patients were included if they had ≥ 12 migraine days during the 4-week (28-day) baseline phase. The ITT population included 59 patients (topiramate, n = 32; placebo, n = 27). The primary efficacy variable was the change in mean number of monthly migraine days from baseline to the last 4 weeks of the double-blind phase.

Topiramate significantly reduced mean (\pm SD) monthly migraine days compared with placebo (-3.5 ± 6.3 vs 0.2 ± 4.7 ; $P = .020$). The change in monthly migraine days from baseline to the entire double-blind phase was greater in the topiramate-treatment group than for placebo-treated subjects (-3.5 ± 6.7 vs 0.4 ± 4.6 ; $P = .019$). Topiramate also significantly reduced the mean number of migraine periods and attacks at all time points during the double-blind phase (except week 8) compared with

placebo. Unlike the US study, analysis of the number of total headache days was not conducted in the European trial. However, the total MIDAS score significantly decreased in subjects treated with topiramate, compared with patients treated with placebo (25.8 ± 61.4 vs $+3.1 \pm 21.2$; $P = .042$).⁵⁴ The most common topiramate-associated AEs were consistent with those observed in previous clinical trials and included paresthesia (53% vs placebo 7%) and nausea (9% vs placebo 0%).⁵⁴

A key difference between the US and European trial was that patients were allowed to take acute rescue medication as usual during the European trial (Table). Interestingly, the benefits of topiramate extended to the subgroup of patients overusing acute medications (topiramate, $n = 23$; placebo, $n = 23$), as demonstrated by significant reductions in mean monthly migraine days (-3.5 days) compared with

placebo (0.8 days, $P = .03$). Although topiramate decreased the number of days per month with acute medication intake vs placebo (reduction of 3 days/month for topiramate vs 0.7 days for placebo), the difference was not statistically significant ($P = .11$). An interesting finding in the European trial was the lack of placebo response. This between-study difference may be due, in part, to the differences in the spectrum of overused medications and the limit on the number of days with medication overuse imposed in the US trial (up to 16 days/month) vs the European trial (no limit). Another possible explanation is a change in pain modulatory systems – down-regulation of 5-HT synthesis and/or receptor number and function,^{32,33} decreased pain thresholds,³⁴ and a facilitation of trigeminal pain processing^{35,36} – with medication overuse. As a result, these patients might no longer respond to placebo. Alternatively, patients with more

Table.—Differences Between Patient Populations

Parameter	US Trial	European Trial
Key inclusion criteria	Baseline: ≥ 15 days/month with migraine attack lasting ≥ 30 minutes*	Migraine for ≥ 1 year; chronic migraine for ≥ 3 months (≥ 15 migraine days per 4 weeks); baseline: ≥ 12 migraine days per 4 weeks
Key exclusion criteria	Failure of >2 adequate trials of migraine preventive or failure of adequate trial of topiramate due to lack of efficacy or adverse events; cluster headaches or basilar, ophthalmoplegic or hemiplegic migraines; migraine onset after age 50	Other primary headache (except medication overuse); severely depressed mood (Beck Depression Inventory score ≥ 30); inadequate contraception
Primary efficacy end point	Change from baseline in mean monthly migraine/migrainous days over entire double-blind phase	Change from baseline in mean monthly migraine days to end of double-blind phase
Chronic migraine diagnostic criteria	Silberstein-Lipton	International Classification of Headache Disorders 2 criteria
Concomitant migraine preventive therapy	Not allowed	Allowed
Acute medication overuse	Permitted medication use of no more than 4 days/week†	Acute medication overuse permitted
Target topiramate dose	100 mg/day	100 mg/day (up to 200 mg/day)
Mean topiramate dose during double-blind period	75 mg/day	100 mg/day
Mean topiramate dose during maintenance phase‡	88 mg/day	100 mg/day

*According to the International Headache Society (IHS) criteria, a migraine must last at least 4 hours; therefore, all attacks in US patients during baseline may not have satisfied the IHS criteria for migraine.

†Some subjects could be classified as having medication overuse headache based on the current IHS definition.

‡Differences may explain why proportionately more US patients stopped because of lack of efficacy compared with patients in the European trial.

apparently medically intractable headache, or their physicians, have less expectation of success, and expectation is crucial in driving the placebo response.⁵⁵

Key differences between the patient populations who participated in these 2 multicenter studies are presented in the Table. Despite these differences, both trials demonstrated that topiramate is effective and safe in the treatment of patients with CM. Topiramate efficacy appears to be maintained in the presence or absence of medication overuse and/or in the presence of other concomitant migraine preventive treatments. Treatment with topiramate also reduced the use of acute medication.

PROPOSED PATHOPHYSIOLOGY OF MIGRAINE TRANSFORMATION AND A MECHANISM OF NEUROSTABILIZERS

The pathophysiology of migraine transformation is not fully understood. Several animal studies have provided insight into potential mechanisms for the initiation and maintenance of chronic headache.^{32,33,56,57} These mechanisms include decreased central 5-HT synthesis and dysregulation of associated 5-HT receptors, hyperexcitability of central pain pathways, low β -endorphin levels, and n-methyl-D-aspartate (NMDA) receptor dysfunction.^{58,59} Sensitization and facilitation of pain transmission in central trigeminal sensory pathways (central sensitization) may play a particularly important role in the development of chronic headache. When central sensitization occurs, the requirement for external input is circumvented. In other words, central trigeminal vascular neurons can spontaneously propagate pain information along the neural pathway in the absence of further external stimuli.²⁹ Repeated episodes of migraine with central sensitization could chronically sensitize nociceptors, lowering the threshold for future attacks and, in this way, contribute to the transformation of migraine to a chronic disorder. Several psychophysical and electrophysiological studies lend support to this theory by demonstrating a clear facilitation of trigeminal pain processing in patients with chronic headache.³⁴⁻³⁶

The primary mechanism of action of preventive neurostabilizers, like topiramate, is to decrease neuronal hyperexcitability through antagonism of

excitatory glutamatergic neurotransmission and a concomitant enhancement of GABAergic inhibition.⁶⁰ Several animal studies have shown that systemic administration of topiramate inhibits trigeminovascular activation.^{61,62} Given the potential importance of central sensitization to the establishment of CM, treatments designed to prevent the initiation of central sensitization may be considered first order preventive strategies. Topiramate has proven efficacy in reducing migraine attack frequency and has the potential to inhibit the transmission of pain information from peripheral neurons to sensory cortices, and thus may alter the progression of migraine to a chronic condition. Alternatively, there may be little difference in the pathophysiology of episodic and CM, and the outcome reflects a position that frequent and infrequent migraine are more similar (in terms of biology) than different. One might predict that well-powered studies of other preventives that are effective in EM would show efficacy in CM. In practice, that is precisely what clinicians currently do.

SUMMARY

Patients with EM who also have high headache/migraine frequency, high BMIs, or who frequently consume acute headache medications are at high risk of developing CM. Currently, there are few treatment options with demonstrated efficacy to treat this disabling disorder. Three randomized, controlled trials support the use of topiramate as a safe and effective preventive treatment for EM. Until recently, evidence supporting its use in the treatment of CM was limited to several open-label studies and 1 small-scale placebo-controlled trial. Results from 2 multicenter, randomized, double-blind, placebo-controlled trials now suggest that topiramate may be an effective treatment option for this difficult-to-treat patient population. Arguably, the 2 most important modifiable risk factors for the acceleration of migraine to a chronic condition are frequent, recurring migraine episodes and overuse of acute migraine medication. Studies reviewed herein demonstrate that topiramate both reduces migraine frequency and reduces reliance upon acute medication. Mechanistically, topiramate may augment nociceptive hypersensitivity and thereby prevent the establishment of a permanent

status of central sensitization. Based on positive results with topiramate in preventing and treating CM, further evaluation of treatment strategies for the prevention of migraine progression is warranted.

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