Commentary

Topiramate (TPM) is a sulfamate-substituted monosaccharide with utility for a variety of epilepsy syndromes, including focal-onset seizures, primary generalized tonic–clonic (GTC) seizures, and seizure types associated with the Lennox–Gastaut syndrome. It was synthesized in 1979 and approved in the United States in 1996 for adjunct use against partial-onset seizures after several multicenter trials.[1]Subsequent randomized, double-blind, multicenter trials have demonstrated safety and efficacy as monotherapy in adults and children 10 years of age and older.[2]The adverse effect profile is also well known. TPM can cause memory problems, word-finding, and calculation difficulty, confusion and concentration problems, especially when titrated too quickly. It can also cause paresthesias at the fingertips and perioral region, dysgeusia (particularly for carbonated soft drinks), renal stones (particularly in those who have had them previously), and can precipitate narrow-angle glaucoma, all likely related to its secondary action as a carbonic anhydrase inhibitor. Other "side effects" include weight loss, which may or may not be problematic, and TPM has demonstrated efficacy for prevention of migraine headaches. Given how much is already known about this well-studied drug, what can we learn from a single site, unrandomized, open-label study?

The open-label, add-on trial of TPM in this issue of *JNRP*[3] reports on 106 patients older than 2 years who were treated with TPM starting at 25 mg (or 1 mg/kg) twice a day, increasing by 50 mg daily every 2 weeks as tolerated up to a maximum of 250 mg twice a day. The treatment period lasted at least 6 months after a 12-week baseline on the existing antiepileptic drug (AED) regimen, and other AEDs were reduced if TPM resulted in seizure freedom or reduction. The population was almost 2:1 male, with median age 21.5 years and median duration of epilepsy of approximately 6-7 years. Complex partial (focal dyscognitive) seizures were the most common (53%), followed by GTC seizures (39%), with a few patients exhibiting simple partial or absence seizures. This was a relatively refractory population with 55% on 2 other AEDs and 38% on 3 or more; median seizure frequency was 6.5 per month for GTC seizures and 10 per month for partial seizures. Almost 80% of patients were classified as "responders" with 50% or greater reduction in seizure frequency. Both GTC and complex partial seizures responded well, and 2 of 3 patients with absence were responders. Seizure freedom occurred in 17% of patients with partial seizures and 12% of patients with generalized seizures. The minimum effective dose of TPM was 100 mg per day, with highest number of responders at 200 mg daily. Side effects included anorexia (37%), "giddiness" (17%), asthenia (13%), weight loss (13%), headache (12%), anxiety or insomnia (12%), paresthesias (8%), and psychomotor slowing (8%). It is unclear how much overlap exists between "giddiness," asthenia, anxiety, and psychomotor slowing; the overlap between anorexia and weight loss is probably significant. No renal stones were reported, and no patients dropped out due to adverse effects.

The high responder rate in this trial is remarkable in a refractory population on multiple AEDs. Moreover, TPM appeared to be effective in patients with a variety of seizure types of focal or generalized onset. Information is not provided about the presence of specific epilepsy syndromes, although patients with nonepileptic spells, treatable causes of seizures, or progressive neurologic disorders were excluded from the trial. Four patients with simple partial seizures maintained seizure-freedom after all of their other AEDs were tapered off, and reduction by 1 drug was possible in 47% of patients and 2 drugs in 20%.

These results are fairly typical of other adjunctive trials of TPM, both randomized and open label, and confirm that TPM has broad utility for a variety of seizure types in both adults and children, and that it is generally well tolerated. Because TPM has also shown efficacy for migraine prevention,[4] essential tremor,[5] and obesity,[6] conditions that may be comorbid with epilepsy, TPM may offer additional benefit for many patients with refractory seizures. Caution should be exercised in those with a history of renal stones, low body weight or a history of anorexia, or pre-existing cognitive difficulties.

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