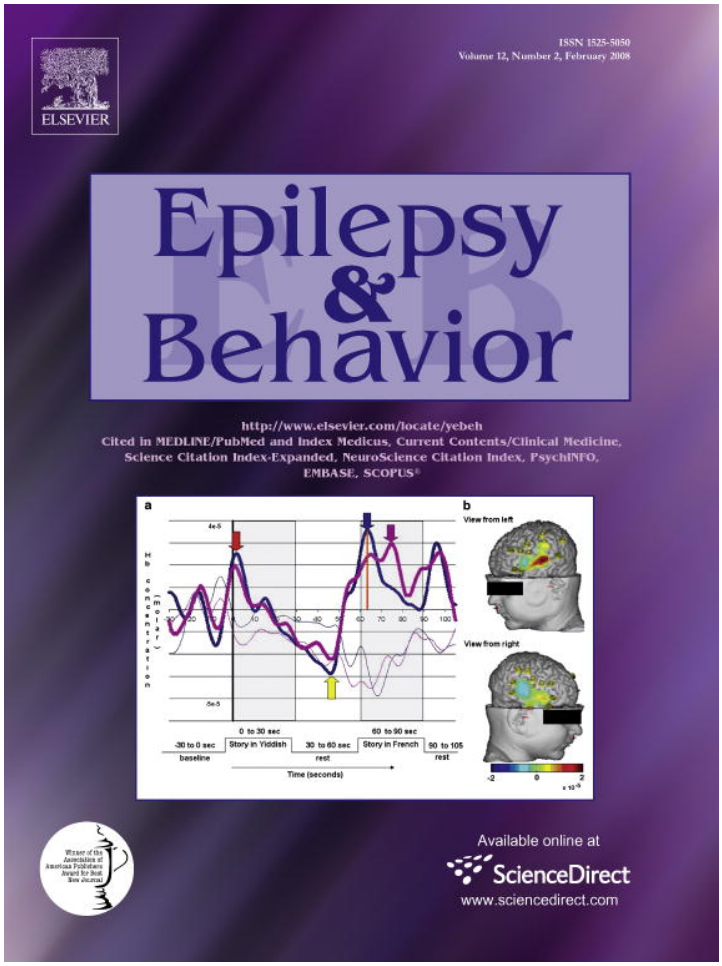

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# Topiramate in children and adolescents with epilepsy and mental retardation: A prospective study on behavior and cognitive effects

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**Abstract**

The aim of the present study was to assess the behavioral and cognitive effects following treatment with topiramate in children and adolescents with epilepsy with mild to profound mental retardation. The study group comprised 29 children, 16 males and 13 females, aged 3 to 19 years, affected by partial (4) and generalized (25) crypto/symptomatic epilepsy and mental retardation (7 mild, 5 moderate, 15 severe, 2 profound), who were administered topiramate (TPM) as add-on therapy to their baseline antiepileptic treatment. At baseline, 3 months, 6 months, and 12 months, parents or caregivers of each patient were administered a questionnaire based on the Holmfrid Quality of Life Inventory. After a 3-month follow-up, the add-on topiramate caused overall mild to moderate cognitive/behavioral worsening in about 70% of children and adolescents with mental retardation and epilepsy. After 6 and 12 months of follow-up, global worsening persisted in 31 and 20.1% of cases, respectively. In conclusion, this trial confirms that TPM can have significant adverse cognitive and behavioral side effects, even in mentally disabled children and adolescents.


*Keywords:* Topiramate; Mental retardation; Epilepsy; Behavior; Cognition

## 1. Introduction

Topiramate (TPM) is a novel antiepileptic drug that has been used successfully, either as single or an adjunctive therapy, to control both partial and generalized epileptic seizures in pediatric patients [1–14]. TPM has multiple mechanisms of action [15,16], and it has been associated with adverse effects. Among these side effects, cognitive and behavioral effects in pediatric patients, including cognitive dulling, language impairment, and irritability with sedation, have been reported. Diagnosis is undoubtedly easier in developmentally normal or mildly developmentally delayed children. Conversely, in moderate or severely mentally retarded subjects, such adverse events may be easily overlooked.

The aim of the present study was to assess the behavioral and cognitive effects following treatment with topiramate by means of an inventory including items to score the clinical changes in epilepsy in children and adolescents with mental retardation.

## 2. Methods

The study group comprised consecutive patients recruited on the basis of the following inclusion criteria: (1) age $\geqslant 3$; (2) Intelligence Quotient (IQ) $< 70$; (3) partial or generalized epilepsy with clearly recognizable and reliably documented epileptic seizures; (4) topiramate as monotherapy or as add-on therapy to no more than two baseline AEDs; (5) informed consent from parents/caregivers.

Exclusion criteria were: (1) neurometabolic or progressive neurological diseases and (2) poor compliance from parents/caregivers. The study was conducted after approval by the ethics committee of the medical faculty.

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At entry, each patient was evaluated for age, sex, type of seizures and epilepsy syndrome, seizure frequency, and awake and sleep EEG recordings. Mental level was assessed by means of Wechsler Intelligence Scale for Children—Revised or Terman–Merril test and Vineland Scale for Adaptive Behavior. Mental retardation was scored following DSM-IV-TR criteria: mild (IQ from 50–55 to 70); moderate (IQ from 35–40 to 50–55); severe (from 20–25 to 35–40); profound (below 20–25).

Before starting topiramate, seizure type and frequency, awake and sleep EEG recordings, and hematological and hepatic tests, together with blood levels of baseline AED(s), were monitored in all patients. At baseline, 3 months, 6 months, and 12 months, parents or caregivers of all patients were administered the Holmfrid Quality of Life Inventory [17]. This inventory systematically evaluates the following domains: Alertness, Concentration, Activation/Tiredness, Drowsiness, Depression, Aggressiveness, and Hyperactivity. The answers for each domain were scored on a 5-point Likert scale (from 0 = no problems to 4 = severe problems). The inventory was completed by two neuropsychologists, unaware of the clinical outcome, who read it to the parents/caregivers. A total score was calculated adding the different domain scores. The higher the score, the higher the degree of worsening.

Statistical analysis was performed with the SPSS Program for Windows. The means of paired samples at different times were compared with Student's $t$ test.

## 3. Results

Thirty-four patients were enrolled into the study. Five dropped out when TPM therapy was withdrawn within the first 2 weeks because of the following adverse side effects: marked irritability and insomnia (three patients), and seizure worsening (two patients).

The study group comprised 29 children, 16 males and 13 females, aged 3–19 years, affected by partial (4) and generalized (25) crypto-/symptomatic epilepsy and mental retardation (7 mild, 5 moderate, 15 severe, 2 profound), in whom topiramate (TPM) was added on to their baseline antiepileptic treatment. Before starting TPM, 2 patients were on monotherapy (valproate, carbamazepine) and 27 on bitherapy (valproate + phenobarbital, 4; valproate + carbamazepine, 6; valproate + lamotrigine, 3; carbamazepine + $\gamma$-vinyl-GABA, 2; carbamazepine + phenobarbital, 5; valproate + felbamate, 2; valproate + ethosuximide, 3; carbamazepine + clobazam, 2).

Brain MRI scans revealed brain atrophy in 12, hypothalamic hamartoma in 1, tuberous sclerosis in 1, cortical dysplasia in 3, ring 13 syndrome in 1, porencephaly in 2, and mesial temporal sclerosis in 2 patients.

The epilepsy diagnoses included: Lennox–Gastaut syndrome (3), severe myoclonic epilepsy in infancy (2), multifocal epileptic encephalopathy (5), generalized symptomatic epilepsy (5), gelastic epilepsy (1), and symptomatic partial epilepsy (13).

Thirteen patients (44.8%) had cerebral palsy including spastic tetraparesis (8), spastic diplegia (1), and congenital hemiplegia (4).

The mean total numbers of seizures per month were 4.7, 3.8, and 2.6, at 3, 6, and 12 months of follow-up, respectively. The mean numbers of EEG abnormalities (spikes and spike–waves) recorded at 6 and 12 months did not change significantly in the patients treated with TPM. There was no change in antiepileptic treatment throughout the trial, in all patients.

Overall, in none of our patients was there severe worsening of the total score; accordingly, slight worsening and moderate worsening were considered together. At 3 months, worsening of the total score on the questionnaire was recorded for 20 of 29 patients (69%). In the other 9 children, there were no significant changes.

At 6 months, 9 of 29 children dropped out of the study, 7 because of the persistence of seizures and 2 because of unacceptable adverse side effects (aggressiveness and psychotic-like behavior in one, decreased appetite in the other). For the remaining 20 patients, the total score remained worsened in 9 (31%) and unchanged in 11.

At 12 months, 2 more patients dropped out from TPM therapy because of poor efficacy in reducing seizure frequency. In the remaining 18 patients, the total score remained worsened in 6 (20.1%) and was unchanged in 12 (Fig. 1).

Fig. 2 illustrates how the domains of Behavior and Concentration were modified by TPM therapy. Behavior exhibited overall worsening in 19 patients (66%) at 3 months. Among the four domains of behavior, Activation/Tiredness and Drowsiness turned out to be the most affected. At 6 and 12 months of follow-up, Behavior scores remained worsened in 65 and 45% of cases, respectively.

As for the other domains, Concentration (38%) and Alertness (24%) exhibited moderate to marked worsening at 3 months. At the end of follow-up (12 months), some of the items, such as Drowsiness and Concentration, improved significantly ($P \leqslant 0.05$). Only 2 patients (6.8%) dropped out of the study because of behavioral problems (decreased appetite and psychotic-like condition, respectively).

## 4. Discussion

In the present study, topiramate as an add-on drug caused, overall, early mild to moderate cognitive/behavioral worsening in about 70% of children and adolescents with mental retardation and epilepsy. After 6 and 12 months of follow-up, global worsening persisted in 31 and 20.1% of cases, respectively. Thus, topiramate has

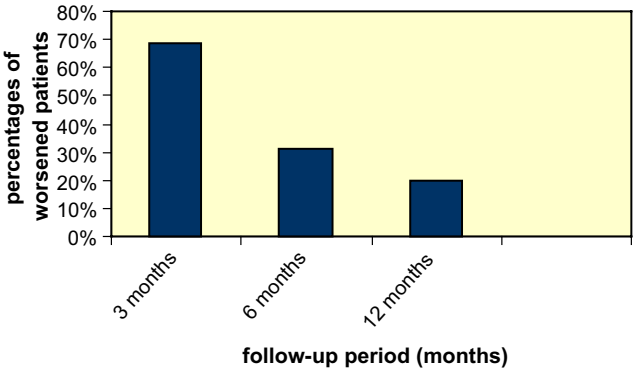


Fig. 1. Percentages of children who exhibited cognitive and behavioral worsening over the 1-year follow-up.

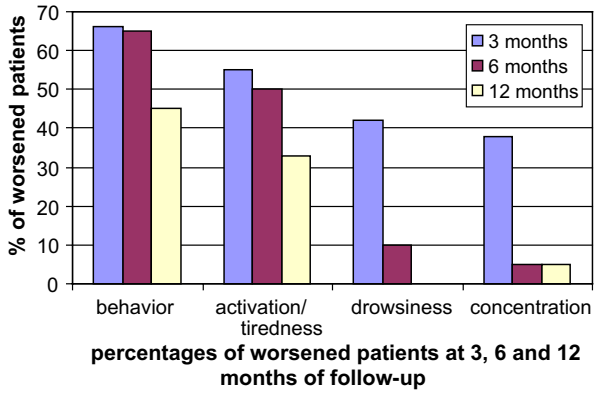


Fig. 2. Patient outcome with respect to the different domains over the 1-year follow-up.

negative cognitive and behavioral effects in a consistent percentage of these patients, and these effects, though to a lesser extent, tend to persist over time.

Concern over adverse cognitive effects in children and adolescents treated with topiramate has been reported. Indeed, Dooley et al. [5] reported significant cognitive dulling in 27% of their children with refractory epilepsy. Mohamed et al. [11] reported that most adverse events in their series were represented by behavior or cognition disorders, including depression, marked irritability or aggression, psychosis, and aphasia. Similarly, Moreland et al. [18] and Uldall and Bucholdt [13] described behavioral and cognitive side effects in 53 and 21% of their pediatric patients, respectively. Moreover, Gerber et al. [19] confirmed behavioral and cognitive abnormalities in children receiving TPM and demonstrated that a previous history of behavioral problems and concurrent use of lamotrigine may be predisposing factors. Unfortunately, we have studied only three patients treated with a combination of TPM and lamotrigine and, therefore, cannot confirm this as a predisposing factor.

Drowsiness was one of the most commonly reported adverse side effects in two controlled studies in young patients with partial epilepsy and Lennox–Gastaut syndrome, although disturbances of mood, aggressive reactions, "nervousness," and other behavioral problems were also recorded in between 10 and 21% of patients [6,8].

Interestingly, the previously reported data are mostly those of patients with normal or mildly delayed mental functioning. To our knowledge, this is the first report entirely dedicated to detection of even mild adverse effects on behavior and cognition in young patients with severe mental retardation. These effects may be easily overlooked in such patients.

The effect of adjunctive TPM therapy has been assessed only by means of parental reports; any report made by the children themselves would, of course, be unreliable. Cognitive worsening refers mainly to concentration and alertness as assessed by parents through the Holmfrid Quality of Life Inventory. Nonetheless, other studies reported that, when feasible, the general line of report was similar in adults and children [20].

Though one of the major drawbacks of this study is that TPM has been evaluated as an add-on drug, it seems partially responsible for the cognitive and behavioral changes reported by parents/caregivers. Seizures did not seem to be a significant variable influencing cognition and behavior, as seizure frequency remained substantially unchanged throughout the study in all cases. On the whole, behavior and mood were the most affected, exhibiting a persistent decline throughout the 1-year follow-up in a consistent number of patients.

Our study confirms the occurrence of these important adverse effects and demonstrates, for the first time, that these effects are present also in mentally retarded children in whom they are difficult to detect. Despite these adverse side effects, TPM was not discontinued in most of our patients because of its efficacy in reducing seizure frequency.

In conclusion, this trial confirms that TPM can cause significant adverse cognitive and behavioral side effects, even in mentally disabled children and adolescents.

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