Topiramate for pediatric migraine prevention

Teeranai Sakulchit MD Garth D. Meckler MD Ran D. Goldman MD FRCPC

Abstract

Question I have several teenagers in my clinic with migraine headache and some of them have frequent episodes that cause considerable interference with daily activity. I would like to offer them prophylactic therapy to reduce the frequency of their migraine episodes. Is topiramate an effective and safe option for adolescents?

Answer Both Health Canada and the US Food and Drug Administration have approved the use of topiramate for migraine prevention in adults; however, only the US Food and Drug Administration has approved topiramate for migraine prophylaxis in adolescents 12 to 17 years of age. Although several studies support its effectiveness in preventing migraine, most of these studies are small; and a recent large multicentre, randomized placebo-controlled trial was stopped early when no benefit was shown over placebo. Adverse effects of topiramate are mild and typically resolve over time. The recommended dosage is 2 mg/kg per day, up to an adult dose of 100 mg/d.

Migraine is a primary headache disorder that can cause serious impairment to quality of life in both children and adults.[1] In a review of 64 cross-sectional studies in 32 countries including more than 200 000 subjects, the prevalence of migraine in children and adolescents up to 20 years of age is reported to be 9.1%. Migraine is more common in females, with a prevalence of 10.5% compared with 7.6% in males.[1]

Migraine can occur with or without aura.[2] Migraine with aura is characterized by transient focal neurologic symptoms that typically precede but might accompany the headache, such as blurred vision, fortification spectra (zigzag lines), scotomata, pins and needles, numbness, or speech disturbances.[2] Headaches are usually recurrent, unilateral, pulsating in quality, and aggravated by normal activity such as walking or climbing stairs. Associated symptoms include nausea, vomiting, photophobia, or phonophobia. However, symptoms in children might not be typical: the headache is more often bilateral, and photophobia and phonophobia in young children might be inferred by parents from their behaviour.[2] The criterion standard for diagnosis of migraine is clinical using the *International Classification of Headache Disorders*, 3rd edition.[2]

The management of migraine consists of avoiding identified triggers (foods, sleep deprivation, dehydration, etc), abortive medication for acute headache, and consideration of prophylaxis for frequently recurring headaches.[3,4] Choices for abortive therapy include acetaminophen, ibuprofen, naproxen, triptans, and dopamine antagonists.[4]

Some guidelines suggest that prophylactic therapy should be considered in children who have more than 3 migraine attacks a month and in those who experience a considerable level of impairment owing to their headaches.[5] Categories of prophylactic agents include nutraceuticals (coenzyme Q10, riboflavin, magnesium), calcium channel blockers or β-blockers, antidepressants (amitriptyline), and anticonvulsants including valproate, levetiracetam, or topiramate.[6]

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to **www.cfp.ca** and click on the Mainpro+ link.

Cet article se trouve aussi en français à la **page 532**.

Topiramate for migraine prevention

Topiramate is hypothesized to prevent migraine by inhibiting sodium channels, increasing γ-aminobutyric acid–induced chloride flux, and inhibiting glutamate and carbonic anhydrase.[6] Topiramate has received official approval from both Health Canada and the US Food and Drug Administration for migraine prophylaxis in adults.[3,7,8] In 2014, the US Food and Drug Administration also approved it as the first drug for migraine prevention in adolescents aged 12 to 17.[8]

Efficacy of topiramate

In a study of 100 Iranian children 5 to 15 years old with migraine who were treated with topiramate (3 mg/kg per day) for 3 months, a 50% reduction in monthly headache frequency was seen in 74% of children.[9] Monthly headache frequency decreased from a mean (SD) of 15.34 (7.28) to 6.07 (3.16) attacks, headache severity levels decreased from 6.21 (1.74) to 3.15 (2.22), and headache duration decreased from 2.28 (1.55) to 0.94 (0.35) hours (all significant with a *P* value of <.05). The Pediatric Migraine Disability Assessment (PedMIDAS) score reduced from a

mean (SD) of 32.48 (9.33) to 15.54 (6.16) ($P<.05$). Adverse effects, including hyperthermia, anorexia, weight loss, and drowsiness, were documented in 21% of patients, which resolved within 1 to 2 weeks. While results were promising, this study had no control group for comparison.

Topiramate vs placebo

Several randomized controlled trials have compared the efficacy of topiramate with placebo in preventing pediatric migraine. Among 44 Indian children 8 to 14 years of age, the decrease in mean monthly migraine frequency from baseline to 4 months of treatment was significantly greater in the topiramate (100 mg/d) group compared with the placebo group ($P=.025$).[10] At least a 50% reduction in monthly migraine days was noticed in 95% of those in the topiramate group compared with 52% in the placebo group ($P=.002$). The decreases in the PedMIDAS score and school absenteeism were also significant ($P<.05$). Reported adverse effects in the topiramate group included weight loss, loss of appetite, decreased concentration in school, paresthesia, sedation, and abdominal pain. Most of these adverse effects did not result in dropout from the study or disruption of daily activities.

Conflicting results were reported in a recent multicentre study in the United States (US) comparing amitriptyline (1 mg/kg per day), topiramate (2 mg/kg per day), and placebo in 328 children and adolescents aged between 8 and 17 with migraine.[11] The proportion of children who experienced a 50% reduction in headache frequency from baseline to the final 28 days of a 24-week trial was 55% in the topiramate group versus 52% in the amitriptyline group versus 61% in the placebo group ($P=.48$), and there were no significant differences between the topiramate and placebo groups with regard to headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Adverse effects reported in the topiramate group included paresthesia and weight loss.

Topiramate vs other agents

Several studies have compared the efficacy of topiramate with other prophylactic medications for migraine.

One study with 48 children who received headache treatment with either topiramate (2 mg/kg) or sodium valproate (15 mg/kg)[12] found significant differences in the reduction of mean monthly migraine frequency, intensity, duration, and PedMIDAS score after treatment with both agents ($P<.05$); however, there was no significant difference in outcomes between topiramate and sodium valproate.

A retrospective study from South Korea evaluated 261 children and adolescents aged 6 to 18 receiving either topiramate (1 mg/kg per day) or flunarizine (5 mg/d) for at least 3 months after diagnosis of migraine.[13] The proportion of children experiencing at least a 50% reduction in headache days per month was similar between groups (81% vs 80%, respectively; $P=.71$). Drowsiness, paresthesia, memory or language decline, and anorexia were seen in 10% of children in the topiramate group, while 6% of children receiving flunarizine experienced weight gain, drowsiness, and dizziness. Adverse effects in both groups were mild and transient.

Two studies from Iran compared the efficacy of topiramate with that of propranolol. The first study included 100 children 5 to 15 years old who received either topiramate (3 mg/kg per day) or propranolol (1 mg/kg per day) for 3 months.[14] Of the children in the topiramate group, 82% had at least a 50% reduction in monthly headache frequency compared with 62% of those in the propranolol group, suggesting topiramate ($P=.02$) is more effective than propranolol for migraine prophylaxis in children. Both drugs were effective in reduction of monthly frequency, severity, and duration of headache, as well as PedMIDAS score. Both drugs were associated with transient and mild side effects, which occurred in 18% of the topiramate group (hyperthermia, anorexia, weight loss, and drowsiness) and in 10% of the propranolol group (hypotension and dizziness) ($P=.249$). Another study comparing topiramate with propranolol among children aged between 3 and 15 found both agents to be effective in reducing the frequency, severity, and duration of headache ($P=.001$), but did not find a significant difference in these outcomes between the groups ($P>.05$).[15]

Finally, a large multicentre, randomized controlled trial comparing topiramate with amitriptyline found no significant difference between agents in the proportion of children with at least a 50% reduction in the number of headache days from baseline (55% for topiramate and 52% for amitriptyline; $P=.49$) and no difference between either medication and placebo.[11] Secondary outcomes were also similar among all 3 study arms.

Safety and tolerability

The safety profile of topiramate is good. Among 12- to 65-year-old participants from several countries, dose-dependent adverse events associated with topiramate included paresthesia, fatigue, nausea, and difficulty with concentration.[16] Most withdrawals from the study that were owing to these effects occurred during the titration (23%) phase compared with the maintenance period (5%), suggesting that these symptoms were transient.

Paresthesia is common in patients taking topiramate for both migraine and epilepsy. However, 2 studies reported that patients with migraine were more likely than patients with epilepsy to report paresthesia.[17,18]

Topiramate also affects neurocognitive function. A US study analyzed these effects using the Cambridge Neuropsychological Test Automated Battery and reported that topiramate (100 mg/d) for migraine was associated with a slight increase in score, indicating slowing from

baseline when compared with placebo in 3 Cambridge Neuropsychological Test Automated Battery measures: 5-choice reaction time ($P = .028$), pattern recognition memory mean correct patency ($P = .027$), and rapid visual information processing mean latency ($P = .040$).[19] Other common cognitive and neuropsychiatric adverse events were anorexia, insomnia, and dizziness. Learning, memory, and executive function were unchanged.

Appropriate dosage of topiramate

Several studies have been conducted to find the most effective and safe dose of topiramate for pediatric migraine prophylaxis. A US retrospective study reported that most adverse effects occurred in children and adolescents who took topiramate at dosages of more than 2 mg/kg per day.[20] Similar results were also seen in a subsequent prospective study from Iran.[21] The frequency, intensity, and duration of migraine headache after treatment were not statistically different between children who received a topiramate dosage of less than 2 mg/kg per day and those who received a dosage of more than 2 mg/kg per day.

A study comparing a 100 mg/d dose of topiramate with a 50 mg/d dose for migraine prophylaxis found a statistically significant reduction in the monthly migraine attack rate and the total monthly migraine days among adolescents who received the 100 mg/d topiramate dose compared with placebo; these outcomes did not differ between those who received a 50 mg/d dose of topiramate compared with placebo.[22] Finally, a study comparing 100 mg/d and 200 mg/d doses of topiramate found no difference between these 2 doses, but it did find both doses to be statistically significantly better than placebo when comparing mean monthly migraine frequency.[23] Taken together, these studies suggest that, if topiramate is used, the target dose should be 100 mg/d.

Conclusion

Although topiramate has been approved for adult migraine prophylaxis in both Canada and the US, its use in adolescents aged 12 to 17 has been approved only in the US. While a number of studies have reported efficacy of topiramate for migraine prophylaxis, it might be equally as effective as other prophylactic agents, and a recent randomized, double-blind trial suggests that it is no more effective than placebo. Adverse effects are usually minor and resolve over time. The recommended dosage of topiramate should not exceed 2 mg/kg or 100 mg per day to avoid adverse events.

Competing interests
None declared

Correspondence
Dr Ran D. Goldman; e-mail **rgoldman@cw.bc.ca**

References

1. Wöber-Bingöl C. Epidemiology of migraine and headache in children and adolescents. *Curr Pain Headache Rep* 2013;17(6):341.
2. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33(9):629-808.
3. Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol* Sci 2012;39(2 Suppl 2):S1-59.
4. Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET, et al. Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst* Rev 2016;(4):CD005220.
5. Deaton TL, Mauro LS. Topiramate for migraine prophylaxis in pediatric patients. *Ann Pharmacother* 2014;48(5):638-43. Epub 2014 Feb 24.
6. Eiland LS, Jenkins LS, Durham SH. Pediatric migraine: pharmacologic agents for prophylaxis. *Ann Pharmacother* 2007;41(7):1181-90. Epub 2007 Jun 5.
7. Government of Canada [website]. *Details for: act topiramate*. Ottawa, ON: Government of Canada; 2016. Available from: **https://hpr-rps.hres.ca/details.php?drug productid=1910&query=topiramate**. Accessed 2017 May 2.
8. *FDA approves Topamax for migraine prevention in adolescents* [news release]. Silver Spring, MD: US Food and Drug Administration; 2014. Available from: **https://web.archive-it.org/7993/20170112222908/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391026.htm.** Accessed 2017 May 2.
9. Fallah R, Akhavan Karbasi S, Shajari A, Fromandi M. The efficacy and safety of topiramate for prophylaxis of migraine in children. *Iran J Child Neurol* 2013;7(4):7-11.
10. Lakshmi CV, Singhi P, Malhi P, Ray M. Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. *J Child Neurol* 2007;22(7):829-35.
11. Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. *N Engl J Med* 2017;376(2):115-24. Epub 2016 Oct 27.
12. Ünalp A, Uran N, Oztürk A. Comparison of the effectiveness of topiramate and sodium valproate in pediatric migraine. *J Child Neurol* 2008;23(12):1377-81.
13. Kim H, Byun SH, Kim JS, Lim BC, Chae JH, Choi J, et al. Comparison of flunarizine and topiramate for the prophylaxis of pediatric migraines. *Eur J Paediatr Neurol* 2013;17(1):45-9. Epub 2012 Oct 27.
14. Fallah R, Divanizadeh MS, Karimi M, Mirouliaei M, Shamszadeh A. Topiramate and propranolol for prophylaxis of migraine. *Indian J Pediatr* 2013;80(11):920-4. Epub 2013 Feb 15.
15. Tonekaboni SH, Ghazavi A, Fayyazi A, Khajeh A, Taghdiri MM, Abdollah Gorji F, et al. Prophylaxis of childhood migraine: topiramate versus propranolol. *Iran J Child Neurol* 2013;7(1):9-14.
16. Adelman J, Freitag FG, Lainez M, Shi Y, Ascher S, Mao L, et al. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. *Pain Med* 2008;9(2):175-85.
17. Luykx J, Mason M, Ferrari MD, Carpay J. Are migraineurs at increased risk of adverse drug responses? A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine. *Clin Pharmacol Ther* 2009;85(3):283-8. Epub 2008 Nov 5.
18. Sedighi B, Shafiei K, Azizpour I. Topiramate-induced paresthesia is more frequently reported by migraine than epileptic patients. *Neurol Sci* 2016;37(4):585-9. Epub 2016 Jan 25.
19. Pandina GJ, Ness S, Polverejan E, Yuen E, Eerdekens M, Bilder RM, et al. Cognitive effects of topiramate in migraine patients aged 12 through 17 years. *Pediatr Neurol* 2010;42(3):187-95.
20. Cruz MJ, Valencia I, Legido A, Kothare SV, Khurana DS, Yum S, et al. Efficacy and tolerability of topiramate in pediatric migraine. *Pediatr Neurol* 2009;41(3):167-70.
21. Abbaskhanian A, Sadeghi HR, Erfani A, Rezai MS. Effective dose of topiramate in pediatric migraine prophylaxis. *J Pediatr Neurosci* 2012;7(3):171-4.
22. Lewis D, Winner P, Saper J, Ness S, Polverejan E, Wang S, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. *Pediatrics* 2009;123(3):924-34.
23. Freitag FG, Forde G, Neto W, Wang DZ, Schmitt J, Wu SC, et al. Analysis of pooled data from two pivotal controlled trials on the efficacy of topiramate in the prevention of migraine. *J Am Osteopath Assoc* 2007;107(7):251-8.

Child Health Update is produced by the Pediatric Research in Emergency Therapeutics (PRETx) program (**www.pretx.org**) at the BC Children's Hospital in Vancouver, BC. **Drs Sakulchit** and **Meckler** are members and **Dr Goldman** is Director of the PRETx program. The mission of the PRETx program is to promote child health through evidence-based research in therapeutics in pediatric emergency medicine.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in children? We invite you to submit them to the PRETx program by fax at 604 875-2414; they will be addressed in future **Child Health Updates**. Published **Child Health Updates** are available on the *Canadian Family Physician* website (**www.cfp.ca**).