Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Topiramate
June 2013

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the drug topiramate at their May 2013 meeting. Topiramate is currently FDA approved for the following indications: monotherapy for epilepsy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy in epilepsy for adults and pediatric patients (2-16 years) with partial onset seizures or primary generalized tonic-clonic seizures and patients ≥ 2 years of age with seizures associated with Lennox-Gaustaut syndrome, migraine headache prophylaxis in adults, and for weight loss (in combination with phentermine). The review focused mainly on non-approved uses of topiramate including alcohol dependence, bipolar I disorder with acute manic or mixed episodes, other mood disorders, obesity, eating disorders, adjunct agent for obese patients with diabetes mellitus type 2, pain (diabetic peripheral neuropathy), essential tremor, and prophylaxis of cluster headaches.

Discussion:
Migraine Prevention: Topiramate was found to be superior to placebo in reducing migraine frequency at doses of 100 and 200mg/day. It also was superior to placebo in reducing migraine frequency 50% or more. Topiramate was found to have similar efficacy to both propranolol and sodium valproate in preventing migraines.

Alcohol Dependence: Two studies conclude that topiramate appears to be effective in improving drinking outcomes, physical and psychosocial well-being of alcoholics and may be an effective pharmacotherapy option for alcohol dependence. Topiramate for use in alcohol dependence does need to be studied further.

Bipolar disease: A Cochrane review on bipolar disorder concluded that there is insufficient evidence for use of topiramate in any phase of bipolar illness, either in monotherapy or as adjunctive treatment. A Cochrane protocol for pharmacotherapy for bipolar disorder in older people was recently published and will likely include topiramate. NICE guidelines do not recommend topiramate for acute mania nor for promoting weight loss in patients with bipolar disease. An analysis of 4 randomized clinical trials (RCT) showed no difference in topiramate and placebo as monotherapy for acute mania with lithium being superior to both. Another 12 week RCT utilizing topiramate as an adjunct to lithium or valproate found no significant differences between topiramate and placebo.

Borderline personality disorder: NICE guidelines found no evidence to support the use of topiramate as a mood stabilizer and no good quality evidence on its acceptability and tolerability. A Cochrane review assessed the effect of topiramate on specific behaviors. Behaviors that statistically favored topiramate were interpersonal relations, impulsivity, anger, and anxiety. However, there were few trials for each behavior and had small numbers. They concluded that studies of larger numbers and longer treatment periods need to be completed.

Obesity: A meta-analysis of 10 RCTs noted increased weight loss with topiramate versus placebo. There was a lack of direct comparisons with other weight loss agents. Weight loss increased with longer treatment duration with topiramate and other agents tend to plateau at 6 months. Topiramate may be useful adjunctive agent in treating obesity, especially in people with another indication for use. Guidelines from the Endocrine Society do not recommend use of topiramate for childhood obesity.

Eating disorders: Topiramate versus placebo was looked at for binge eating disorder and the obese population. There was a statistically significant improvement in binge eating days per week in the topiramate group (median dose 300mg/day). For bulimia nervosa, topiramate showed a significant

reduction in binge and purge days versus placebo. Study authors concluded that the role of topiramate needs to be better defined in treating bulimia.

Adjunct in obese Type 2 diabetes mellitus: Topiramate was studied as add on treatment to diet and lifestyle changes or in combination with metformin. Topiramate was found to decrease both weight and A1C significantly versus placebo at both doses studied (96 and 192 mg/day). Withdrawals from the study due to adverse effects increased with increasing dose of topiramate.

Neuropathic pain: Topiramate was found to be superior to placebo in treating trigeminal neuralgia in one poor quality study. Topiramate is superior to placebo in both diabetic and postherpetic neuralgia. Doses in diabetic neuropathy studies ranged from 75 to 600mg/day. Topiramate is an option in the treatment of neuropathic pain, but should not be used first or second line.

Essential tremor: Topiramate in doses up to 400mg/day was found to reduce tremor with about 20% improvement compared to 1% with placebo in one trial. Drop out rates of 40% seen due to adverse effects in the topiramate group. The American Academy of Neurology gave topiramate a B level recommendation for use in both its original practice parameters in 2005 and in the update published in 2011. A Cochrane review is at the protocol stage.

Prophylaxis of cluster headaches: Several studies suggest that topiramate may be an effective therapy to induce remission and prevent cluster headaches. Doses started at 25 to 50mg and titrated to effect or 200mg/day. All studies included in the review were open-label. Randomized controlled trials are needed to further clarify the role of topiramate in cluster headache prophylaxis.

Adverse effects were commonly reported in all trials and are a major reason for patient self discontinuation of topiramate. Common adverse reactions include the following: paresthesias, weight decrease, fatigue, cognitive problems, difficulty with concentration/attention, confusion

Findings:
NPTC **added topiramate** to the National Core Formulary (NCF). As a result of the discussion about topiramate, the NPTC will review antiepileptic agents at a future date. The committee feels that a review of antiepileptics as a class is warranted as the NCF does not list many individual agents. The committee will also review weight loss agents at a future date, to include Qsymia (phentermine/topiramate).

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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