Migraines affect 3-11% of children and may impact school performance, social interactions, and family life. Current therapies for migraine prophylaxis include tricyclic antidepressants, β-blockers, calcium channel blockers, antihistamines, and the antiseizure medications valproic acid and topiramate. Topiramate was approved by the Food and Drug Administration (FDA) in 1996 as an antiseizure medication and later found to be an effective therapy for the prevention of migraines. Based on clinical trials in adults, the FDA approved an indication for migraine prophylaxis in 2004. Although not yet approved for this use in children, topiramate has shown promise as a means of preventing migraines in the pediatric population as well.1,2

Mechanism of Action
Topiramate has a number of physiologic effects that may play a role in migraine prevention, including dose-dependent inhibition of voltage-gated sodium and calcium channels, augmentation of GABA-induced chloride flux, and inhibition of glutamate-related excitatory neurotransmission.1-3 In addition, it produces inhibition of carbonic anhydrase.1

Pharmacokinetics
The pharmacokinetic profile of topiramate has been evaluated in adults and children. Absorption after oral administration is rapid, with a peak serum concentration occurring in 2-4 hours. Bioavailability is approximately 80% and is not altered in the presence of food. Topiramate is 15-40% protein bound; the fraction bound decreases as plasma concentrations increase. Approximately 70% of a dose is excreted in the urine as unchanged drug. Six metabolites have been identified, but are present in small quantities. The clearance of topiramate is more rapid in children than adults.1,4 In a study of 18 children 4-17 years of age, mean elimination half-life increased from 7.7-8 hours in children 4-7 years of age to 11.3-11.7 hours in children 8-11 years of age and 12.3-12.8 hours in adolescents (12-17 years of age).4

Clinical Experience
Since 2002, over two dozen studies have been published describing the use of topiramate in children with migraines.3-8 These include observational and retrospective studies, as well as randomized, blinded placebo-controlled, dose-ranging, and comparison trials. A 2008 meta-analysis of pediatric migraine prophylaxis studies identified topiramate as one of only two drugs with adequate evidence to demonstrate its efficacy in the pediatric population.14

Three placebo-controlled studies have shown the benefit of topiramate in reducing migraine frequency.3,7,8 In 2005, Winner and colleagues randomized 162 children, ages 6-15 years, with migraines to receive topiramate or placebo.7 Topiramate was initiated at 15 mg once daily and titrated to a final dose of 2-3 mg/kg/day over 8 weeks (maximum dose 200 mg/day). The final dose was then maintained for another 12 weeks. Migraine frequency decreased by a similar degree in the two groups, with a mean reduction of 2.3 migraines/month in the topiramate group and 2.0 in the placebo group (p = 0.061). There was a significant difference, however, in the percentage of patients experiencing a reduction in migraines of 75% or greater (32% of the topiramate patients versus 14% of controls, p = 0.02). There was no difference between the groups in the discontinuation rate due to lack of efficacy or adverse effects.

A second placebo-controlled topiramate trial enrolled 44 children with migraines between the ages of 8 and 14 years.5 Children in the topiramate group received an initial dose of 25 mg, with weekly titration by 25 mg-increments as needed to a maximum of 100 mg/day (given as 50 mg twice daily). This was followed by a 12-week maintenance phase. The mean reduction in migraine frequency in the topiramate group (from 16.14 ± 9.35 events per month at baseline to 4.27 ± 1.95 at completion) was significantly greater than that in the placebo group (13.38 ± 7.78 to 7.48 ± 5.94, p = 0.025). The number of patients with a 50% or greater reduction in
migraine frequency was also significantly higher in the treatment group (95.2% compared to 52.4% of controls, p = 0.002). There were no differences in migraine severity or duration, or in the number of rescue medications needed.

Impact on quality of life, as assessed by the Pediatric Migraine Disability Assessment Scale (PedMIDAS) was reduced by topiramate use. Children in the treatment group had a mean reduction in PedMIDAS score from 50.7 ± 32.1 to 10.4 ± 6.4 by the end of 4 months, while the placebo group decreased from 42.7 ± 27.5 to 23.7 ± 19.1 in the controls. School absenteeism was also significantly improved in the topiramate group, falling from 4.04 days/month at baseline to 0.38 days/month at 4 months, compared to the placebo group, where the baseline rate of 0.04 days/month had increased slightly to 0.38 days/month at 4 months (p = 0.002).3

In 2009, Lewis and colleagues reported the results of a placebo-controlled topiramate study in 103 adolescents (12-17 years of age) with migraines.8 The patients were randomized to receive topiramate, at a dose of 50 mg or 100 mg, or placebo for 16 weeks. The number of patients achieving a 50% or greater reduction in migraine frequency was 83% in the 100 mg/day group, 46% in the 50 mg/day group, and 45% in the placebo group (p = 0.002 for the 100 mg/day group and p = 0.957 for the 50 mg/day group). The patients receiving 100 mg/day had a significantly greater percent reduction in monthly migraine rate compared to placebo (median 72.2% versus 44.4%, p = 0.016). In addition, more than half of patients in the 100 mg/day group were migraine-free during the last 4 weeks of the study. None of the other outcome measures for the 50 mg/day group were significantly different from placebo. Six subjects withdrew because of adverse effects, including fatigue in two patients, and nervousness, emotional lability/depression, renal stones, and hypokalemia each in one patient. The mean weight change from baseline was 1.7 ± 3.8%, -0.1 ± 3.0%, and -0.6 ± 5.2% for the placebo, 50 mg/day, and 100 mg/day groups, respectively. No patient had a weight change of more than 10% from baseline.

In all three trials, one or more outcome measurements related to migraine frequency showed a significant improvement from baseline in the patients who received a placebo. This high rate of placebo response has also been observed in studies of acute migraine treatments, particularly in those conducted in children and adolescents. A meta-analysis of 13 pediatric acute migraine studies found a pooled placebo response rate of 46%.15

Topiramate has been compared to amitriptyline, sodium valproate, and flunarizine, a calcium channel blocker with histamine (H1) blocking properties available in other countries but classified as an orphan drug in the United States.11,13 In each of the three comparison studies, topiramate was found to produce a reduction in headache or migraine frequency equivalent to the comparator.

In 2013, Sezer and colleagues conducted a pilot study comparing topiramate to amitriptyline in children with chronic daily headaches.13 The authors randomized 57 children between 9 and 16 years of age to receive either amitriptyline 0.5 mg/kg/day or topiramate 25 mg/day initially, with titration up to 100 mg/day. After 4 months, 55% of the children given amitriptyline and 61% of those given topiramate had achieved a 50% or greater reduction in headache frequency. The number of children who were headache-free (defined as having no events in one month or more) was also similar between the groups: 28% and 31%, respectively. Adverse effects were mild, 10% of patients receiving amitriptyline and 7% of those receiving topiramate reported drowsiness, nervousness, or dizziness. No patients withdrew because of adverse effects. The mean weight change was +1.8 kg with amitriptyline and -1.1 kg with topiramate.

A multicenter study is currently underway to compare the effectiveness of topiramate, amitriptyline, and placebo in children and adolescents with migraine. The CHAMP study, sponsored by the National Institute of Neurological Disorders and Stroke and National Institutes of Health, will enroll 675 children between 8 and 17 years of age at 40 centers throughout the United States.16 The drugs will be titrated over an 8-week period to a target dose of 2 mg/kg/day for topiramate and 1 mg/kg/day for amitriptyline, then continued for a total of 24 weeks. The primary outcome measures will be the percentage of patients with a 50% or greater reduction in migraine frequency between the end of titration and the final 28 days of treatment and the mean change in PedMIDAS scores.

Warnings and Precautions
Patients taking topiramate and their families should be aware of the risk for oligohidrosis and hyperthermia associated with its use. The majority of these cases have been in children receiving topiramate for seizure prophylaxis, but it has been reported in a child enrolled in a topiramate migraine study. Elevated environmental temperatures should be avoided and caution should be used if patients require a second agent that has the potential to produce these effects, such as another carbonic anhydrase inhibitor or an anticholinergic.1

Topiramate has also been associated with the development of a hyperchloremic, non-anion gap metabolic acidosis as a result of the bicarbonate loss resulting from carbonic anhydrase inhibition. It may occur at any time, but the
majority of cases have been early in therapy. Metabolic acidosis appears to occur more frequently in younger children. In studies of children given topiramate as an antiseizure drug, up to 67% experienced a decrease in serum bicarbonate levels, with 11% having levels less than 17 mEq/L or a decrease from baseline greater than 5 mEq/L. Early symptoms of metabolic acidosis include hypoventilation and fatigue, and may progress to arrhythmias. Chronic metabolic acidosis may result in nephrolithiasis, nephrocalcinosis, osteomalacia, or impaired growth. Baseline and periodic measurement of serum bicarbonate is recommended.1

Hyperammonemia has been identified in up to 10% of children and 40% of adolescents receiving topiramate as part of an investigational program for migraine prophylaxis. This response appeared to be dose-related. Twenty-six percent of the adolescents treated with 50 mg/day and 41% of those given 100 mg/day had ammonia levels above the upper limit of normal, compared to 22% in the placebo group. Markedly elevated ammonia levels (those greater than 50% above the upper limit of normal) occurred in 6% of patients in the placebo and 50 mg/day groups and 12% of the 100 mg/day group.1 Families should be made aware of the need to bring any child receiving topiramate who develops unexplained lethargy, vomiting, or altered mental status to their healthcare provider.

As with all antiseizure drugs, topiramate carries a warning for suicidal ideation or behavior. Although rare, this has been reported with topiramate use. In the study by Winner, one patient withdrew because of suicidal ideation.7 Acute myopia and secondary angle closure glaucoma have also been reported in a small number of patients receiving topiramate.1

**Adverse Effects**

The adverse effects reported in at least 5% of children with epilepsy enrolled in topiramate trials have included somnolence (1-16%), nervousness (7%), difficulty with concentration or memory (1-10%), fatigue (5%), mood lability (1-8%), anorexia and weight loss (7-24%), nausea (5%), diarrhea (8-9%), infections (1-18%), purpura (8%), paresthesias (3-12%), gait abnormalities (5%), fever (1-12%), and cutaneous flushing (1-5%).1

Similar adverse effects have been reported in studies of topiramate for pediatric migraine prophylaxis.1-13 Somnolence has been observed in 6-20% of children, with parathesias in 2-24%. Adverse cognitive effects, including difficulties in concentration, forgetfulness, word finding, and thinking have been reported in 8-19% of children taking topiramate for migraines. While effects on cognition appear to lessen with time in many children, some have discontinued topiramate because of these effects.5 Weight loss, typically 1-2 kg, has been reported in up to 10-81% of children, with anorexia in 9-24% and abdominal pain in 8-14%.

**Drug Interactions**

Administration of topiramate with other carbonic anhydrase inhibitors, such as acetazolamide or zonisamide, or anticholinergics may increase the risk for metabolic acidosis and nephrolithiasis. The concomitant use of topiramate and valproic acid may increase the risk for hyperammonemia and encephalopathy. In an investigational treatment program of patients 1-24 months of age receiving the combination for seizures, the incidence of hyperammonemia increased with topiramate dose (0% in the placebo and the 5 mg/kg/day group, 7% in the 15 mg/kg/day group, and 17% in the 25 mg/kg/day group). The mechanism for the increased incidence of hyperammonemia with the combination is not known, but may involve an exacerbation of an underlying metabolic defect. Hypothermia has also been reported in patients taking both topiramate and valproic acid. The incidence of these reactions in patients taking lower doses for migraine prophylaxis is not known.1

Concomitant use of phenytoin or carbamazepine can decrease topiramate concentrations by 40-50%. Topiramate can decrease serum phenytoin concentrations by up to 25%. The use of valproic acid or lamotrigine can decrease topiramate concentrations by 13-14%. Adults receiving topiramate at higher doses (up to 600 mg/day) in combination with lithium were found to have an average 27% elevation in peak lithium serum concentrations. Amitriptyline concentrations may be increased when given with topiramate. While the average increase in serum concentrations is only 10%, some patients may experience a significantly greater increase.1

Topiramate may decrease concentrations of glyburide, pioglitazone, and oral contraceptives. Coadministration with metformin may decrease metformin clearance by approximately 20%. Metformin is contraindicated in patients with metabolic acidosis, which may occur with topiramate use. It is recommended that these two agents not be used in combination.1

**Availability**

Topiramate is available as the brand product (Topamax®; Janssen Pharmaceuticals, Inc.) and generics in two forms: 25 mg, 50 mg, 100 mg, and 200 mg tablets or 15 mg and 25 mg sprinkle capsules.1 A 6 mg/mL extemporaneous oral suspension of topiramate may be prepared from the tablets for patients requiring smaller doses or unable to swallow the tablets or sprinkle beads.17

**Dosing Recommendations**

The usual maintenance dose of topiramate for migraine prophylaxis in adults is 50 mg
administered twice daily. Therapy should be initiated with a gradual titration, beginning with 25 mg in the evening the first week, followed by 25 mg twice daily for a week, 25 mg in the morning and 50 mg in the evening for a week, and then the final dose of 50 mg twice daily. In pediatric studies enrolling children as young as 6 years of age, topiramate has been initiated at 15-25 mg once daily and titrated on a weekly basis to 100-200 mg/day as needed. Alternatively, a weight-based dose of 2-3 mg/kg/day may be divided and given twice daily.2,3-15

It is recommended that the dose of topiramate be reduced by 50% in patients with kidney impairment. Although plasma concentrations may be higher in patients with hepatic impairment, no specific dosing adjustment is recommended. Topiramate may be taken with or without food. The sprinkle capsules may be swallowed whole or opened and the beads swallowed with a small spoonful of soft food.1

Summary
Topiramate appears to offer a useful alternative to amitriptyline or other traditional agents for reducing the frequency of migraines. Studies conducted in children and adolescents suggest that at a dose of 2-3 mg/kg/day, topiramate is both effective and well tolerated. Results from the on-going CHAMP study should further add to our understanding of the place of topiramate in the prevention of pediatric migraine.

The editors would like to thank Dr. Howard Goodkin for reviewing this article prior to publication.

References

Formulary Update
The following actions were taken by the Pharmacy and Therapeutics Committee at their June meeting:
1. Hexaminoevulinate HCl (Cysview®) was added to the Formulary for use during cystoscopy to aid in the detection of non-muscle invasive papillary cancer of the bladder.
2. Two delayed release mesalamine products, a 400 mg capsule (Delzicol®) and a 1200 mg tablet (Lialda®), were added for the treatment of mildly- to moderately-active ulcerative colitis.
3. Cefpodoxime 100 mg/5 mL suspension and cefdinir 250 mg/5 mL suspension were added to the Formulary to provide additional options during shortages of cefpodoxime 50 mg/5 mL.
4. Ado-trastuzumab emtansine (Kadcyla™) was added for the treatment of HER2-positive metastatic breast cancer.
5. Prothrombin complex, human (Kcentra™) was approved for the reversal of vitamin K antagonists in patients with acute major bleeding. This product will not be available until its guidelines for use have been implemented.

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