TOPIRAMATE FOR MIGRAINE PROPHYLAXIS

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Abstract

Topiramate is an antiepileptic drug that is currently under evaluation for the prevention of migraine. Previous randomized, controlled studies have shown it to be effective in migraine prevention in patients with migraine diagnosed using International Headache Society criteria. The study reported here is a 56-week extension of the original double-blind, placebo-controlled trial of topiramate as preventive treatment for episodic migraine. The original double-blind phase lasted 16 weeks. The results showed continued reductions in migraine frequency during the open-label phase as well as high response rates. In the open-label study, 80% of those who had received topiramate during the entire study period (ie, double-blind and open-label) were responders. Of all patients who entered the open-label phase, 52% were responders. These findings indicate that patients who remain on topiramate for 1 year can expect sustained improvements in monthly migraine frequency and the benefits extended to those who had taken placebo originally.

To topiramate is under clinical investigation for use as a prophylactic agent for migraine and other headache disorders; however, it is currently only Food and Drug Administration approved for certain types of seizures. The exact mechanism of action of topiramate in prophylaxis is not known, but is thought to involve 1 or more of the following mechanisms: limiting sustained repetitive firing via state-dependent inhibition of voltage-dependent sodium channels; reducing amplitude of voltage-activated L-type calcium channels; potentiating gamma aminobutyric acid (GABA)-mediated chloride flux via a non-benzodiazepine site on GABA receptors; inhibiting glutamate-mediated excitation via alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid/kainite receptors; and weakly inhibiting carbonic anhydrase isoforms II and IV.

The first double-blind, placebo-controlled study of topiramate for migraine prophylaxis was published almost 1 year ago. Other studies are currently under way, but the results of several of the studies have been presented. The study reported here is a 56-week extension of the original double-blind, placebo-controlled trial of topiramate as preventive treatment for episodic migraine. In this study, patients were included if they had International Headache Society-defined migraine for more than 1 year with at least 2 migraines per month.

Concomitant prophylactic medications were permitted if the dose and type were stable for 3 months prior to enrollment. A total of 40 patients enrolled in the double-blind phase, of which 35 completed the study. A total of 30 patients enrolled in this open-label phase; the double-blind phase lasted 16 weeks.
after a 4-week baseline phase. Topiramate (100 mg bid) was given in the open-label phase for 56 weeks: 8 weeks titration and 48 weeks at maintenance dose. At the end of the double-blind phase, there were reductions in monthly migraine frequency (36% topiramate vs 14% placebo, \( P = .004 \)). The percentage of patients achieving at least a 50% reduction in monthly migraine frequency was more than 2.5 times that of those in the placebo group (26% topiramate vs 10% placebo, \( P > .05 \)).

During the open-label phase, mean monthly migraine frequency dropped to 1.7, compared with 2.0 at the end of the double-blind phase and 4.7 at baseline, for a 64% reduction since study entry. The data also showed there was a sustained benefit with topiramate treatment over 1 year. The subgroup of patients who had been taking placebo during the double-blind phase experienced a 46% reduction in mean monthly migraine frequency.

“Responders” are those who have at least a 50% reduction in monthly migraine frequency. In the open-label study, 80% of those who had received topiramate during the entire study period (ie, double-blind and open-label) were responders. Of all patients who entered the open-label phase, 52% were responders.

Minor adverse events were not unusual, with the most common being paresthesias (n = 21), followed by altered taste (n = 9), sleep disturbance (n = 6), blurred vision (n = 5), and dry mouth (n = 2). A total of 8 patients discontinued treatment, only 3 of whom discontinued were due to adverse events. The adverse events were not the cause of significant discontinuation. Another 3 patients discontinued due to protocol violations, 1 was lost to follow-up, and 1 was categorized as “other.”

These results indicate that patients who remain on topiramate for 1 year can expect sustained improvements in monthly migraine frequency. However, confirmatory data in larger patient populations is required.

**REFERENCES**