Topiramate in Migraine Prevention: A 2016 Perspective

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Background.—In evidence-based guidelines published in 2000, topiramate was a third-tier migraine preventive with no scientific evidence of efficacy; recommendation for its use reflected consensus opinion and clinical experience. Its neurostabilizing activity, coupled with its favorable weight profile, made topiramate an attractive alternative to other migraine preventives that caused weight gain. When guidelines for migraine prevention in episodic migraine were published in 2012, topiramate was included as a first-line option based on double-blind, randomized controlled trials involving nearly 3000 patients. The scientific and clinical interest in topiramate has generated a large body of data from randomized controlled trials, meta-analyses, patient registries, cohort studies, and claims data analyses that have more fully characterized its role as a migraine preventive.

Aim.—This article will review the profile of topiramate that has emerged out of the past decade of research and clinical use in migraine prophylaxis. It will also address the rationale for extended-release (XR) formulations in optimizing topiramate therapy in migraine.

Summary.—Topiramate has activity at multiple molecular targets, which may account for why it is effective in migraine and most other, more specific, anticonvulsants are not. Based on randomized controlled trials, topiramate reduces migraine frequency and acute medication use, improves quality of life, and reduces disability in patients with episodic migraine and in those with chronic migraine with or without medication overuse headache. Its efficacy in chronic migraine is not improved by the addition of propranolol. Topiramate's ability to prevent progression from high-frequency episodic migraine to chronic migraine remains unclear. Consistent with clinicians' perceptions, migraineurs are more sensitive to topiramate-associated side effects than patients with epilepsy. Paresthesia is a common occurrence early in treatment but is rarely cause for terminating topiramate treatment. Cognitive problems occur much less frequently than paresthesia but are more troublesome in terms of treatment discontinuation. Cognitive complaints can often be managed by slowly increasing the topiramate dose in small increments to allow habituation. As with other carbonic anhydrase inhibitors, topiramate has metabolic effects that favor the development of metabolic acidosis and possibly renal stones. Because migraineurs have an increased risk of renal stones independent of topiramate exposure, clinicians should counsel all migraine patients to maintain hydration. Abrupt onset of blurring, other visual disturbances, and/or ocular pain following topiramate's initiation should be evaluated promptly since this may indicate rare but potentially sight-threatening idiosyncratic events. Postmarketing evidence has shown that first-trimester exposure to topiramate monotherapy is associated with increased occurrence of cleft lip with or without cleft palate (Pregnancy Category D). Even though topiramate's long half-life would seemingly support q.d. dosing, randomized controlled migraine trials used b.i.d. administration of immediate-release (IR) topiramate, which has more favorable plasma concentration-time profile (ie, lower peak concentrations and higher trough concentrations) than q.d. IR dosing. Given the sensitivity of migraineurs to topiramate-related adverse events, particularly cognitive effects, pharmacokinetic profiles should be considered when optimizing migraine outcomes. The extended-release (XR) formulations Qudexy® XR (Upsher-Smith Laboratories) and Trokendi XR® (Supernus Pharmaceuticals) were specifically designed to achieve the adherence benefits of q.d. dosing but with more favorable (ie, more constant) steady-state plasma concentrations over the 24-hour dosing interval vs IR topiramate b.i.d. Intriguing results from a study in healthy volunteers showed consistently less impairment in neuropsychometric tests of verbal fluency and mental processing speed with an XR topiramate formulation (Trokendi XR) vs IR topiramate b.i.d. These findings suggest a pharmacodynamic effect associated with significantly reducing plasma concentration fluctuation when topiramate absorption is slowed. Results of retrospective studies in migraineurs treated with XR topiramate appear to support a clinically meaningful benefit of XR topiramate vs IR topiramate in terms of significantly fewer cognitive effects, improved adherence, and overall better outcomes of migraine prophylaxis with topiramate.

Key words: extended-release, migraine prevention, topiramate, Trokendi XR, Qudexy XR

Migraine is a disabling primary episodic headache characterized by recurrent attacks of headache, gastrointestinal and autonomic nervous system dysfunction and, in some patients, aura. Migraine is the third most common disease globally and the

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Headache

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Table 1.—Pharmacodynamic Effects of Topiramate (adapted from White[12])

Molecular Target	Modulatory Effect	Potential Functional Implications
Voltage-activated Na^+ channels	Negative	• Block action potential propagation • Stabilize neuronal membranes • Decrease/prevent neurotransmitter and vasoactive peptide release • Decrease focal firing • Decrease spreading depolarization
High-voltage activated Ca^{2+} channels	Negative	• Decrease/prevent neurotransmitter and vasoactive peptide release • Decrease sustained membrane depolarization • Elevate migraine threshold
$GABA_A$ receptor	Positive	• Increase membrane hyperpolarization • Elevate migraine threshold • Decrease focal firing
AMPA/kainate receptor	Negative	• Decrease fast excitatory neurotransmission • Prevent synchronous firing • Decrease/prevent neurotransmitter and vasoactive peptide release
Carbonic anhydrase	Inhibition	• Decrease excitatory neurotransmission • Enhance inhibitory neurotransmission • Activate a hyperpolarizing K^+ conductance • Stabilize neuronal membranes

seventh highest cause of disability.[1] It accounts for 3% of all years lost to disability but more than half of all years lost due to neurologic disorders.[1] Despite the individual and societal burden, migraine has historically not been a high priority in public health policy as demonstrated by the lack of parity between national funding of headache/migraine research ($0.41 per $1000 costs in 2007) and funding for other chronic disorders such as epilepsy ($8), multiple sclerosis ($14), and Parkinson's disease ($372).[2] Migraine's direct and indirect costs in the U.S. total more than $40 billion annually.[2] Per capita costs of chronic migraine are more than three times greater vs episodic migraine,[3,4] while episodic migraine is about 10 times more common. The goal of migraine prevention is to reduce the frequency, duration, or severity of attacks. Additional benefits include enhancement of response to acute treatments, improvement of a patient's ability to function, and reduction of disability and healthcare costs. In addition, migraine prevention may impede the transformation from episodic to chronic migraine.

In the mid-1990s, recognition of migraine as a public health problem resulted in evidence-based reviews[5] of migraine diagnosis and management that became the foundation for "best practices" guidelines published in 2000.[6] Based on nearly 300 studies of approximately 70 products,[7] four drugs available in the U.S. (amitriptyline, valproate/divalproex, propranolol, timolol) were recommended as first-line migraine preventives based on scientific evidence of efficacy.[6] For any one drug, the total number of patients in double-blind, randomized controlled trials was less than 500 patients. Due to the absence of scientific evidence of efficacy, topiramate was recommended as a third-tier agent, reflecting clinical experience and consensus opinion that it was effective.

The efficacy of topiramate in migraine has since been evaluated in numerous studies. When evidence-based guidelines on episodic migraine prevention were updated in 2012, the inclusion of topiramate as a first-tier agent was supported by randomized controlled trials involving nearly 3000 patients.[8,9] Topiramate has been studied in different populations and settings that have established its usefulness in migraine as well as its safety profile. Topiramate is now the most commonly prescribed migraine preventive. This paper will review topiramate in migraine prevention, highlighting its mechanism(s) of action, efficacy, and adverse events (AEs). It will also address the role that extended-release (XR) formulations can play in optimizing outcomes of migraine prophylaxis.

MOLECULAR TARGETS/MECHANISM(S) of ACTION

Topiramate is an analog of fructose-1,6-diphosphate that has no direct hypoglycemic activity despite being synthesized as a potential inhibitor of fructose-1,6-biphosphatase and thus gluconeogenesis.[10,11] At therapeutically relevant concentrations, topiramate acts at multiple molecular targets to enhance neuronal inhibition and decrease neuronal excitation (Table 1).[10-12] Topiramate blocks voltage-activated Na^+ [13-19] and Ca^{2+} channels[20-23] and modulates voltage-gated K^+ channels.[22,24] It inhibits

kainate and AMPA subtypes of glutamate receptors,[25-31] particularly the GluR5 (ie, GluK1) kainate receptor,[27,32] but has no direct effect on NMDA receptor function.[28,30] Topiramate can either enhance or have no effect on $GABA_A$-mediated activity.[10,11,24,32-36] Based on observations that stimulated dopamine increases were blocked by topiramate, topiramate may also alter neurotransmitter concentrations via a direct effect on proteins involved in synaptic vesicle exocytosis.[11,37,38] Topiramate reduced extracellular glutamate and aspartate in conditions of excess concentrations[39,40] and enhanced synaptic GABA release.[41] GABA concentrations in the occipital lobe increased shortly after oral administration of 100–400 mg topiramate, suggesting an effect that increases intracellular GABA in GABAergic neurons.[42-44] Topiramate is also a moderately potent inhibitor of carbonic anhydrase II[11,45,46] and aquaporin-4 water channels.[47] The effects of carbonic anhydrase inhibition on microenvironment pH could modulate pH-dependent voltage- and receptor-gated ion channels.[12] Activation of a hyperpolarizing K^+ conduction by topiramate has been attributed, in part, to topiramate's inhibition of carbonic anhydrase.[24] Topiramate's multiple effects may be due to its binding to dephosphorylated receptors and subsequent inhibition of phosphorylation-mediated regulation of protein kinases (eg, cAMP-dependent protein kinase A, protein kinase C, calmodulin-activated kinase) or protein phosphatases (eg, calcineurin).[10,11,30,48]

Why is topiramate effective in migraine prophylaxis yet other voltage-sensitive Na^+ channel blockers (eg, lamotrigine) are not? Drugs with multiple molecular targets may be more effective than highly selective single-target agents in complex multifactorial disorders characterized by drug resistance.[49] Topiramate's cumulative pharmacodynamic effects involving glutamate, $GABA_A$, and voltage-gated Ca^{2+} channels may account for its benefits in migraine prophylaxis.[50] Its effects on GABA-mediated neuroinhibition and voltage-gated Ca^{2+} channels may raise the migraine threshold and prevent initiation of a migraine attack and/or the spread of depolarization.[12] Topiramate may interfere with activation and sensitization of primary afferent and central neurons via negative modulation of AMPA/kainate-receptor mediated excitatory neurotransmission, coupled with negative modulatory effects on Na^+ and Ca^{2+} channels, to reduce or prevent release of neurotransmitters and vasoactive peptides. The primary migraine pathway(s) targeted by topiramate has yet to be determined. Topiramate inhibits nociceptive neuronal firing in the trigeminocervical complex[51] and subsequent dural vasodilation in pain pathway models.[52-54] It acts centrally, directly within the trigeminocervical complex, the thalamus, and cortex.[50] Glutamatergic kainate receptors with GluR5 (GluK1) subunits in structures of the ascending migraine pathway were specifically inhibited by topiramate.[53] Treatment response to topiramate in patients with high-frequency episodic migraine was reported to be associated with polymorphisms in GRIK4, a gene coding for a glutamate kainate receptor, suggesting involvement of kainate receptors.[55] By blocking high voltage-gated Ca^{2+} channels, topiramate may inhibit stimulated release of calcitonin gene-related peptide (CGRP)[52,56-58] and glutamate[57] from trigeminovascular nerve terminals. Topiramate inhibited evoked cortical spreading depression (CSD)[58-62] and CSD in a model of medication overuse headache.[63] Multiple targets of topiramate have been implicated in CSD. Na^+ channels and glutamate receptors influence the initiation of CSD-related vascular changes, while glutamate receptors also play a key role in the spreading wave of blood flow changes. $GABA_A$ receptors reduce the threshold to the vascular changes.[62]

PIVOTAL TRIALS IN EPISODIC MIGRAINE

The efficacy of topiramate as a migraine preventive was initially established in three similarly designed multicenter, double-blind, placebo-controlled trials in which patients with episodic migraine (3–12 migraines but no more than 15 headache days per month) were treated for 6 months.[64-66] At the time these trials were conducted, they were the largest ever controlled trials of any migraine preventive, randomizing a total of more than 1500 patients. Two were conducted in North America and assessed the efficacy and tolerability/safety of 50, 100, and 200 mg/day topiramate.[65,66] In the first trial, the responder rate (patients with $\geq$50% reduction in monthly migraine frequency) was 36% with 50 mg ($P=.04$), 54% with 100 mg ($P<.001$), and 52% with 200 mg ($P<.001$) compared with 23% with placebo.[64] The 200-mg dose was not significantly more effective than 100 mg. The responder rates in the second trial were 39% (50 mg, $P=.01$), 49% (100 mg, $P<.001$), and 47% (200 mg, $P<.001$) vs 23% with placebo. A third randomized, double-blind, parallel-group trial was conducted outside North America and compared two doses of topiramate (100 mg or 200 mg) to placebo or propranolol (160 mg/day). Topiramate 100 mg was superior to placebo as measured by average monthly migraine frequency, rate of rescue medication use, and responder rate (37% vs 22%).[66] Topiramate 200 mg did not produce incrementally better outcomes than 100 mg. Secondary efficacy variables were similar for topiramate and propranolol.

When data were pooled, the 50-mg dose in the two North American studies produced significantly greater reductions in migraine frequency vs placebo.[8] The difference favoring topiramate (100 and 200 mg combined) over placebo was significant within the first week of double-blind treatment, demonstrating an early onset of effect.[67] Approximately half of patients in these three trials had a clinically meaningful response ($\geq$50% reduction) in migraine frequency, while one

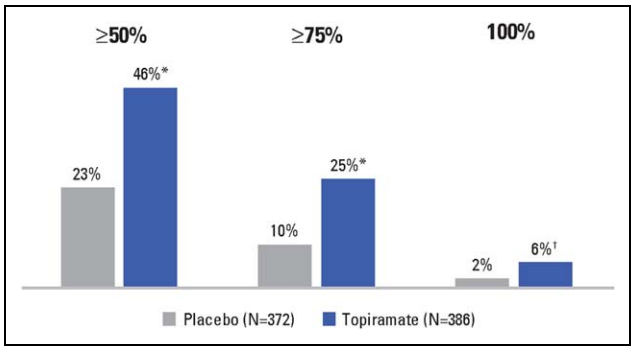

Fig. 1.—Percent patients with ≥50%, ≥75%, and 100% reduction in monthly migraine frequency during 26-week double-blind treatment with topiramate 100 mg/day. *$P<.001$; †$P<.01$ vs placebo. Data from Bussone et al.[68] [Color figure can be viewed at wileyonlinelibrary.com]

in four patients had an even greater degree (≥75%) of migraine reduction (Fig. 1).[68] Importantly, these studies demonstrated that treatment with topiramate 100 mg produced significantly greater improvements in daily activities and patient functioning relative to placebo, which were sustained throughout the 6-month treatment interval.[69] Patients with ≥50% reduction in migraine frequency showed significantly greater improvements than those with <50% reduction.[70]

These trials clearly documented topiramate's efficacy as a migraine preventive; subsequent trials characterized the scope of its clinical utility. Several trials of varying quality compared topiramate with other migraine preventives in episodic migraine. Efficacy of topiramate in these trials was similar to that of other first-line preventives (amitriptyline, propranolol, valproate).[8] Side effect profiles differed qualitatively. In a comparison of topiramate 100 mg/day and amitriptyline 100 mg/day, topiramate was associated with a 2.4 kg mean weight loss while amitriptyline was associated with a mean weight gain of 2.4 kg.[71]

CHRONIC MIGRAINE WITH OR WITHOUT MEDICATION OVERUSE HEADACHE

In a large, well-designed double-blind trial performed in the U.S., patients with chronic migraine (≥15 headache days per month, at least half being migraines) were randomized to 16 weeks of treatment with placebo or topiramate titrated to 100 mg/day over 4 weeks.[72] Use of acute pain medications could not exceed 4 days/week during the baseline period. Migraine/probable migraine frequency declined 37% from baseline with topiramate and 26% with placebo ($P=.01$). A critical question addressed by this study was whether reduced migraine frequency had a significant impact on the emotional distress, headache-related disability, and overall health-related quality of life associated with chronic migraine. Relative to placebo, topiramate was associated with significant and clinically meaningful improvement in patient-reported outcomes such as ability to perform daily activities and sense of frustration and/or helplessness.[73,74] Between-group differences emerged within the first 4 weeks of treatment; improvement continued over the 16-week course of treatment, suggesting that patients will achieve greater benefit if topiramate treatment is continued for a longer duration.[73]

In a smaller study conducted in Europe, the initial target dose of 100 mg/day topiramate could be adjusted according to clinical need (50–200 mg/day).[75] Other preventive therapy was allowed but had to remain stable during double-blind treatment and patients could take acute medications as usual. Reductions in migraine frequency were significantly greater vs placebo as were proportion of patients with ≥50% reduction (22% vs 0%, $P=.02$). Compared with placebo, topiramate was associated with significantly less time lost from work/school and daily activities.

Acute migraine medication overuse is an important contributor to headache frequency and severity and may diminish the effectiveness of preventive therapy. Therefore, post-hoc analyses of these two studies assessed response in the subset of chronic migraine patients meeting criteria for medication overuse in the baseline period.[76] In the European study, migraine frequency reduction was significantly greater for topiramate in the medication overuse subset. In the U.S. study, the between-group difference trended towards but did not reach statistical significance. Medication overuse patterns differed between studies (Europe: almost exclusively triptans; U.S.: triptans and analgesics, usually in combination). These two studies demonstrated that topiramate is an effective preventive in patients with chronic migraine, including patients with medication overuse headache, particularly those using triptans for acute pain relief. These findings support a chronic migraine management strategy in which preventive therapy is initiated first, with concurrent or later withdrawal of overused acute medications.[76]

TOPIRAMATE AS COMBINATION PREVENTIVE THERAPY

Because a single preventive medication is inadequate in many migraine patients, two agents of different classes – eg, topiramate and a β-blocker – are often used in combination. In the first double-blind, randomized controlled study of its kind, the Chronic Migraine Treatment Trial (CMTT) conducted by the National Institute of Neurological Disorders and Stroke (NINDS) Clinical Research Collaboration compared propranolol (up to 240 mg/day) with placebo when added to topiramate (up to 100 mg/day) in patients with

inadequately controlled chronic migraine (≥10 headaches/month).[77] Study enrollment was terminated early after the Data Safety Monitoring Board reviewed data on 171 patients (propranolol + topiramate, n = 85; placebo + topiramate, n = 86). It was determined that, even if the study were fully enrolled (N = 250), it would be highly unlikely to show a significant difference favoring the propranolol/topiramate combination over topiramate alone in reducing headache frequency. The monthly frequency of moderate-to-severe headache at 6 months was reduced 4.0 days for the combination vs 4.5 for topiramate alone ($P = .57$). None of the many efficacy or quality-of-life assessments showed a significant between-group difference at 3 or 6 months. Thus, the addition of propranolol to topiramate in chronic migraine patients with an inadequate response to topiramate alone is unlikely to produce a clinically meaningful benefit.

The reasons for this negative outcome are unclear. Perhaps propranolol is effective in episodic but not chronic migraine or its mechanism is not complementary or additive to that of topiramate in this population. More effective management strategies in chronic migraine will ultimately require a better understanding of chronic migraine's pathophysiology in order to identify more effective treatment strategies.

DISEASE MODIFICATION: PREVENTION OF EPISODIC-TO-CHRONIC MIGRAINE TRANSITION

For a subset of migraineurs, migraine frequency gradually escalates, evolving into chronic migraine. High migraine frequency and acute medication overuse are risk factors for migraine chronification. Thus, effective preventive therapy targeting these risk factors may be disease-modifying. In a post-hoc analysis of pooled data from the initial double-blind, placebo-controlled trials in episodic migraine, 2.1% of patients receiving topiramate 100 mg/day and 4.3% in the placebo group reported ≥15 headaches during the last month of double-blind treatment (odds ratio, 2.11; $P = .08$), suggesting a beneficial effect of topiramate on migraine progression.[78] A subsequent exploratory double-blind trial compared rates of transformation from high-frequency episodic migraine (9–14 migraine headache days and <15 total headache days monthly) to chronic migraine (≥15 migraine or non-migraine headache days monthly) in patients randomized to placebo or topiramate 100 mg.[79] Consistent with previous studies, topiramate was associated with significantly greater reductions in migraine frequency and acute medication use relative to placebo; only 1.4% of topiramate-treated patients met criteria for chronic daily headache at month 6. However, because the transition rate in the placebo arm (2.3%) was far lower than the 10–20% rate expected from epidemiologic data, the study failed to demonstrate a significant topiramate treatment effect vs placebo in preventing progression to chronic migraine. Various study design factors may have contributed to this failure, including an observation period of 6 months vs the 1-year period typically used in studies that assessed migraine progression risk factors and transition rates. In addition, high migraine frequency was the only risk factor used to select a population with an elevated risk of developing chronic migraine; acute headache medication overuse was specifically excluded as was failure of more than two adequate trials of preventive medication. Studies of longer duration are needed to determine whether preventives such as topiramate can alter the natural history of progressive migraine.

PEDIATRIC MIGRAINE

The pivotal studies of topiramate in episodic migraine included a small subset of adolescents 12–18 years of age.[64–66] Effects of topiramate in adolescents mirrored those in the overall study population.[80] In a subsequent double-blind, randomized controlled study limited to adolescents 12–17 years of age meeting diagnostic criteria for pediatric migraine, patients were randomized to placebo or topiramate (50 or 100 mg/day) titrated over 4 weeks.[81] During the subsequent 12-week maintenance phase, topiramate 100 mg, but not 50 mg, produced a significantly greater reduction in migraine frequency vs placebo. The treatment effect of topiramate increased over time but plateaued in the placebo group after 8 weeks. In the topiramate 100-mg group, median migraine frequency reduction was 100% for the last 4 weeks of double-blind treatment, indicating that at least 50% of adolescents were migraine-free. This study supported FDA approval of Topamax® (Janssen Pharmaceuticals) for use as a migraine preventive in adolescents (≥12 years of age).

Topiramate was part of the largest pediatric migraine study to date – a three-way double-blind NINDS-funded trial comparing placebo, topiramate, and amitriptyline in nearly 700 children (8–17 years of age).[82] Study enrollment was terminated early after the Data Safety Monitoring Board determined that, even if the study were fully enrolled, it would be highly unlikely to show a significant difference favoring active drugs over placebo.

DURATION OF PREVENTIVE THERAPY

Based on randomized controlled migraine prevention trials, patients, as a group, start to improve within the first month of treatment. For individual patients, an interval of at least 2 months at an optimal or maximum tolerated dose is considered adequate to assess whether a migraine preventive will be beneficial.[8] Pooled data for topiramate 100 mg/day in episodic

migraine showed steady improvement over the course of 6 months sustained treatment,[67,68] suggesting that patients who respond to topiramate within the first 1–2 months should continue treatment at least 6 months in order to achieve maximum benefit. To assess the potential benefits of a longer course of treatment, patients prospectively treated with open-label topiramate at individualized dosages (50–200 mg) for 6 months were randomized to double-blind treatment with topiramate for an additional 6 months or placebo (topiramate withdrawn).[83] Cessation of topiramate treatment (placebo group) was accompanied by an increase in migraine days in the first 4 weeks. At the end of 6-months' double-blind treatment, the number of migraine days and days with acute medication were significantly higher in the placebo group vs the group continuing topiramate. In the double-blind phase, quality of life was stable with continued topiramate, but declined in the placebo group when topiramate therapy was stopped. In the placebo group, headache frequency did not return to pre-topiramate levels, suggesting a long-term effect. These findings support an initial course of at least 6 months of topiramate treatment before considering lowering the dose or stopping the medication. For those with a partial response or who worsen after dose reduction, treatment can be extended to 12 months with increased benefit.

In an open-label study in a specialty headache clinic, topiramate was slowly withdrawn after 6 months of successful therapy, then reintroduced for an additional 6 months if headache frequency/intensity worsened.[84] The process was repeated at 6 months. When topiramate was first withdrawn, migraine worsened in 50% (40/80) of patients. When topiramate was restarted and withdrawn 6 months later (after 12 months continuous treatment), 95% (38/40) of patients worsened and topiramate therapy was once again restarted. These observations complement the randomized controlled withdrawal study by providing an estimate of the proportion of patients in whom migraines may relapse after 6 months of topiramate treatment (perhaps 50%). An initial relapse after topiramate's discontinuation may be a marker of more refractory disease with a high probability of relapse when topiramate is withdrawn.

REAL-WORLD MIGRAINE OUTCOMES WITH TOPIRAMATE

Randomized controlled trials have demonstrated that topiramate is an effective migraine preventive that can reduce migraine frequency and use of acute medications, while improving patient function and reducing disability. In clinical practice, topiramate can reduce healthcare use, as demonstrated by a retrospective analysis of pharmacy and medical claims data before and after initiation of topiramate therapy.[85] In the first 6 months after the index topiramate prescription, emergency department visits were reduced by 46% ($P<.0001$), diagnostic procedures such as CTs and MRIs by 39% ($P<.0001$), and hospitalization days by 43% ($P<.0001$). Over the subsequent 6 months (12 months after topiramate start), physician office visits were lower by 35%, diagnostic procedures by 72%, and hospitalization days by 67%. Triptan use was reduced 8% and 20% in the sequential 6-month follow-up periods ($P<.0001$). Use of laboratory tests and ambulance service was also reduced in the period following topiramate's start. Similar analyses of pre- and post-topiramate patterns in healthcare use have confirmed significant reductions in healthcare resource use and that such reductions can at least partially offset the cost of topiramate treatment.[86-88] However, these studies did not account for adherence (taking medication as instructed) and persistence (continuation of treatment) rates. Separate claims database analyses have found relatively low rates of adherence and persistence with oral migraine prophylaxis, including topiramate, in clinical practice.[89,90] At 6 months, only ~30% of chronic migraine patients had sufficient topiramate medication available for ≥80% of treatment days.[90] Among all migraine patients (≥2 attacks monthly), the estimated persistence rate for topiramate was 23% at 6 months, which was significantly higher than with other oral migraine preventives.[89] These data demonstrate the potential for even greater reductions in healthcare resource use if adherence and persistence with topiramate therapy were improved.

TOLERABILITY/SAFETY

After more than two decades of clinical trials and postmarketing experience, topiramate has a well-established tolerability/safety profile in a broad spectrum of disorders. Many of the adverse events (AEs) associated with topiramate including fatigue, dizziness, somnolence, mood changes, and suicidal ideation are common to CNS-active drugs. Topiramate is also associated with a distinct cognitive syndrome involving word-finding problems, slowed thinking/mental processing, and concentration/attention and memory difficulty. These have often been amenable to measures that alter the pharmacokinetic profile, eg, slowing the rate of drug introduction and lowering the dose. Other adverse effects can be attributed to topiramate's inhibition of carbonic anhydrase, including paresthesia, renal calculi, metabolic acidosis, hypokalemia, and taste disturbances. Ophthalmic effects such as acute angle closure glaucoma and visual problems without intraocular pressure elevation have been reported with other sulfonamide medications and appear to be idiosyncratic in nature. Finally, some "adverse effects," namely decreased appetite and weight loss, have been used for therapeutic purposes, as in the

development of an XR topiramate-phentermine combination for obesity.

The incidence of AEs associated with topiramate is disorder dependent. In an analysis comparing data from double-blind, randomized controlled trials of topiramate in migraine and in newly diagnosed epilepsy, the incidence of paresthesia associated with 50–200 mg/day topiramate was more than two-fold higher in migraine than in epilepsy patients,[91] a finding confirmed in an observational study.[92] Cognitive symptoms were more frequent in migraine patients when compared with epilepsy patients.[91] Discontinuation rates in randomized controlled trials were 17% for 50 mg, 21% for 100 mg, and 29% for 200 mg in migraine patients compared with 7%, 17%, and 28% respectively, in epilepsy patients. The "number needed to harm" (number who had to be treated to cause one AE-related dropout or serious AE) was 2.5 times higher in epilepsy vs migraine patients (95% CI: 2.03, 2.98) at the 50-mg dose and 20% higher (95% CI: 0.89, 1.56) at the 100-mg dose. The greater susceptibility of migraineurs to drug-related AEs in general may reflect increased sensitivity of the migraine brain.

Across the pivotal double-blind, placebo-controlled trials in episodic migraine, the most common AEs associated with topiramate were paresthesia, fatigue, nausea, decreased appetite, dizziness, diarrhea, weight loss, concentration/attention difficulty, and somnolence.[93] Adverse events were generally of mild or moderate severity and tended to be dose dependent. Most AEs began during the titration period, with most AE-related discontinuations occurring during titration. If a patient did not have AEs within the first 6 weeks of initiating topiramate, they were unlikely to occur.

An analysis of pooled data in patients assigned to 100 mg/day topiramate identified the AEs most likely to cause treatment discontinuation and therefore limit adherence in clinical practice.[94] For this analysis, confusion, concentration/attention difficulty, and memory difficulty were grouped together as "any cognitive symptom." Adverse events with significantly higher discontinuation rates vs placebo were paresthesia, any cognitive symptom, fatigue, insomnia, and anxiety. Paresthesia was a common occurrence (50% incidence) and persisted beyond titration but was cause for discontinuation in only 8% of patients. Paresthesia is therefore not likely to be a major cause of nonadherence with topiramate treatment. If intervention is needed, potassium chloride (20–40 mEq/day) has been useful in reducing or eliminating persistent paresthesia.[95] Cognitive problems, fatigue, insomnia, and anxiety occurred less frequently than paresthesia but were substantially more troublesome to patients and much more likely to result in discontinuation (Fig. 2).[94] Approximately one in three patients who experienced any cognitive symptom or fatigue and roughly 40–50% of patients who experienced insomnia or anxiety discontinued topiramate.

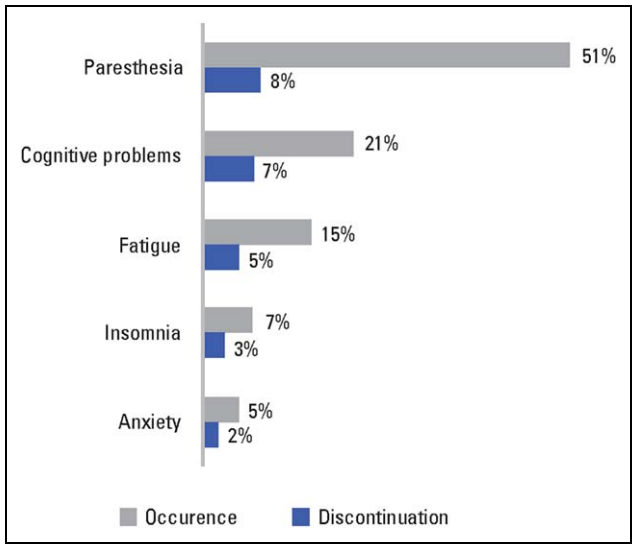

Fig. 2.—Adverse events with significantly greater discontinuation rates for topiramate vs placebo, comparing occurrence and discontinuation rates in pooled data for topiramate 100 mg/day in double-blind, placebo-controlled trials in episodic migraine. Data from Lainez et al.[94] [Color figure can be viewed at wileyonlinelibrary.com]

Carbonic anhydrase inhibitors such as topiramate have metabolic effects that favor the formation of urinary calculi, including increased urinary pH, increased urinary calcium excretion, and decreased urinary citrate excretion.[96–98] In randomized controlled trials of topiramate in migraine, urinary calculi occurred in 0.8% (n = 3) of patients receiving 100 mg/day topiramate and 1.6% (n = 8) receiving 200 mg/day.[93] To assess the risk of urolithiasis occurrence with topiramate exposure in clinical practice, a population-based study compared a cohort of patients (epilepsy and migraine) receiving topiramate and matched controls, finding no significant difference between groups.[99] A separate population cohort study compared urolithiasis in individuals with migraine and matched controls without migraine.[100] Migraineurs were at significantly increased risk of developing urinary calculi, independent of topiramate exposure. When adjusted for all confounding factors, topiramate treatment increased the risk of urinary calculi two-fold vs migraine patients not treated with topiramate. Possible mechanisms of migraine-associated urolithiasis include alterations in ureteral motility due to elevated plasma CGRP levels and urine crystallization secondary to oxidative stress. In light of these findings, clinicians should anticipate the potential for stone formation in all migraine patients and counsel patients about maintaining adequate hydration. Potassium citrate has been shown to reduce topiramate-induced hypocitraturia in migraine patients and is

therefore recommended as primary prevention in patients at high risk for stone formation (eg, prior stone history, family stone history).[98]

Diplopia and nystagmus are relatively common dose-related AEs with CNS drugs such as topiramate. Topiramate has also been associated with rare idiosyncratic and potentially serious visual complications such as acute angle closure glaucoma, myopic shifts without elevations in intraocular pressure, and visual field defects.[101] With timely treatment discontinuation, these complications typically resolve without permanent sequelae. Palinopsia, a relatively common but under-recognized phenomenon in migraine patients,[102] as well as Alice in Wonderland syndrome have occurred in conjunction with topiramate therapy in migraine patients with no previous history of these visual disturbances. The potential for visual complications should be considered in migraine patients reporting blurred vision or visual disturbances after starting topiramate. Confusing these events with the visual aura and/or pain of a migraine attack could lead to topiramate dosage increases and/or delay timely discontinuation and ophthalmic evaluation that could prevent permanent injury associated with elevated intraocular pressure.[101]

The effects of migraine preventives on weight are of considerable concern since obesity increases the frequency of migraine and migraine chronification.[103] Consistent with this migraine-obesity association, more than half of patients in double-blind, placebo-controlled trials of topiramate in episodic migraine were overweight or obese at baseline. Across all dosages, topiramate caused weight loss or was weight neutral in 88% of patients.[93] After 6 months, the mean change with 100 mg/day topiramate was −2.5 kg vs +0.1 kg with placebo; weight loss increased with obesity status (ie, normal BMI, −1.9 kg; obese, −3.1 kg; very obese, −3.0 kg).[68] Observations of weight loss with topiramate treatment have been relatively consistent across migraine populations. However, in adolescents who were predominantly of normal weight at baseline, weight changes resulted in only a slight BMI reduction (−0.4 kg/m^2 with 100 mg topiramate after 12 weeks).[81] Because changes in migraine frequency do not correlate with weight changes during migraine prophylaxis,[104] the beneficial/negative effects of weight changes are important primarily for their impact on patient health and adherence with long-term therapy.

In March 2011, labeling for all topiramate formulations was revised to report human data of an increased risk of oral cleft (cleft lip with/without cleft palate, CL/P) following first-trimester exposure to topiramate monotherapy (Pregnancy Category D).[105] In a recent meta-analysis of published studies that included nearly 3500 first trimester exposures to topiramate across all doses and all indications and more than 1.2 million controls, the risk of CL/P was increased sixfold with topiramate.[106] Clinicians should counsel women of reproductive age regarding the potential increased risk of CL/P associated with topiramate exposure in the first trimester of pregnancy. In women electing to use hormonal contraceptives, topiramate doses less than 200 mg do not affect contraceptive efficacy. In women who are planning to become pregnant, preventive therapy should be discontinued, recognizing that the frequency and severity of migraine attacks tend to be substantially reduced during pregnancy.[107]

EXTENDED-RELEASE TOPIRAMATE

In randomized controlled migraine prophylaxis studies, topiramate was administered b.i.d. as an immediate release (IR) formulation even though an elimination half-life exceeding 24 hours[108] would support once-daily (q.d.) dosing.[8,109] However, b.i.d. and q.d. administration of IR topiramate produce distinctly different plasma concentration-time profiles (Fig. 3A). With q.d. dosing, peak topiramate concentrations are higher and trough concentrations are at least 30% lower compared with b.i.d. administration.[110] This pharmacokinetic profile may be less favorable for optimizing migraine treatment. Doses high enough to offset lower average and minimum concentrations over the 24-hour dosing interval increase the risk of AEs, particularly CNS/cognitive AEs in a population that is demonstrably more susceptible to such effects.[91] Nonadherence (delayed or missed dose) would have a much greater impact on the plasma concentration-time profile when IR topiramate is dosed q.d. vs b.i.d.[110] Once-daily dosing with IR topiramate may improve adherence, but can lead to greater concentration fluctuations.

Once-daily dosing is clearly preferred in terms of adherence with oral migraine prophylaxis.[111] Extended-release (XR) formulations slow drug absorption and deliver more constant plasma concentrations with less frequent dosing to mitigate AEs associated with peak concentrations, enhance adherence, and improve overall outcomes. Appropriately designed XR formulations can also increase "forgiveness," ie, margin of therapeutic effect following a missed dose.[112] The two XR formulations of topiramate (Qudexy® XR, Upsher-Smith Laboratories; Trokendi XR®, Supernus Pharmaceuticals) currently available prolong topiramate release and slow absorption.[113] Although the two products use different technologies to control drug release, both formulations dosed q.d. are bioequivalent with IR topiramate b.i.d. (Topamax) at steady-state.[114,115] That is, 90% confidence intervals for XR/IR ratios were within 80–125% limits for maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), and 24-hour exposure measured as area under the curve ($AUC_{0\text{-}24}$), as well as in exposure in shorter segments of the dosing interval.[116,117] Despite bioequivalence, the formulations significantly ($P<.001$ vs IR topiramate) reduced C_{max} (Qudexy XR,

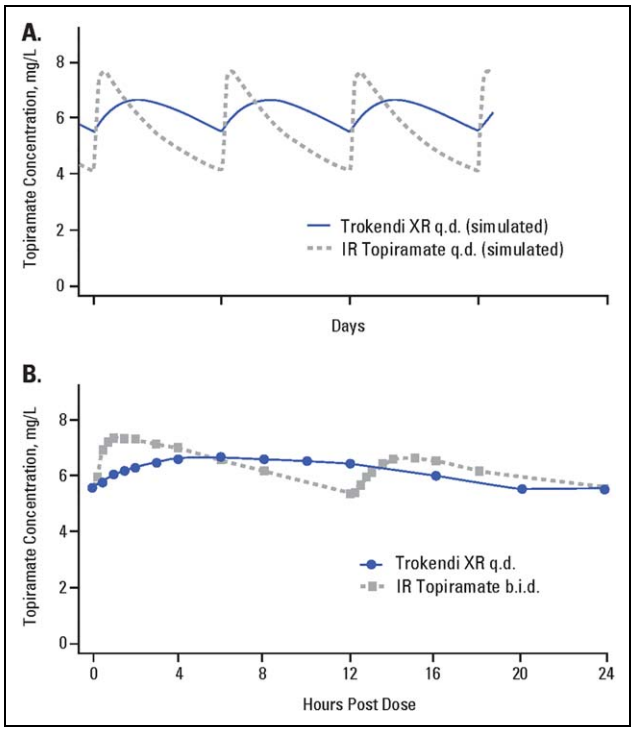

Fig. 3.—(A) Simulated topiramate plasma concentration-time profiles with q.d. dosing of IR and XR topiramate formulations (200 mg). Simulations used a population PK model developed from plasma concentration-time data collected in studies comparing Trokendi XR q.d. and Topamax b.i.d. in healthy adults and adults with epilepsy. Adapted from Brittain and Wheless.[110] (B) Mean steady-state plasma concentration-time profiles in a crossover bioequivalence study in healthy volunteers, comparing the XR topiramate formulation Trokendi XR (200 mg q.d.) and Topamax (100 mg b.i.d.) as the IR topiramate formulation. Adapted from Johnson et al.[117] [Color figure can be viewed at wileyonlinelibrary.com]

6%; Trokendi XR, 12%) relative to IR topiramate.[116,117] In similarly designed bioequivalence studies in healthy volunteers, the peak-to-trough fluctuation of steady-state topiramate plasma concentrations was 38% with Qudexy XR vs 53% with IR topiramate[110,114] and 26% vs 40% ($P<.001$) with Trokendi XR vs IR topiramate.[111] Thus, fluctuations were reduced by 26% with Qudexy XR,[110,114] and 36% with Trokendi XR.[109] With the prolonged release/absorption profiles of these products, mean effective half-lives of topiramate are 53 hours and 65 hours with Qudexy XR and Trokendi XR, respectively. Based on an in vitro dissolution study, topiramate release from Trokendi XR was significantly altered at higher alcohol concentrations; alcohol use should therefore be avoided 6 hours before and 6 hours after Trokendi XR administration.

Pharmacokinetic-pharmacodynamic (PK-PD) modeling in epilepsy patients suggests that topiramate's efficacy is related to steady-state trough concentrations.[118] Results of chronic oral topiramate dosing in a CSD model suggested a PK-PD relationship in which magnitude of CSD suppression correlated with topiramate plasma concentration.[119] Based on the PK-PD relationship for topiramate in epilepsy, bioequivalent formulations of XR topiramate q.d. and IR topiramate b.i.d. are presumed to be therapeutically equivalent despite substantial differences in their plasma concentration-time profiles (Fig. 3B), making double-blind, randomized controlled trials of XR formulations unnecessary. Thus, the FDA is expected to approve Qudexy XR and Trokendi XR for migraine prevention on the basis of bioequivalence and clinical pharmacology, without randomized controlled efficacy trials.

More constant steady-state topiramate plasma concentrations would not be expected to influence the efficacy of XR topiramate q.d. vs IR topiramate b.i.d., but plasma concentration fluctuations may impact signature adverse cognitive effects such as word-finding difficulty and psychomotor slowing. The occurrence and severity of these and other CNS AEs associated with topiramate are influenced by dose,[120] rate of dose escalation,[121,122] and plasma topiramate concentrations.[120,123–128] Given this PK-PD relationship, a bioequivalence study comparing an XR formulation (Trokendi XR q.d.) to IR topiramate b.i.d. (Topamax) in healthy volunteers included neuropsychological tests of verbal fluency and working memory after 1 week of dosing at 50, 100, 150, and 200 mg/day.[129] Changes in verbal fluency scores consistently showed less impairment with XR topiramate q.d. vs IR topiramate b.i.d.; the difference between formulations was significant at 100 mg and over the 1-month treatment period. Similar patterns for working memory changes favored XR topiramate but did not reach statistical significance. Fewer subjects reported cognitive AEs during exposure to XR topiramate q.d. Differences in cognitive function tests were not explained by topiramate plasma concentrations; these were virtually identical at the time of testing, which was conducted at the end of the 24-hour dosing interval (24 hours after the last XR topiramate dose; 12 hours after the last IR topiramate dose).

The most notable pharmacokinetic differences between XR topiramate q.d. and IR topiramate b.i.d. are the slower absorption rate with XR products (24-fold slower vs morning IR topiramate dose in the case of Trokendi XR[130]) and the significant reduction in the magnitude and frequency of plasma concentration fluctuations. Because topiramate rapidly penetrates the CNS[131] and concentrations of unbound topiramate in plasma and CSF are virtually identical,[44,132] the brain would presumably be subject to the same pattern of fluctuations over a 24-hour dosing interval. In a study demonstrating the bioequivalence of a single 100-mg dose of topiramate administered intravenously with a single 100-mg dose of oral

IR topiramate, reductions in verbal fluency scores were concentration-related and were observed as early as 15 minutes, indicating rapid diffusion of topiramate into the CNS.[131] The two formulations were bioequivalent, but IV topiramate had a stronger negative effect on verbal fluency than the oral IR formulation. These data show that bioequivalent formulations with different input rates can have different effects on cognitive function. Thus, the underlying PK-PD relationship is more complex than simply differences in topiramate plasma concentrations at the time of testing. Why input rates and/or plasma concentration fluctuations would influence cognitive performance is not known largely because the mechanism(s) underlying topiramate's cognitive effects has not been determined.

Prospective studies are needed to determine whether the effect observed with one XR topiramate formulation is shared by all such formulations and demonstrate that the signal is clinically relevant in migraineurs, ie, is associated with improved tolerability and adherence/persistence, reduced healthcare costs, and improved productivity. Results of two retrospective studies seem to support the potential for fewer adverse cognitive effects, greater persistence rates, and less healthcare resource use with XR topiramate when compared with IR topiramate.[133,134] As in randomized controlled trials with IR topiramate, a multisite medical record review showed that migraineurs treated with XR topiramate (Trokendi XR) were more susceptible vs epilepsy patients to topiramate-related AEs, particularly cognitive effects and paresthesia.[133] However, compared with patients' previous treatment with IR topiramate, XR topiramate was associated with significantly fewer cognitive complaints in the overall patient population and in the migraine cohort. A claims data study comparing parallel cohorts of migraine patients treated with IR or topiramate (Trokendi XR) showed better health outcomes with the XR formulation, including significantly greater adherence, lower risk of discontinuation, longer treatment duration, outpatient visits, and lower use of migraine-related medications.[134]

CONCLUSION

The diagnosis and management of migraine have clearly improved in the 15+ years since the first evidence-based guidelines were published. Clinicians have more tools at their disposal for both acute and preventive treatment. However, gaps clearly remain. Too many patients who are suitable candidates for migraine prophylaxis go untreated or discontinue prematurely. Topiramate has become the most commonly prescribed migraine preventive due to a sizeable body of evidence demonstrating its ability to improve outcomes in migraine patients in terms of reduced disability and improved quality of life. These improvements have also reduced the use of healthcare services. However, as with other migraine preventives, adherence and persistence are frequent issues. Extended-release topiramate formulations that are specifically designed for q.d. dosing and deliver more constant plasma concentrations over the 24-hour dosing interval are another tool for clinicians to optimize migraine prophylaxis outcomes.

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