1-1-2011

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Publication Info

Journal of Central Nervous System Disease, 2011, pages 155-68.

Journal of Central Nervous System Disease

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REVIEW

Topiramate: Safety and Efficacy of its Use in the Prevention and Treatment of Migraine

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Abstract: Migraine headaches are typically episodic in nature and may affect nearly 10% of the population. In addition to treatment, prevention of subsequent episodes or progression to a chronic migraine state is an important therapeutic area. Topiramate is a centrally acting medication approved for both the prevention of seizures and migraine headache. At this time, the exact mechanism of how topiramate assists in migraine prevention is unknown. Several large randomized, controlled trials have aided in establishing topiramate's role in migraine prevention. Despite a favorable pharmacokinetic and adverse effect profile established in clinical trials, several additional studies, case reports and toxicology reports have demonstrated topiramate as a cause of cognitive and behavioural changes. The use of topiramate in migraine prevention can improve a patient's quality of life and is a cost-effective option for migraine prevention.

Keywords: topiramate, migraine, prophylaxis

Journal of Central Nervous System Disease 2011:3 155–168

doi: 10.4137/JCNSD.S4365

This article is available from http://www.la-press.com.

Introduction

Headache is a common disorder, with an estimated prevalence of 5 to 12% based on data obtained from an international survey conducted in five countries. Migraine headache occurs in 9% of the general population.[1] The International Headache Society (IHS) defines migraine without aura as a recurrent headache disorder with attacks lasting from 4 to 72 hours. Typical characteristics include headache pain that is unilateral, pulsatile, and of moderate to severe intensity, and symptoms are often associated with nausea, photophobia or phonophobia. Routine physical activity can worsen the headache. Migraine with aura is defined by the IHS as a recurrent disorder presenting as attacks of reversible focal neurological symptoms that usually develop gradually over 5 to 20 minutes and continue for a duration of up to 60 minutes. Headache with the characteristics of migraine without aura typically occur after the aura symptoms. Migraine headaches can also be classified as episodic or chronic. Approximately 3% of patients with episodic migraine will advance to chronic migraine in one year.[2] From both a clinical and economic perspective, data also support the need to prevent the progression of episodic migraine to chronic migraine.[3,4] Interventions can be taken to decrease the risk for progression of migraine from episodic to chronic.[5]

Topiramate was originally developed and marketed for epilepsy. It is proposed that epilepsy and migraine share some of the same pathophysiological mechanisms including abnormal function of voltage-gated sodium and calcium channels, reduced GABA- mediated inhibition, and increased glutamate-mediated excitation.[6,7] Additional proposed commonalities include a low threshold for activation of cortical hyperexcitability and genetics.[8] Evidence also suggests that epilepsy and migraine are comorbid conditions.[9] The efficacy of topiramate as an antiepileptic drug (AED) was proven in controlled trials in the United States and Europe. Since that time, various trials have proven the efficacy and safety of topiramate in migraine prevention and treatment. It is approved for prophylactic treatment of migraine by the United States Food and Drug Administration (FDA).

The American Academy of Neurology recommends numerous therapies for the prevention of migraines.[10] It recommends initiating treatment for migraine prophylaxis when a patient experiences either recurring migraines that significantly interfere with activities of daily living despite the use of acute treatment; frequent headaches and a contraindication, adverse event; or overuse of the acute medications. Patients who experience unusual migraine conditions such as migraine with prolonged aura or a migrainous infarction are also candidates for preventive therapy.[10] The guidelines include topiramate therapy as a class III recommendation, however numerous additional data have been published since their recommendations in 2000.

Mechanism of action and pharmacology

The exact mechanism of topiramate is unknown, but several activities are theorized to contribute to its efficacy for migraine prophylaxis. Since migraine and epilepsy are thought to share various pathophysiologic properties, it is thought that topiramate exhibits similar mechanisms of action in both disorders. During both migraine and epilepsy, topiramate is predicted to exhibit its action through the blockade of sodium channels, L-type calcium channels, and also blockade of α-amino-3-hydoxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate currents.[11,12] The enhancement of gamma-aminobutyric acid (GABA)-mediated inhibition is also a potential mechanism of topiramate in both paroxysmal disorders.[13] Topiramate is proposed to inhibit carbonic anhydrase.[14] It is also believed that topiramate prevents phosphorylation of locations on some receptors, channels and proteins.[15]

The theorized pharmacologic mechanisms of action of topiramate relate to the proposed etiology of migraine to potentially explain its effects on the disease. Through sodium and calcium blockade, topiramate is able to modulate the abnormal function of these channels in migraine to possibly result in decreased neurotransmitter release and decreased blood vessel dilatation.[16,17] A decrease in GABA-mediated inhibition is thought to play a role in migraine development. The modulation of GABA receptors simply results in an enhancement of GABA-mediated inhibition.[13] An increase in glutamate-mediated excitation is also proposed to have a key role in the development of migraine. Therefore, the inhibition of AMPA and kainate currents result in less excitation by inhibiting trigeminal firing.[16] The inhibition of carbonic anhydrase activity results in an overall decrease in

excitatory neurotransmission and an increase of inhibitory neurotransmission.[18]

Pharmacokinetics

Pharmacokinetic studies demonstrate that topiramate has a wide therapeutic range and low interpatient variability. Early studies of topiramate in humans established the plasma and renal pharmacokinetic parameters. The study examined pharmacokinetic changes for five different doses of topiramate.[19] Topiramate is rapidly absorbed with 80% bioavailability and peak plasma concentration occurring approximately two hours after oral intake of a 400 mg dose.[20] Rate of absorption is slightly decreased when topiramate was administered with food; however, the decrease was not enough to produce changes of clinical importance.[19]

Within the blood concentration range of 0.5–250 μg/mL, topiramate is 15 to 41% bound to human plasma proteins.[20] Topiramate is not extensively metabolized, and approximately 70% of the orally administered dose is excreted unchanged in the urine. In patients with moderate to severe renal failure, the renal clearance was reduced by 42 to 54%. Therefore it is recommended to decrease the starting dose and maintenance dose by one-half in patients with moderate to severe renal failure.[20]

An open-label, randomized sequence, two-period cross-over study was conducted on 28 healthy male volunteers in Mexico.[21] The purpose of the study was to determine the bioequivalence of two oral forms, a generic form and a branded form, of a single, 100 mg daily dose of topiramate. Both formulations were rapidly absorbed from the gastrointestinal tract. Topiramate was detected in the first plasma sample which was obtained 0.25 hours after administration. C_{max} was reported as 1.914 μg/ml for the generic product and 1.908 μg/ml for the branded one. Half-life was 26.22 hours for the generic and 27.21 hours for the branded. The study did not find any statistically significant differences among the pharmacokinetic parameters. The researchers concluded that the generic form of topiramate was bioequivalent to the branded form.

A small study (n = 15) examined the pharmacokinetics in pregnant women.[22] Blood samples at baseline and during all trimesters were only available for 10 of the women. The researchers calculated the dose to plasma concentration ratio (D/C) to compare levels among study participants. At baseline, the patients' daily dose of topiramate ranged from 100 to 400 mg. Nine patients experienced a dose change during pregnancy. The mean dose to concentration ratio was 37.3 L/day at baseline, 49.4 L/day, 67.5 L/day, and 65.1 L/day during the first, second, and third trimesters (The $P < 0.0001$ for increase from baseline). The study participants displayed high variability among the increased ratios. The increase in dose to plasma concentration ratios ranged from 19 to 164%. The authors suggest monitoring topiramate levels during pregnancy.

In summary, topiramate has a linear relationship between dose and plasma concentrations, low oral clearance, a relatively long half-life and renal excretion of unchanged drug as a major pathway for elimination. Topiramate is almost completely absorbed from the gastrointestinal (GI) tract and does not significantly inhibit or induce other drug metabolizing enzymes.[14] Topiramate is not extensively metabolized and it easily crosses into the CNS.[23]

Dosing

The recommended total daily dose of topiramate for the treatment of migraine prophylaxis is 100 mg/day in two divided doses. A four-week titration is recommended in order to achieve the target dose. Week one dosing starts at 25 mg in the morning and 25 mg in the evening. The total daily dose is increased by 25 mg per week until a total daily dose of 100 mg is achieved.[20]

Clinical trials

The efficacy and safety of topiramate has been examined in multiple clinical trials for a variety of indications including seizure, alcohol withdrawal, weight loss and migraine prophylaxis in both adult and pediatric patients. This review is limited to its use in migraine prophylaxis in adult patients. For a discussion of its use for other indications and in other populations, the reader is referred elsewhere.[24,25]

Topiramate use in migraine prophylaxis has been studied in both placebo and active controlled trials. The trials will be presented based on the American Academy of Neurology classification for level of evidence (Table 1). Three large, randomized, placebo-controlled trials have established the efficacy of topiramate in the

Table 1. AAN classification of evidence for therapeutic intervention.[10]

Class I	Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: (a) Primary outcome(s) is/are clearly defined (b) Exclusion/inclusion criteria are clearly defined (c) Adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias
Class II	Prospective matched group cohort study in a representative population with masked outcome assessment that meets (a)–(d) above OR a RCT in a representative population that lacks one criteria (a)–(d).
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in are presentative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion.

prevention of migraines. The first level one evidence trial assessed the safety and efficacy of topiramate in migraine prevention. It was a randomized, double-blind, placebo-controlled, multicenter trial at 49 locations within the United States.[26] A total of 487 patients were randomized into four groups: placebo (n = 117), topiramate 50 mg/day (n = 125), 100 mg/day (n = 128) or 200 mg/day (n = 117). Topiramate was started at 25 mg/day and increased by 25 mg/week for 8 weeks until the maximum assigned dose given in divided doses in the morning and evening was reached. The primary endpoint was a decrease in mean monthly migraine frequency from baseline until the end of the six month treatment phase. The primary endpoint decreased significantly for the groups receiving topiramate 100 mg/day [mean ± SD, (5.4 ± 2.2 to 3.3 ± 2.9, $P < 0.001$)] and 200 mg/day [mean ± SD, (5.6 ± 2.6 to 3.3 ± 2.9, $P < 0.001$)]. The mean change from baseline of migraine frequency was also greater for patients who received topiramate administered in doses of 100 mg or 200 mg per day ($P < 0.001$).[26]

A second level one evidence trial assessed the efficacy and safety of topiramate for migraine prevention. The randomized, double-blind, placebo-controlled 26-week study was conducted at 52 North American clinical centers.[27] The primary outcome was the change from baseline in mean monthly migraine frequency. A total of 483 participants were randomized to one of four groups. The groups consisted of placebo (n = 114), topiramate 50 mg/day (n = 116), topiramate 100 mg/day (n = 120) and topiramate 200 mg/day (n = 117). For patients receiving the 100 mg/day of topiramate, mean migraine frequency decreased from 5.8 ± 2.6 to 3.5 ± 3.5 headaches per month. For patients receiving 200 mg/day, mean migraine frequency decreased from 5.1 ± 2.0 (SD) to 3.0 ± 2.2) headaches monthly. The change from baseline was statistically significant for patients receiving 100 mg/day ($P = 0.008$) or 200 mg/day ($P < 0.001$) doses relative to placebo. The significant decrease in monthly migraine frequency occurred within the first month of preventative therapy with topiramate at doses of 100 mg/day and 200 mg/day and continued throughout the remainder of the double-blind phase. There was also a decrease in the number of days per month that patients in the 100 mg/day ($P = 0.01$) or 200 mg/day ($P = 0.005$) needed acute migraine rescue treatment.

The third level one evidence trial examined migraine frequency after the end of prophylaxis treatment, which is typically recommended for 6 to 9 months.[28] The trial took place in 88 clinics throughout 21 countries. A total of 559 patients completed the 26-week open-label phase of the study. A total of 514 patients completed the 26-week randomized, double-blind, placebo-controlled phase of the trial. Patients were assigned to topiramate (n = 255) or placebo (n = 259).The investigators found that the mean increase in number of migraine days before and after topiramate discontinuation was greater in the placebo group (1.19 days in 4 weeks, $P < 0.0001$) compared to the topiramate (0.10 days, $P < 0.5756$) group. The investigators also discovered that topiramate has persistent effects after discontinuation because even after

therapy completion the number of migraine days per month remained less than pre-treatment values. The study participants were also given the migraine disability assessment test to assess quality of life (QOL). The results showed that QOL was higher in patients who continued treatment with topiramate than those who received placebo during the second half of the study. The authors suggest that some patients should be given the option to continue treatment past the 6 months of standard treatment.[28]

A smaller trial examined the ability of topiramate to reduce the number of headache days in chronic migraine.[29] The study design was randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to study the efficacy of topiramate in patients with chronic migraine with and without medication over use.[29] The intent-to-treat population was 32 patients in the topiramate group and 27 patients for the placebo group. Topiramate was titrated by 25 mg per week until the target dose of 100 mg per day was achieved. The duration of study treatment for the topiramate group was 100 days versus 92 days in the placebo group. The investigators concluded that topiramate significantly reduced the mean number of migraine days per month from baseline by 3.5 ± 6.3 (SD) days. The placebo group had an increase of 0.2 ± 4.7 days.[29] A significant percentage of patients (22%) who received topiramate had a 50% or more reduction in mean monthly migraine days as compared to no patients in the placebo group.[29] Study participants were also given multiple migraine related QOL questionnaires and tests. They completed the Migraine Specific Quality of Life Questionnaire (MSQ), the Headache Impact Test (HIT) and the Migraine Disability Assessment (MIDAS) questionnaire. No significant differences were found between the two groups with the MSQ or HIT. The MIDAS questionnaire reflected improvement in the topiramate group versus placebo. This trial indicates that topiramate is superior to placebo in reducing the number of headache days in patients with chronic migraine, but its effects on headache-related quality of life were not well-established.

Two studies have been conducted that compare topiramate to propranolol. The first study is a randomized, double-blind, parallel-group, multicenter trial that compared topiramate to placebo and uses propranolol as an active control. The trial was conducted in centers throughout 13 countries.[30] The core double-blind phase of the trial consisted of an 8 week titration phase and an 18 week maintenance phase. Subjects (n = 575) were randomized to receive topiramate 100 mg/day (n = 139 intent-to-treat), topiramate 200 mg/day (n = 143), propranolol 160 mg/day (n = 143) or placebo (n = 143). Topiramate also decreased average monthly migraine frequency by 1.6 headaches per month, compared to an average 0.8 headache decrease in the placebo group ($P = 0.011$). The topiramate 100 mg/day group also experienced a decrease in the number of days of rescue medication use, with 1.5 days fewer than baseline with topiramate 100 mg/day compared to 0.8 days fewer in the placebo arm. When examining the results for mean number of migraines per month, there was no difference between topiramate 100 mg/day and propranolol groups.[30] Unfortunately, a complete statistical comparison of the results between topiramate and propranolol was not conducted. When considering the results of the study, the authors advise that topiramate dosed at 100 mg/day had the best benefit-risk relationship.[30]

A second, relatively small trial compared low-dose topiramate to propranolol for migraine prophylaxis. The double-blind, randomized trial consisted of 62 patients in Iran, who were studied for a total of 8 weeks. The groups were randomized to receive topiramate 50 mg/day or propranolol 80 mg/day.[31] The patients were titrated up to these doses over a period of 1 week. The parameters examined by the investigators were average frequency of migraine per month, headache intensity, and duration of each migraine episode. Both groups reported a decrease in all of the parameters being measured. The topiramate group had a significantly larger reduction in intensity of migraine. The authors conclude that low-dose topiramate is effective for migraine prophylaxis despite larger trials that have found little to no benefit for the 50 mg/day dose of topiramate.

A prospective, observational 12 week study examined the use of topiramate for migraine prophylaxis in the Asian population.[32] Sixty subjects were started on topiramate 25 mg daily and were titrated over four weeks to an initial target daily dose of 50 or 100 mg. The mean and maximum daily doses given during the

study were 80 mg and 200 mg, respectively. The mean number of migraine attacks decreased by 1.9 in four weeks. The authors concluded that the effective daily dose in some patients was as low as 25 mg.

A single randomized trial compared topiramate and amitriptyline. This double-blind, double-dummy, parallel-group, multicenter trial was conducted as a 26-week noninferiority trial in adult migraineurs. The study included 32 sites across the United States. A total of 331 subjects with episodic migraines were included in the intention-to-treat population.[33] Subjects were divided into two groups and randomized to receive a target dose of 100 mg/day of either topiramate or amitriptyline. The intent-to-treat population included 172 patients for the topiramate arm and 159 patients for the amitriptyline arm. The primary outcome of the study, change from baseline in the number of monthly migraines, was not different between groups. The change in the mean monthly frequency of migraine episodes from the baseline was not identified to be significantly different between the two groups. There was no difference in secondary outcomes including changes from the prospective baseline phase to the end of the double-blind phase in average monthly rate of days with migraine, mean monthly headache days, mean monthly rate of acute migraine medication use, mean monthly migraine duration, and monthly migraine severity. Additional secondary variables included mean severity of migraine-associated symptoms, change in the average frequency of migraine-associated vomiting and response rates. Subjects in the topiramate group also reported a significant ($P = 0.040$) improvement in their average functional disability scores during a migraine attack compared with the amitriptyline group.[33] The authors conclude that topiramate 100 mg/day is as effective as amitriptyline 100 mg/day in reducing the average number of migraine episodes per month.[33]

An additional trial examined the use of topiramate for 14 months as an open-label extension of two large trials.[26,27,34] The primary goal was to demonstrate that topiramate is effective and well-tolerated when used up to 14 months for the prevention of migraines.[34] The study enrolled 567 patients previously enrolled in one of the two large 26-week trials conducted in the US and Canada. Patients either completed the entire 26-week trial or withdrew after 4 weeks because of lack of efficacy. The open-label extension was conducted within an 8 month time period of the subject's study completion. A physician titrated all patients up to a safe and effective dose. The level of titration was based on the patient's response. The mean daily dose during the open-label extension of the study was 150.3 mg ± 65.7 (SD). The primary outcome was the mean change in monthly migraine frequency throughout the 8-month open-label extension phase from both the double-blind baseline and the double-blind endpoint. Their study determined that the clinically significant reduction in mean monthly migraine frequency for patients who received topiramate 100 mg/day or 200 mg/day during the double-blind phase continued during the open-label extension phase. For patients receiving 100 mg/day during the double-blind phase, the mean monthly migraine frequency decreased from 3.2 headaches at the end of the double-blind phase to 2.1 headaches at the end of the open-label phase. For patients receiving 200 mg/day, the mean monthly migraine frequency decreased from 3.1 to 2.1.[34] Patients that were switched from placebo or topiramate 50 mg/day to the open-label extension topiramate dose also experienced a decrease in the average number of migraines per month. The rates of adverse events were less during this phase than the double-blind phase of the studies. The authors conclude that based on their data, topiramate has the potential to be safe and effective when used long-term.[34]

In a randomized, double-blind, placebo-controlled trial, Silberstein et al. examined the efficacy and safety of topiramate in the treatment of chronic migraine.[35] The trial consisted of 16 weeks of the double-blind phase at 46 sites within the United States.[35] A total of 328 subjects were randomized to receive placebo or topiramate at a dose of 100 mg/day. A total of 92 subjects in the original topiramate group of 165 subjects completed the study. A total of 90 subjects from the original placebo group of 163 completed the double-blind phase of treatment. The primary endpoint was change from baseline in the mean monthly number of migraine/migrainous days. Patients treated with topiramate had a statistically significant ($P = 0.010$) mean reduction of migraine/migrainous headache days compared to placebo. Topiramate patients had a mean reduction of 6.4 migraine/migrainous days per month. Placebo patients had a mean reduction of 4.7 migraine/migrainous days per month. The most common reason given for leaving the study early

was listed as inadequate efficacy.[35] The researchers completed an intent-to-treat analysis for the statistical results. The majority of this population had received either drug or placebo for approximately 85 days. Withdrawal from the study because of adverse events was 10.9% of the patients from the topiramate group, and 6.1% of patients in the placebo group. The authors conclude that topiramate was safe and well-tolerated in their group of patients suffering from chronic migraine.[35]

Safety and tolerability

Paresethesias, fatigue, gastrointestinal side effects, memory difficulty, and taste perversion are common side effects with topiramate therapy. The incidence of these side effects in patients who were receiving 100 mg per day of topiramate in one of four randomized controlled trials or the open-label extension trial is found in Table 2.[26,27,30,34,35] Only side effects with a 10% incidence or greater are included in the table. Additional trials either did not report an adverse effect that occurred in 10% or more of the study population, or a standardized dose of 100 mg per day of topiramate was not used.

During the OLE trial, upper respiratory tract infection and sinusitis occurred in 13.8% and 10.5% of patients respectively. Data for these side effects were not reported in the three large randomized controlled trials. Renal calculi were reported in a total of 10 patients out of all three randomized controlled trials. Warnings and precautions associated with topiramate therapy include metabolic acidosis, acute myopia and secondary angle closure glaucoma, oligohydrosis and hyperthermia, cognitive-related dysfunction and psychiatric disturbances.[20] The incidence of metabolic acidosis in controlled clinical trials was 15% for 50 mg per day dose. The incidence for cognitive dysfunction is 22% at a daily dose of 100 mg of topiramate.[20] Precaution should be taken when a patient receives both topiramate and valproic acid. The use of both of these medications at the same time is linked to hyperammonemia with or without encephalopathy. At the most prevalent dosing range, topiramate was not shown to significantly interact with oral contraceptives containing ethinylestradiol or norethidrone.[15] Studies have been conducted to examine additional drug-drug interactions.[36]

Upon initial approval, topiramate was designated as Pregnancy Category C by the United States Food and Drug Administration (FDA). In March 2011, the FDA changed the designation to Pregnancy Category D indicating that positive evidence of human fetal risk exists, but that the potential benefits of the use during pregnancy may outweigh the risks in some women.[20,37] New data emerged from the North American Antiepileptic Drug Pregnancy Registry indicating an increased risk of cleft lip and cleft palate in babies born to women who took topiramate during pregnancy, especially during the first trimester. The prevalence of oral clefts in infants exposed to topiramate monotherapy is 1.4%, while the prevalence in infants exposed to other antiepileptic drugs is 0.38 to 0.55%. The prevalence in infants of mothers without epilepsy or treatment with antiepileptic drugs is 0.07%.[37] Data from the UK Epilepsy and Pregnancy Register also validate the results that were reported in the United States.[38] Four out of 178 (2.2%) live births that were exposed to topiramate during the first trimester resulted in oral clefts. Topiramate is also associated with a low birth weight.

Table 2. Adverse effects of topiramate.*

	Silberstein et al[26]	Brandes et al[27]	Diener et al[30]	Rapoport et al[34]	Silberstein et al[35]
Paresthesia	59	59	55	19.1	28.8
Fatigue	14	17	19	9.9	11.9
Nausea	20	12	13	5.3	8.8
Anorexia	16	16	17	1.3	5.0
Difficulty with memory	9	12	4	3.9	6.9
Weight decrease	12	13	7	4.6	NR
Taste perversion	13	10	5	NR	9.4
Diarrhea	NR	13	NR	5.9	NR

Note: *As reported for daily dose of 100 mg, all numbers are reported as a percentage.
Abbreviation: NR, not reported.

The UK Epilepsy and Pregnancy Register report that 14.3% of infants exposed to topiramate monotherapy were small for gestational age. The effects appear to be additive with other antiepileptic drugs such that 19.4% of babies exposed to topiramate and additional antiepileptic drugs were small for gestational age.[38]

Adelman and colleagues conducted an analysis of the safety and tolerability data from more than 1500 patients that participated in the 4 controlled trials that were examining the use of topiramate for migraine prevention.[26,27,30,39] All four trials were randomized, double-blind, placebo-controlled, parallel-group studies examining the use of topiramate in migraine prevention. The early pilot trial was not published. Three of the four studies were pivotal trials, the fourth study was a pilot study conducted in the United States. The studies occurred in 111 centers across the United States and 70 centers throughout Australia, Canada, Denmark, Finland, France, Germany, Italy, Korea, the Netherlands, South Africa, Spain, Sweden, Taiwan, and the United Kingdom. The authors included all patients who took at least one dose of medication during the double-blind phase of all four studies. The authors' safety assessments were conducted from reports of adverse events, results of clinical laboratory tests, vital sign measurements, changes in body mass index (BMI) and body weight, and neurological findings. Clinical visits occurred two or three times during the titration phase and every 28 days during the maintenance phase. Laboratory tests, vital signs and body weight were recorded at every clinical visit.[39]

The most common topiramate related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, diarrhea, weight decrease, difficulty with concentration/attention and somnolence.[39] Overall, there was a dose-dependent relationship between the incidence of adverse events and topiramate dose. For patients receiving placebo, 50, 100, or 200 mg/day of topiramate, the incidence of adverse events that led to a dose reduction or temporary pause in the study was 12% for placebo, 15% for 50 mg, 20% for 100 mg and 24% for 200 mg. A serious adverse event that investigators considered unlikely to have been a result of the treatment occurred in 2% of the topiramate patients and 3% of the placebo patients. Only two patients reported metabolic acidosis. One suicide-related event was reported during the open-label extension phase. No deaths were reported. After analyzing the laboratory data, the researchers discovered a dose-dependent decrease in serum-bicarbonate levels. They also observed dose-dependent increases in serum chloride levels.[39] Renal calculus was documented in eleven patients. No cases of glaucoma, oligohydrosis/hyperthermia, or hyperammonemia were reported in any of the four studies. No clinically significant changes in vital signs or change in neurological function was reported. A significant decrease in mean body weight from baseline to the last recorded measurement was observed. Significant dose-dependent changes in body weight from baseline also occurred. The study reports that 43% of patients, who received topiramate at any dose, lost 1 to 6% of their initial body weight. Paresthesias accounted for 51% of all topiramate related adverse events for patients receiving 100 mg/day. Cognitive adverse events, which the authors defined as confusion, psychomotor slowing, difficulty with memory, difficulty with concentration/attention, and speech or language problems, occurred in 22% of patients receiving 100 mg/day. The incidence of adverse events and discontinuation because of adverse events was higher in the titration phase versus the maintenance phase of the studies. The analysis concluded that topiramate is tolerated better at doses of 100 mg/day than 200 mg/day when used for the prevention of migraine. The authors also suggest titrating to the target dose in increments of 25 mg per week. They also recommend a 2 to 3 month trial of topiramate at the target therapeutic level may be required before the maximal benefit is noticed.[39]

A small, non-randomized, prospective, open-label study at a single center in South Korea investigated the relationship between side effects and drug efficacy of topiramate in migraine prevention.[40] The researchers included 118 patients who participated in a 4-week screening phase, a 4-week titration phase to 100 mg/day, and a 20-week maintenance phase. They included subjects with more than 3 migraine episodes per month. Headache improvement was defined as a reduction in headache days of 50% or more. Patients reporting paresthesia (n = 73) reported fewer headache days then the patients not experiencing paresthesia (n = 60) both at 3 months ($P = 0.026$) and 6 months ($P = 0.002$). The patients with paresthesia also demonstrated higher responder rates at

3 and 6 months of 57.5% and 65.8%, respectively. Compared to those who did not experience paresthesia (38.3% and 41.7%). The study investigators found that patients usually experienced paresthesia during the titration phase and that the paresthesia spontaneously subsided after about 2 to 3 months of treatment. A decrease in the number of headache days did not correlate with any other side effects.[40] Based on their data, the researchers concluded that patients who experience paresthesia as a side effect displayed a significantly better response to migraine prevention with topiramate treatment. The authors stated that the patient pool was not representative of the general migraine population and suggest that additional studies should be conducted to prove their finding of a possible link between paresthesia as a side effect and efficacy of topiramate.[40]

Luykx et al compared topiramate related adverse reactions in migraine patients and epilepsy patients since both disorders share risk factors, symptoms, and preventative medications.[41] This meta-analysis included four randomized controlled trials that used topiramate as a comparator drug in epilepsy patients and six randomized controlled trials that compared the same doses of topiramate versus placebo in migraine patients. The researcher's primary objective was to determine if migraineurs are more sensitive to adverse drug reactions (ADRs) than epilepsy patients. All ten studies included in the analysis reported percentages of total adverse effects (AEs).[41] The researchers discovered some adverse effects-AEs that were reported in one group of patients and not the other. Both cognitive complaints and taste alteration were not reported in the epilepsy trials, but were reported in some migraine studies. Based on the six randomized controlled trials that the researchers examined, cognitive complaints were reported for placebo, 50 mg, 100 mg, and 200 mg at 5%, 11%, 13%, and 20% respectively. Also respectively, alteration of taste was reported as an adverse event at 1%, 14%, 7%, and 10%. Paresthesia was a side effect that was reported in both patient groups. The frequency of experiencing paresthesia as a side effect varied significantly between the disorders for all three dosages of topiramate. The authors suggest central sensitization in migraine patients is a possible mechanism as to why there are differences between migraine patients and epilepsy patients when they are given the same preventative drug.[41]

Another analysis of the data obtained from the three pivotal randomized controlled trials that established the efficacy of topiramate for migraine prevention was conducted to determine the time course of adverse events.[42] Instead of focusing on discontinuation rates as a measure of patient tolerability, the researchers chose to examine when an AE was likely to occur and the duration of the AE. The investigators defined the number of days between the start of the double-blind phase of the trials and the first reported occurrence of the AE reported paresthesia by day 31, loss of appetite by day 34, fatigue by day 39, and any cognitive symptom by day 45.[42] The majority of AEs occurred during the titration phase of the study. Throughout the duration of the studies, patients receiving topiramate 100 mg/day experienced paresthesia an average of 65 out of 182 days during the double-blind phase. Approximately 2% of patients receiving topiramate 100 mg/day discontinued treatment during the study period. Among the patients who discontinued, any cognitive symptom was listed as the primary reason, followed by fatigue and then paresthesia. Despite the fact that paresthesia was experienced more frequently, cognitive symptoms contributed more to treatment discontinuation.[42]

The Washington State Toxicology Laboratory reported data regarding topiramate-positive death investigation and impaired-driving cases.[43] Topiramate-positive findings have increased in this area because of the additional prescriptions for off-label use of topiramate. From 1998 to 2004, the laboratory reported 63 death investigations, 68 suspected impaired drivers, and one sexual assault case.[43] The mean reported serum topiramate concentration is 8.4 mg/L. In the death investigation subset, the mean range for serum concentrations is 1.25 mg/L to 180 mg/L. In the impaired driving subset, the mean range was from 1 to 20.4 mg/L. In most of the cases, the person was positive for at least one other drug, which was typically a narcotic analgesic. One of the cases was ruled as a suicide and the cause of death was ruled as quetiapine and topiramate toxicity. One death was ruled as suicide by topiramate toxicity alone. The subject's serum concentration of topiramate was 49.2 mg/L.[43] All of the people in the driving cases were noted to be extremely impaired, unable to verbalize coherently to the officer and displayed marked confusion. Alcohol was a confounding factor

in only 5 of the 68 cases. One report described a man who slurred his words, and had coordination and balance difficulties. His topiramate concentration was reported as 3.7 mg/L. It was revealed that he was also taking lamotrigine which can potentiate the actions of topiramate.[43]

A case report presented information regarding a 29 year old Caucasian female who developed myoclonus and psychosis two weeks after a 25 mg increase in her daily topiramate dose that she was taking for migraine prophylaxis.[44] The patient's admitting diagnosis was catatonia and dehydration. She had a history of cerebral palsy, migraines, chronic muscle spasticity, constipation, and depression. The patient's mother stated that her daughter started experiencing paranoid thoughts along with episodes of crying and yelling. Afterwards, she became withdrawn, anorexic, and started displaying jerking movements of her arms and head. A thorough physical exam, vital signs, and laboratory data was obtained. Laboratory data included a urine drug screen and pregnancy test, blood cell count, basic metabolic panel and liver function test. All were unremarkable except for a temperature of 38.2 ºC. Additional tests were performed to rule out other causes of the patient's symptoms. A venous ultrasound of her legs, an electroencephalogram, and a computed tomography scan of her brain did not provide any possible causes of patient's condition. A neurological exam was performed 24 hours after the patient was admitted to the hospital. The exam revealed arm jerking, lip smacking, bilateral leg myoclonus that was induced by arm and leg stimulation, severe bilateral ankle myoclonus and absent deep-tendon reflexes. The patient's home medications were reconciled and no changes had been made within the last year except for the addition of topiramate. It was concluded that a relationship existed between the patient's condition and the increase of her daily dose of topiramate. After being in the hospital for 24 hours, her daily dose of topiramate was decreased to 50 mg. The daily dose was decreased to 25 mg for four days, and then discontinued. The patient's condition was stabilized and she was discharged from the hospital 24 hours after topiramate therapy was discontinued. Follow-up visits were conducted at three and six months. The patient continued to experience depression with psychosis, but she has not experienced any additional episodes of myoclonus.[44]

A case report presented data regarding a 37 year old female with a history of bipolar disease who tried to commit suicide by ingesting a large, unknown amount of topiramate.[29] She had been prescribed topiramate 100 mg twice a day for her bipolar disorder. She was also taking diazepam and ibuprofen. The patient experienced movement in the emergency room (ER) that was interpreted as seizure activity. The patient remained unresponsive after receiving naloxone. She was intubated in order to protect her airway. An arterial blood gas drawn in the ER revealed nonanion gap metabolic acidosis. Ethanol levels were not detectable. The patient was in a coma and remained on a ventilator for 18 hours without exhibiting agitation or paralysis and without requiring sedation medications. Her brainstem reflexes, pupils, and response to painful stimuli were all intact. Liver function tests, complete blood count and coagulation studies were all within normal limits. Even though she was comatose, the patient did not exhibit respiratory depression or abnormal vital signs. The results of a comprehensive urine drug screen revealed topiramate, ibuprofen, and 10-hydroxytopiramate. Serum topiramate level was measured to be 356.6 mcg/mL. Reference range at this institution is 5–20 mcg/mL. The patient was extubated on hospital day two. The authors report that her speech was slurred for the next 24 hours. She also displayed ataxia, nystagmus, and mild persistent somnolence. All of these signs and symptoms gradually improved over the next 24 hours. Multiple serum topiramate levels were drawn in order to calculate elimination toxicokinetics. First order linear elimination was observed. The calculated serum half-life was 16 hours. The patient was transferred on hospital day 3 to an inpatient psychiatric facility. Her condition improved despite the fact she still had metabolic acidosis and and elevated topiramate levels.[45]

Patient preference

A randomized, double-blind, placebo-controlled multicenter trial in 483 patients examined the ability of topiramate to improve the daily activities of patients suffering from migraines.[46] The duration of

the trial was 13 months. The researchers utilized both disease-specific and general instruments to quantify the impact of migraine on daily activities. Patients reported data from the MSQ and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). The secondary outcome instruments included two activity-related MSQs (role restrictive and role prevention) and two activity-related SF-36 forms (role physical and vitality).[46] The improvement in scores for each questionnaire and survey were calculated by measuring the area under the curve during the maintenance phase compared to the baseline. The results from the MSQ role restrictive and role prevention domains demonstrated that patients in this trial who received any dose of topiramate (50, 100, or 200 mg/day) displayed significant improvement in various measures of their daily activities when compared to placebo. Some examples of the influence of migraine on their daily activities are present in their work, family, social activities and the physical components of their well-being. A statistically significant improvement in the SF-36 role physical domain was also reported in patients receiving 100 mg or 200 mg/day of topiramate ($P = 0.02$). At baseline, SF-36 role physical mean score was 42.5 and 42.6 for the 100 mg/day and 200 mg/day groups respectively. At endpoint, the scores had increased to 68.5 and 69.1. An increase in the SF-36 role physical score is interpreted as an improvement in functional status within the domains of physical function and role physical. As the mean monthly migraine frequency decreased for patients receiving 100 or 200 mg/day of topiramate, their functional status improved. None of the groups showed a statistical significance with respect to the SF-36 for vitality. The study provided information regarding the link between increase in productivity and decrease in migraine frequency.[46]

In a second randomized, placebo-controlled trial, Silberstein et al examined the relationship between quality of life and topiramate treatment for migraine prevention. All subjects were required to have a baseline MIDAS exam.[47] The trial examined numerous prespecified secondary outcomes. The study found that treatment with topiramate led to statistically significant increases when measuring the worst daily headache severity, severity of photophobia, frequency of vomiting, phonophobia, photophobia, monthly rate of unilateral pain, pulsatile pain, pain worsened because of physical activity, and the role function-restrictive and emotional function domains of the MSQ. The researchers also concluded that migraine therapy prophylaxis improves health-related quality of life. The improvement in their daily life is most likely a result of decrease in the severity and frequency of migraines.[47]

Another trial examined comorbidities in chronic frequent headache patients (CFH) among the general population. They also examined the impact of CFH and comorbidity on quality of life.[48] The study was conducted in the Netherlands. The researchers placed subjects in a CFH group or infrequent headache (IH) group. The most prevalent comorbidities in both groups were gastrointestinal disorders and musculoskeletal/skin disorders. CFH subjects also reported more psychiatric and somatic disorders than the IH subjects. The investigators measured quality of life by using the RAND-36 which is described as a Dutch version of Short-Form 36. They used the Cumulative Illness Rating Scale (CIRS) to measure comorbidities. All quality of life domains from the RAND-36 were negatively correlated to the CIRS score for comorbidity. In summary, comorbidities were found to negatively influence the quality of life from patient suffering from infrequent or frequent headache.[48]

Place in therapy

Several factors are critical to the selection of topiramate in patients with migraine, including comorbidities and cost. Depression, obesity, anxiety, stroke, epilepsy, sleep disorders, ulcer disease, asthma and other pain disorders are commonly associated comorbidities in patients with migraine.[49] One study evaluated the benefits and limitations of using monotherapy versus polytherapy for migraine prevention in patients with comorbid conditions.[49] Risk of treating only one condition, risk of choosing suboptimal medication, treatment timelines, and risk of poor tolerability when a third condition is present are all presented as limitations to monotherapy. Topiramate may also be an appropriate choice in patients with both epilepsy and migraine.

Cost-effectiveness of medication plays an important role in establishing its use in clinical practice for

many patients. A study was conducted to examine the cost-effectiveness of topiramate in migraine prevention. Since migraine often affects young individuals, the economic burden to employers, health systems, and society can be significant.[50] The investigators used a decision-analytical model to simulate model outcomes for patients taking topiramate over a specific duration. The model was composed of a preventative module and an acute module. The researchers also relied on pooled data obtained from two US clinical trials. Their results estimated that patients treated with topiramate 100 mg/day would experience 4.15 migraines per month versus 6 per month for untreated patients. The cost of acute treatment for topiramate-treated patients was about $27 less than the cost estimate for untreated patients.[50] Additionally, the savings in acute care costs offset about 24% of the monthly cost of drug therapy. Topiramate treatment also prevented a loss of $51 of wages per month. Total savings related to treatment with topiramate off-set approximately 68% of the $113 monthly cost of the topiramate prescription. The number of quality-adjusted life years (QALYs) gained was calculated to be 14.5 days over one year. The cost-effectiveness ratio was determined to be $26,191 per QALY.[50] The authors suggest that the cost of utilizing topiramate for migraine prophylaxis makes it a reasonable option.[50]

Based on the European Federation of Neurological Societies (EFNS) guidelines, topiramate at a recommended daily dose of 25 to 100 mg per day is an appropriate first line treatment option for the prevention of migraines with an "A" level of evidence.[51] The EFNS guidelines were last published in 2009. Level A rating is defined by the EFNS as a therapeutic intervention that is established as effective, ineffective, or harmful. A requirement to obtain the designated rating is the completion of at least one class I study that is convincing, or two consistent class II studies that are convincing.[52] According to the American Academy of Neurology (AAN) guidelines, topiramate is recommended for preventative therapy for migraines with a quality of evidence rating of C. The AAN guidelines were last published in 2000. Level C rating for quality of evidence is defined by the AAN as a recommendation in the absence of relevant randomized controlled trials. They recommend to give drugs with an evidence rating of C an adequate trial of 2 to 3 months.[10] The last publication of the evidenced-based guidelines from the American Headache Society was published in April, 2000. Topiramate was not included in these guidelines. Data from two of the large randomized controlled trials examining the efficacy of topiramate in migraine prevention were not published until 2004.[26,27] Data from a third large trial were not published until 2007.[29]

Conclusions

Migraine headache is a prevalent, disabling condition worldwide. In 2004, the number of migraine suffers worldwide was reported to be 324.1 million people.[53] Clinical evidence indicates that topiramate is an effective agent in the prevention of migraine headache in patients with headaches that affect quality of life or who are intolerant to rescue medications. It has a number of clinically significant side effects, however few patients discontinue therapy as a result. It has gained popularity over other agents in the prophylaxis and treatment of migraine headache. Relative to other agents, side effects are bothersome, but not disabling. In addition, available evidence for its efficacy in migraine provide reassurance to clinicians regarding its use in this setting. Effective use involves careful dose titration and patient counseling on the possibility of side effects.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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