

## IS TOPIRAMATE TOPS?

**Topiramate Monotherapy in Newly Diagnosed Epilepsy in Children and Adolescents.** Glauser TA, Dlugos DJ, Dodson WE, Grinspan A, Wang S, Wu SC; EPMN-106/INT-28 Investigators. *J Child Neurol* 2007;22(6):693–699. A double-blind, dose-controlled study evaluated topiramate as monotherapy in 470 patients with newly diagnosed (3 months) epilepsy or epilepsy relapse in the absence of therapy. In addition to having at least 2 lifetime-unprovoked seizures, patients had 1 or 2 partial-onset seizures or generalized-onset tonic-clonic seizures during a 3-month retrospective baseline. The trial included a large cohort (N = 151, 32%) of children and adolescents 6 to 15 years of age. Eligible patients were randomized to treatment groups in which topiramate was titrated to target maintenance dosages of either 400 mg/day (n = 77) or 50 mg/day (n = 74). Patients were followed for at least 6 months. Based on Kaplan-Meier analyses, the primary efficacy endpoint of time to first seizure favored the higher topiramate dose in both the overall population and the cohort of children/adolescents. The probability that children/adolescents remaining in the study were seizure free at 6 months was 78% in the 50-mg target dose group and 90% with the higher dose. At 12 months, the probability of being seizure free was 62% and 85%, respectively. The incidence of treatment-limiting adverse events was 4% in the 50-mg target dose group and 14% in the group assigned to 400 mg as a target dose. The most common adverse events, excluding typical childhood illnesses, were headache, appetite decrease, weight loss, somnolence, dizziness, concentration/attention difficulty, and paresthesia. As shown in this subset analysis, topiramate is effective and well tolerated as monotherapy in children and adolescents.

## COMMENTARY

Topiramate is classified as a new antiepileptic drug (AED), although in the near future, it will lose its patent protection and be available as a generic product. In spite of the fact that the drug has been in clinical use for 10 years, much remains unknown about topiramate, such as how efficacious it is for new onset epilepsy as compared with other AEDs, especially for children. Most studies on drug efficacy for children are not performed until late in the drug's development; thus, information regarding use with children always lags behind that of adults. Furthermore, the number of child participants usually falls short of that required to adequately power a study to make a reliable assessment of the agent for this age group. In the study by Glauser and colleagues, the same problematic issues are evident. This trial is a "superiority design," or low-dose/high-dose paradigm, in which a low dose of the drug (50 mg) is compared to a high dose (400 mg); the design permits a relatively small sample size. The purpose generally is to show that the higher dose is more effective in controlling seizures than the lower dose or placebo for U.S. Food and Drug Administration (FDA) approval, as such data are required for the monotherapy labeling. Knowing that 50 mg is not as effective as 400 mg, still omits key

data on whether 100, 200, or 300 mg doses are as effective; these data potentially could avoid an overdose while identifying an optimal response. A problem with this study design is that patients in the lower dose group cannot increase their dose if they fail; thus, the outcome is inherently biased against this group. The end point measure was time to first seizure; in other words, after one seizure the patient had to exit the study. However, if tolerability issues occurred in the high-dose group, patients were allowed to stay in the study but at a lower dose (reductions up to 100 mg)—again a potential study bias. While from clinicians' perspectives, the "noninferiority clinical trial design" is a more useful clinical trial design for new onset epilepsy, it does not satisfy FDA registration requirements—thus the present study's design. However, the question remains: do the findings provide information to successfully treat a child or adolescent with new onset epilepsy?

Glauser et al. had two subsets of patients—those with partial onset seizures and those with generalized tonic-clonic seizures. Analysis was not made as to a specific syndrome classification in the generalized group, however patients with EEGs characteristic of absences or myoclonic seizures were excluded. During a 3-month baseline period, for inclusion in the study, one to two seizures were permitted, but not more, although more seizures were allowed in the time prior to enrollment. After 6 months of treatment, 78% of the 50-mg children/adolescents group and 90% of the 400-mg children/adolescents group were seizure free, while by 1 year the percentages were 62% and 85%, respectively. The results are impressive and better than

the adults assessed alone (i.e., without children/adolescents) for which only 70% were seizure free after 1 year on 400 mg/day (1). When the results were stratified into those patients with partial onset seizures and those with generalized tonic-clonic seizures, the findings then were similar, with 60% of patients in the partial group given 50 mg/day seizure free for a year and 81% in the 400 mg/day group. For the generalized tonic-clonic group, 63% were seizure free for 1 year in the 50 mg/day group and 88% seizure free in the 400 mg/day group.

The negative side effect profile for topiramate has stopped this drug from being used as a first-line therapy, particularly because of issues related to cognitive dysfunction. Indeed, in the Glauser et al. study, 20% of children/adolescents on the 400 mg dose compared with 8% at the 50 mg dose had cognitive problems. No child treated with 50 mg stopped the study because of cognitive side effects, whereas 7 on the 400 mg dose dropped out. Although patients were rated as having mild or moderate intensities of the adverse events, cognitive side effects, albeit mild, can make a significant difference in the life of a school-age child. Therefore, even if very effective, a 400-mg/day dose of topiramate cannot be a recommended starting dose for any child. In Europe, topiramate labeling indicates a starting dose as low as 100 mg; however, 50 mg is effective and may be a preferred initial dose for children, for whom reducing side effects, especially those influencing learning, is of great importance.

In all clinical trials, blood samples are taken to determine drug concentration but are not always disclosed. Therefore, it was a positive factor that Glauser et al. reported blood concentrations, with findings indicating that higher concentrations were associated with a better response to topiramate—indicating that the data could be used to determine optimal dosing. Therapeutic drug monitoring may be helpful, if low-dose topiramate is not effective.

The key points for clinicians from Glauser et al. trial include:

1. Topiramate can be effective at low doses; comparative trials indicate it is at least as good as other low-dose AEDs (2).
2. Low-dose topiramate produces fewer rates of and less intense side effects than higher doses. It is an appropriate initial low-dose treatment for a broad spectrum of seizure disorders, including partial seizures and generalized tonic-clonic seizures.
3. Children tend to respond more favorably than adults to topiramate.
4. Therapeutic drug monitoring of topiramate may be of value in determining the optimal dose, with the least side effects.

Unanswered questions include whether topiramate, or any of the other newer drugs, have antiepileptogenic effects or can prevent the development of refractory epilepsy. One way to assess these issues is to treat patients who become seizure free for 2 years, then randomize them to either stopping or continuing the drug to see if differences in relapse rates appear. Also, the newer AEDs need to be compared with each other so that useful information concerning the best choice of a first AED can be determined.

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## References

1. Arroyo S, Dodson WE, Privitera MD, Glauser T, Naritoku DK, Dlugos DJ, Wang S, Schwabe SK, Twyman RE, EPMN-106/INT-28 Investigators. A randomized dose-controlled study of topiramate as first-line therapy in epilepsy. *Acta Neurol Scand* 2005;112:214–1222.
2. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006;47:1094–1120.