

## POSTMARKETING RESULTS: USEFUL, BUT PROCEED WITH CAUTION

### Topiramate and Word-finding Difficulties in Patients with Epilepsy

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**PURPOSE:** To evaluate the prevalence of word-finding difficulties as a treatment-emergent adverse event in patients with epilepsy taking topiramate (TPM) and to identify a clinical phenotype at risk.

**METHODS:** The authors investigated the relation of word-finding difficulties with TPM titration schedule, seizure frequency and pattern, and EEG and neuroanatomic findings in 431 consecutively and prospectively collected patients taking TPM.

**RESULTS:** Thirty-one (7.2%) patients developed word-finding difficulties. Presence of simple partial seizures (OR, 6.7;  $P = 0.007$ ) and a left temporal EEG epileptic focus (OR, 5.2;  $P = 0.021$ ) were significantly associated with word-finding difficulties.

**CONCLUSIONS:** The presence of word-finding difficulties seems to be a titration schedule-independent phenomenon that occurs in a subgroup of patients with a specific biologic vulnerability.

dose. Therefore it is often necessary to use uncontrolled data from open studies or surveys to assess other risk factors. Not infrequently, such studies have taken the form of retrospective chart reviews. These studies are useful, but must be interpreted with caution, as they may be subject to bias (4,5). The method used in this study was an open, prospective survey of the first 431 patients treated at a single epilepsy center. The 31 patients with word-finding difficulty (7.2% of the sample) were compared with an age- and sex-matched group, also taking TPM, and with the TPM-treated population as a whole. This case-control method, although still subject to some bias, is certainly more rigorous than most open-label studies.

Two risk factors commonly thought to be associated with the development of word-finding difficulty (more rapid titration schedule and polytherapy) were not found to be risk factors in the Mula et al. study. Again, however, the open, uncontrolled nature of the study could have influenced these results. Selection of titration schedule is probably not completely random. Although the authors indicate that the common practice between 1995 and 1998 was to use a titration schedule of 50 mg every other week, cautious practitioners might have preferentially used slower titration schedules for patients who they thought had a greater likelihood of developing adverse events. In this case, a slower titration rate could appear to have a greater association with adverse events than a faster one. Only about one third of all patients had a 50-mg every other week starting regimen. Similar counterintuitive results have been found in other open-label studies. In a prospective evaluation of cognitive dysfunction related to TPM, Tatum and colleagues found that the highest achieved mean daily dose of TPM was substantially lower for patients who discontinued TPM than for those who remained on treatment, and more patients started on 25 mg/week dropped out than did those started on 50 mg/week (4,6). The researchers speculated that patients experiencing adverse events were less likely to achieve higher doses and that titration schedule could have been biased by physician expectations.

Presence of a left temporal electroencephalogram (EEG) focus increased the risk of word-finding difficulty. This result has biologic plausibility, because patients with preexisting language dysfunction might reasonably be expected to have greater sensitivity. However, because detection was by spontaneous patient report, it is difficult to discount the potential bias of a heightened vigilance in such patients—on the part of both the patient and the treating physician.

### COMMENTARY

The study of Mula et al. attempts to determine the risk factors associated with the development of cognitive disturbance, and specifically word-finding difficulties, resulting from treatment with topiramate (TPM). Word-finding difficulty, as an adverse event, appears to be relatively specific for TPM. It was first identified in randomized controlled trials. Even in the randomized trials, language disturbance did not surface as a common adverse event until data were pooled from several studies (1–3). The publications describing the two pivotal United States trials of TPM did not mention specific language issues, although “thinking abnormal” and “concentration impaired” were listed as dose-related problems. The short duration, limited population, and controlled methods intrinsic to these trials are not conducive to determining specific risk factors for the development of adverse events, other than relation to

Three other factors related to increased word-finding difficulty are harder to explain: family history of epilepsy, substitution rather than addition of TPM, and presence of simple partial seizures. Possibly these factors represent surrogates for other factors that were not explored. For example, family history might have been a surrogate for idiopathic generalized epilepsy, which was not evaluated. Another factor that was not explored was the impact of TPM initiation in newly diagnosed versus chronic epilepsy. Certainly patients who had never been treated before might be more or less susceptible to cognitive adverse events such as word-finding difficulty.

In summary, well-designed prospective, open studies can provide useful and important information that cannot be obtained from published randomized controlled trials. Utilization of a case-control method reduces potential bias but does not eliminate it. Any interesting result should be considered as a basis for future controlled investigation.

*by Jacqueline A. French, M.D.*

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