

## COGNITIVE EFFECTS OF LEVETIRACETAM VERSUS TOPIRAMATE

**The Influence of Antiepileptic Drugs on Cognition: A Comparison of Levetiracetam with Topiramate.** Gomer B, Wagner K, Frings L, Saar J, Carius A, Härle M, Steinhoff BJ, Schulze-Bonhage A. *Epilepsy Behav* 2007;10(3):486–494. Levetiracetam (LEV) and topiramate (TPM) are considered highly effective novel antiepileptic drugs (AEDs) in the treatment of focal epilepsies. To explore potential side effects, this study investigated their influence on cognitive functions comparatively by means of a standardized neuropsychological test battery assessing several cognitive domains. In this observational study, cognitive changes were explored in 30 consecutively recruited patients with focal epilepsy treated with LEV and in 21 patients treated with TPM, comparing functions assessed prior to gradual initiation and after reaching steady state of the individual target dosage. Before titration, patient groups did not differ significantly with respect to cognitive performance. Whereas the LEV group manifested no change in cognitive performance after AED titration, the TPM group worsened in the cognitive domains of cognitive speed and verbal fluency, as well as short-term memory. These findings suggest that TPM, unlike LEV, may impair frontal lobe functions. The lack of cognitive side effects related to LEV treatment may be relevant for treatment decisions.

### COMMENTARY

The study by Gomer and colleagues compared the cognitive effects of levetiracetam (LEV) and topiramate (TPM) by examining changes in cognitive function beginning when the antiepileptic drug (AED) was started as an adjunctive therapy for patients with focal epilepsy. They found adverse cognitive effects were worse for TPM compared with LEV. Overall, patients were more likely to experience adverse cognitive effects with TPM, but some patients on TPM exhibited improvements in cognitive scores, and less than half of the patients on TPM deteriorated more than one SD on any measure—except one, block span. Limitations of the study include its observational, unblinded, nonrandomized, parallel design with relatively small sample sizes. Despite the limitations, these comparative findings are consistent with prior studies comparing TPM with other AEDs. TPM was shown to have slightly more adverse cognitive effects than valproate (1,2) and much greater adverse effects than lamotrigine (3). Since the cognitive effects of valproate are similar to carbamazepine (4) and both LEV and lamotrigine have fewer adverse cognitive effects than carbamazepine (5,6), it is not surprising that TPM would exhibit a much greater negative impact on cognitive functioning than LEV. In addition, a pattern of particular sensitivity to tasks involving frontal lobe function previously was reported to be associated with TPM (7), although TPM-induced deficits are not limited to those related to frontal lobe function (3). Gomer et al. note a lack of cognitive side effects related to LEV. The complete lack of effects in the present study probably is due to the small sample size

and other study limitations. During other clinical trials, CNS-related adverse events have occurred, and mild adverse cognitive effects can be seen with an appropriate study design (5). Nevertheless, LEV is very well tolerated and has few cognitive side effects.

The study by Gomer et al. did not find that cognitive tasks were influenced by dosage for either TPM or LEV. The authors support their finding by stating that neither Huppertz et al. (7) nor Kockelmann et al. (8) demonstrated a “clear relationship between daily dosage and cognitive side effects.” However, neither of these studies was conclusive in this regard, as they had limitations and reported some dose-dependent adverse events. The investigation by Huppertz et al. was a nonrandomized, open-label study with only 37 patients, and the authors specifically noted that adverse cognitive effects were decreased in a subset of patients whose doses were reduced 25–150 mg/day. The investigation by Kockelmann et al. was a nonrandomized, retrospective, cross-sectional study with just 42 patients, who received neuropsychological testing only once; however, the study did report significant correlations between TPM serum levels and verbal fluency, verbal memory span, as well as verbal memory (delayed recall and recognition). A recent study by Loring et al. examined dose-dependent cognitive effects of TPM in 183 cognitively normal adults, using a double-blind, placebo-controlled, parallel group, dose-ranging study of 24 weeks duration (9). Dosing was initiated at 32 mg (16 mg/bid) and increased to target doses of 64, 96, 192, or 384 mg/day. The investigators found that the neuropsychological impairment associated with TPM emerges in a dose-dependent fashion. Thus, the lack of a dosage effect in the Gomer et al. report likely is due to the sample size and other limitations of the study.

Gomer et al. state that Aldenkamp and coworkers: “proposed that gradual introduction of TPM could prevent cognitive side effects.” Aldenkamp et al. actually stated that: “gradual

introduction of TPM can reduce the extent of cognitive impairment” (1). Gomer et al. argue against a critical effect of the initial TPM titration, since their study started with a low dose, gradual titration, and testing was carried out under steady-state conditions. The titration rate used in this study was actually twice the recommended rate, and remarkably, there were no dropouts among the 51 consecutive patients, over approximately 4 months and two neuropsychological evaluations. While rapid titration increases the risk of cognitive side effects for virtually all AEDs, these effects are particularly prominent with TPM. For example, an investigation in healthy adults found that an acute dose of TPM at 2.8 mg/kg produces greater cognitive side effects than a slower titration over 4 weeks to a higher dose of 5.7 mg/kg (10).

Gomer et al. also state that: “Loring and Meador ascribed cognitive side effects of TPM to polypharmacy, higher dosages, and blood levels” (11). This sentence does not appear in the referenced article or in any articles by these authors. Indeed, a variety of factors affect the risk of adverse cognitive function by TPM as well as other AEDs, including polypharmacy, higher dosages, higher blood levels, rapid initiation, individual patient susceptibility, and the risk for the specific AEDs (4). Treatment-emergent adverse events, which are centrally mediated, typically are more frequent in adjunctive than monotherapy clinical trials. Dosage and blood level effects on cognition can be difficult to demonstrate within standard therapeutic ranges and may also be obscured if appropriate study design is not employed. Susceptibility to adverse cognitive effects in a patient is due to their individual pharmacokinetic and pharmacodynamic responses. Finally, there are differences across individual AEDs as demonstrated in the present study and prior investigations (4). Clinician awareness of these factors may help to reduce risks of adverse cognitive effects. Drug treatment often requires a balance between the risk of seizures and the risks posed by AEDs—including systemic side effects as well as cognitive function.

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## References

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