EFFECT OF LEVETIRACETAM ON EMOTIONS AND BEHAVIOR IN CHILDREN WITH INTRACTABLE EPILEPSY

Based on a poster presented by Gustafson MC,* Ritter FJ,*† Frost M D,*† Karney V,* Hoskin C*
*Minnesota Epilepsy Group, PA of United Hospital and Children's Hospitals and Clinics, St. Paul, Minnesota; †Department of Neurology, University of Minnesota, Minneapolis

Levetiracetam is generally considered safe and effective for use in pediatric patients, a conclusion re-established most recently by our results in a study group of 22 patients aged 2 days to 22 months.1 However, retrospective reviews of the use of levetiracetam in the pediatric population have indicated that potential common side effects of this antiepileptic drug (AED) in young patients include exacerbation or development of behavioral and/or emotional problems.2,3 [Editor's note: For more background on behavioral changes after AED therapy in children, see the article by Dr Duchowny in this issue of Advanced Studies in Medicine] These AED-related changes in behavior or emotions were also confirmed in a comprehensive review of our own experience with levetiracetam for pediatric patients with both partial-onset and primary generalized seizures.4 However, alterations in behavior and emotions at a young age, especially in children with epilepsy, are often subtle and difficult to detect. Furthermore, the incidence can be impacted by premorbid or comorbid conditions as well as by dosing, titration, or polypharmacy.

To further define the nature of these important drug-related behavioral changes, we reviewed and analyzed the complete medical records of 115 children (aged 1 to 11 years) who had been treated in our clinic with levetiracetam for intractable epilepsy. In addition to basic demographic information, we sought evidence of any history of underlying behavioral or emotional problems (ie, etiology innate to the child, not precipitated by treatment) or of a history of prior medication-induced changes. The 115 patients (61 girls, 54 boys) had a mean age of 5.5 years and had previously received a median of 7.0 failed AEDs. Cognitive impairment was seen in 87% of the patients.

Overall, 23 children’s behavior and/or mood worsened with levetiracetam treatment; 25 were reported to have improved mood after beginning the AED. The negative behavioral changes included aggressiveness in 20 children, oppositional behavior in 16 children, and emotional lability in all 23 children. Emotional problems were noted most often in all those children who had worsening behavior; they were seen in isolation in 3 children.

In the 63 children (55%) with a history of behavioral or emotional problems, parents or caregivers reported that 18 (29%) experienced a worsening of these problems after levetiracetam initiation, 25 (40%) had no change, and 20 (31%) had improvements. Sixty-five percent of these 63 children with a history of past behavioral or emotional problems had previously experienced worsening of problems when given other AEDs.

In the 52 children (45%) with no underlying history of behavioral or emotional problems, parents or caregivers reported that only 5 (10%) had developed behavioral or emotional problems after levetiracetam initiation, 42 (81%) were unchanged, and 5 (10%) were improving. Thirty percent of the 52 patients in this group had previously developed behavioral or emotional problems when given other AEDs.

Thus, the percentage of children with worsening behavior or mood due to levetiracetam was significantly higher in the group with pre-existing behavioral problems (18/63, 29%) than in those without such a history (5/52, 10%) (P = .011). However, it should...
also be noted that the children with pre-existing problems had a significantly greater improvement in behavior/mood after levetiracetam treatment (20/63, 31%) versus those with no such history (5/52, 10%) (P = .04). This implies that the presence of an underlying behavioral or emotional problem predisposes children to a change—for better or worse—with levetiracetam treatment. In those children without a history of prior behavioral or emotional problems, one third had reported developing these side effects when given at least 1 previous AED, but only one tenth developed them while on levetiracetam.

Although children with adverse behavioral effects received a slightly lower median initial and maximum dose of levetiracetam than children without such effects, the changes in the behavioral or emotional status of the children did not correlate with the initial dose (median 8.6 mg/kg/day), the maximum dose (median 46.0 mg/kg/day), or the dosing titration characteristics (70% of patients increased dosing at intervals of every 2 weeks, 20% weekly, and 10% <7 days).

In summary, a history of behavioral and emotional problems may predispose children to an exacerbation of these problems when they are treated with levetiracetam. This was noted in 29% of the children in this study. Another 10% of children with no such history experienced a new onset of behavioral and emotional problems. About two thirds (65%) of children whose behavior worsened after initiation of levetiracetam had experienced a similar change following previous AED treatment courses. Researchers indicate that further studies are needed to define the risk factors that provoke behavioral problems and alter mood (sometimes positively) in children receiving AEDs.

**REFERENCES**


Diabetes and chronic (≥6 month) painful peripheral polyneuropathy. Their diabetes had been stable for at least 3 months before study entry and they were required to have an initial glycosylated hemoglobin (HbA1c) <11%. Topiramate treatment at 100, 200, or 400 mg/day lasted 18 to 22 weeks. The pooled data in this ad hoc analysis were examined to determine topiramate effects on weight and other relevant metabolic parameters.

The mean baseline BMI was 32 to 33 kg/m² in the 3 studies (range 17-65 kg/m²) and the mean baseline HbA1c was 8% (range 5%-12%), with more than half of patients (59%) being obese. Half of all patients were taking oral hypoglycemic drugs, 27% were taking insulin, and 18% to 24% were taking both forms of diabetes therapy. The mean changes in diabetic risk factors between baseline and the end of the topiramate treatment period are summarized in the Table.

As shown, mean reductions in HbA1c were clinically significant. From 39% to 55% of patients taking topiramate had clinically significant reductions in HbA1c of ≥0.7% (P<.001 vs placebo group) and 41% of those patients taking topiramate at 400 mg/day had HbA1c reductions ≥1.0% (P<.001). From 19% to 38% of patients in the topiramate treatment groups had weight loss ≥5% and 10% of those patients taking the highest dose of the AED had a weight loss of ≥10%. The degree of weight loss was dose dependent. However, the reductions in HbA1c did not correlate with weight loss, indicating that the topiramate effects on glycemic control were independent of those on weight. In terms of BMI, the mean reductions in the 385 patients whose baseline measurement was >30 kg/m² in the topiramate 100-, 200-, and 400-mg/day groups were -1.0, -1.2, and -1.5 kg/m², respectively. The topiramate-related reductions in BMI were slightly less in those patients who weighed less than 30 kg/m² at baseline.

The adverse events seen in these 3 trials with diabetic patients (≥5% incidence vs placebo) were similar to those reported in previous trials with epilepsy patients, the most common being fatigue, nausea, paresthesia, somnolence, anorexia, weight loss, and taste perversion. Reports of hypoglycemia and hyperglycemic reactions were similar for the topiramate groups and the placebo groups.

In summary, topiramate treatment significantly improved diabetic glycemic control as indicated by HbA1c over an 18- to 22-week period. Most patients reduced their HbA1c significantly (>0.5%) and lost weight during the trial period. Two to 4 of every 10 patients taking topiramate had significant weight loss (≥5% from baseline weight). As previously noted, a weight gain of just 5 kg can double the risk of diabetes. The researchers conclude that these favorable topiramate effects on the body weight and metabolic profile of patients with diabetes being treated for neuropathy may have implications for the many diabetic/overweight patients who also require treatment for epilepsy.

### REFERENCES


<table>
<thead>
<tr>
<th>Placebo</th>
<th>Topiramate 100 mg/d</th>
<th>Topiramate 200 mg/d</th>
<th>Topiramate 400 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>0</td>
<td>-0.4*</td>
<td>-0.7*</td>
</tr>
<tr>
<td>Weight (%)</td>
<td>+0.7</td>
<td>-0.7</td>
<td>-2.3</td>
</tr>
<tr>
<td>Blood pressure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>-1.9</td>
<td>-3.1</td>
<td>-8.8</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>-1.1</td>
<td>-1.9</td>
<td>-4.6</td>
</tr>
</tbody>
</table>

*P < .001.
TOLERABILITY OF LAMOTRIGINE

Based on a poster presented by Nash M,* Kustra R,† Hammer AE,† Messenheimer JA†

*Dekalb Neurology Associates LLC, Decatur, Georgia; †GlaxoSmithKline, Research Triangle Park, North Carolina

Lamotrigine is a widely used antiepileptic drug (AED) with proven efficacy and safety in a wide range of seizure types. For example, one large double-blind, parallel-group comparison of lamotrigine with phenytoin found that these agents were similarly effective as monotherapies in treating newly diagnosed patients with partial seizures or secondary or primary generalized tonic-clonic seizures.1 In this study, lamotrigine was also better tolerated and produced a lower incidence of central nervous system side effects than the older AED. Another large double-blind evaluation of lamotrigine monotherapy found it to have similar efficacy to carbamazepine monotherapy in newly diagnosed partial-onset seizures and primary generalized tonic-clonic seizures; seizure-free rates were 39% and 38%, respectively, at the end of the study.2 In addition, the adverse event rate with lamotrigine was 15% versus the 27% rate in the carbamazepine group.

Such findings in settings of controlled clinical trials have confirmed lamotrigine efficacy both as monotherapy and as an adjunctive agent for partial and secondary generalized seizures. The published results also indicate that lamotrigine may confer improved tolerability and better quality of life than some of the older AEDs. However, the patients enrolled in these rigorous double-blind clinical trials are, because of the strict inclusion and exclusion criteria built into such trials, a highly select group. Also, the main purpose of such double-blind studies performed in tightly defined settings is to determine efficacy—and not to measure the important but often neglected outcomes such as AED tolerability and patient satisfaction.

The purpose of this 16-week observational study was to evaluate lamotrigine in a diverse group of patients that is representative of the population of epilepsy patients in the general community. The sole intent of the study was to measure lamotrigine tolerability, patient satisfaction, and quality of life.

The study enrolled 547 adult patients (aged ≥16 years) from a large community neurology practice. The mean patient age was 42.7 years (range 16-93 years), the mean duration of epilepsy was 16.7 years, and the baseline seizure rate was 7.6/ month (median = 2.0/ month). All patients had partial epilepsy (simple or complex, with or without secondary generalization) and poor seizure control or unacceptable side effects on their current therapy with 1 or 2 AEDs (but not lamotrigine within previous 30 days). The most common concomitant AEDs at baseline were carbamazepine (38%), phenytoin (35%), and valproic acid (25%). Lamotrigine was titrated on an open-label basis to a mean maintenance dose of either 300 mg/ day (+/- 119) without valproic acid or 201 mg/ day (+/- 106) with valproic acid. A total of 421 patients completed the adjunctive treatment phase and 126 discontinued prematurely (including 60 [11%] due to lamotrigine-related adverse effects, 58 for administrative reasons, and 15 other). As summarized here, 4 types of outcome assessments were made at baseline and then again at the end of the 16-week adjunctive therapy period.

- In the Liverpool Adverse Experience Profile, significant improvements (P<.05) were noted in 18 of 19 domains from the time of screening to the end of the lamotrigine treatment period. For example, positive changes indicating an improvement in adverse events were noted in unsteadiness, tiredness, restlessness, sleepiness, memory problems, weight gain, and difficulty in concentration. The improvement in the category of disturbed sleep was not statistically significant.
- In the Quality of Life in Epilepsy-31 instrument, treatment-related improvement was noted in all domains (P<.01) and 76% of patients experienced an improvement in overall quality of life.
- In the self-rated patient satisfaction measurement, significant improvements (P<.01) were noted at the end of the lamotrigine adjunctive treatment period (eg, fewer patients dissatisfied with treatment and more patients satisfied).
- In the investigator's global assessment of patient clinical status, the majority of patients were rated as having improvements (P<.01) in overall status as well as specific domains such as adverse events, intellectual functioning, seizure duration, seizure frequency, and seizure intensity. However, 50% or more of the patients had no change on scales of motor functioning or social functioning.
The researchers conclude that the majority of patients with partial seizures who add lamotrigine to their current AED therapy will have improved tolerability due to a reduction in adverse events, an overall improvement in quality of life, and increased satisfaction with the AED treatment.

REFERENCES


ADD-ON TOPIRAMATE IN CHILDREN WITH REFRACTORY EPILEPSY

Based on a poster presented by Guerreiro MM,* Squires L,† and Mohandoss E†

*Universidad Estadual de Campinas, Sao Paulo, Brazil; †Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey

Double-blind, placebo-controlled trials have documented the efficacy of topiramate in children with partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Data from smaller pilot studies also suggest effectiveness of this antiepileptic drug (AED) in a range of pediatric epilepsy settings.1-5 To provide further guidance to clinicians on the use of topiramate in nonresearch clinical settings, this study evaluated a planned 6 months of topiramate add-on therapy in children and adolescents (aged 1-18 years) with inadequately controlled epilepsy characterized by partial-onset, generalized tonic-clonic, myoclonic, tonic, or absence seizures. The prospective, open-label, multicenter study enrolled patients whose seizures were inadequately controlled with 1 or more AEDs. Topiramate was titrated weekly in 15- or 25-mg increments to 100 mg/day and then increased weekly in 25- or 50-mg increments to the optimal or maximal tolerated doses (maximum 24 mg/kg/day).

A total of 554 patients were enrolled, 69% with partial-onset seizures and the remainder with generalized seizures. Mean age was 8.7 years. Baseline AEDs included valproate (44%), lamotrigine (30%), carbamazepine (28%), clobazam (19%), and vigabatrin (11%). The median topiramate daily dosage was 4.5 mg/kg/day and the median treatment duration was 8 months.

Analysis of preliminary results from this ongoing trial indicates that topiramate was confirmed effective as adjunctive therapy in a broad spectrum of seizures associated with childhood epilepsy. Overall, 66% of patients with partial-onset seizures and 58% of patients with generalized seizures had a clinically significant response (≥50% reduction in seizures). For most specific seizure types, 50% to 70% of children/adolescents had a significant response to topiramate in terms of seizure frequency and, as with other AEDs, tonic and atonic seizures appeared most resistant to topiramate. At 6 months, 8% of all patients with partial-onset seizures and 13% of all patients with generalized seizures were considered seizure-free. Only 7% of patients discontinued topiramate due to inadequate seizure control during treatment periods that were, in some cases, as long as 2.5 years. According to parents, more than half of the patients had minimal, moderate, or marked improvements in alertness (59%), daily activity performance (68%), interaction with the environment (64%), and response to verbal requests (75%).

The most common adverse events in this trial were loss of appetite (25%), somnolence (21%), upper respiratory tract infection (14%), fatigue (10%), fever (10%), and weight loss (10%). Cognitive and behavioral effects included nervousness (8%), psychomotor slowing (6%), and difficulty with attention/concentration (5%). Nine percent of patients discontinued topiramate due to adverse events, mostly due to appetite loss (3%). However, a close evaluation of weight and body mass index (BMI) changes over the course of the study showed that patients with the lowest BMI percentiles at baseline were the least likely to experience weight loss and most likely to show weight gain. The BMI was reduced to the underweight (ie, <5th) percentile in only 6% of children.
The researchers conclude that topiramate is useful in a spectrum of seizures associated with childhood epilepsy. The low rate of discontinuations due to side effects and the low incidence of cognitive/behavioral effects underscore the tolerability of this AED in children and adolescents with refractory seizures.

REFERENCES


EFFECTS OF ZONISAMIDE ON COGNITIVE FUNCTION

Based on a poster presented by Weatherly G,* Risse GL,* Carlson BE,* Gustafson MC,* Penovich PE†
*Minnnesota Epilepsy Group, PA of United Hospital and Children's Hospitals and Clinics, St. Paul, Minnesota; †University of Minnesota, Minneapolis

Many antiepileptic drugs (AEDs) are associated with impaired cognitive outcomes. Impaired attention, vigilance, and psychomotor speed have all been attributed to the older AEDs (e.g., phenobarbital, phenytoin). The underlying mechanism of such cognitive changes may relate to impaired neuronal excitability. The incidence and speed of onset of these AED adverse clinical effects may depend on factors such as individual AED, the speed of titration, the use of higher doses, and polypharmacy. Cognitive changes can be subtle and difficult to detect. Furthermore, in nonstudy clinical settings, neurologists may also have trouble linking signs of faulty cognition to the AEDs (versus, for example, a connection to ongoing seizures or to underlying comorbid conditions). Despite the difficulty of monitoring AED impact on cognitive outcomes, such ongoing evaluations are needed to help clinicians perceive the full balance between AED efficacy and safety—including impacts on cognition and quality of life.

Few empirical studies have evaluated the cognitive effects of newer AEDs despite a fairly common clinical perception that the entire class continues to cause these problems. One small study found that zonisamide negatively affected verbal learning but did not affect previously learned material (e.g., vocabulary) or psychomotor performance. The degree of impairment was related to the minimum plasma concentration. The purpose of this study was to investigate the effects of zonisamide on distinct and quantifiable aspects of cognitive function in epilepsy patients being treated with a variety of concomitant AEDs.

Researchers evaluated the records of 20 patients (7 men, 13 women) who had been administered a battery of neuropsychological tests prior to and during zonisamide therapy for partial-onset seizures. Patients' ages ranged from 20 years to 76 years (mean age 39.6 years). All patients had baseline IQ's greater than 70. The mean time from zonisamide initiation to the time of the second test was 117 days (range 3-429 days). Mean zonisamide dosage at the time of testing was 405 mg/day (range 100-800 mg/day). Eighteen of 20 (90%) patients were taking at least 1 other AED (median = 2) at the time of the baseline evaluation; these included phenytoin (9 patients), carbamazepine (6), divalproex/valproic acid (5), lamotrigine (5), and 8 other AEDs.

The mean scores on all tests declined after zonisamide initiation relative to baseline: animal naming —6%; controlled oral word association (COWA) —29%; digit span —28%, digit symbol-coding —8%, grooved pegboard —2% to 3%. The reductions in COWA (P = .001) and digit span (P < .001) were statistically significant and indicated declines in verbal fluency and working memory, respectively. These 2 tests also had the highest percentage of patients with a ≥25% decline after the introduction of zonisamide: 70% (14/20) for digit span and 55% (11/20) for COWA. Thus, cognitive processing as
opposed to psychomotor speed (eg, visuomotor processing as measured by digit symbol-coding test) appears to be most sensitive to zonisamide adjunctive therapy.

The researchers conclude that zonisamide, when used in settings reflective of everyday clinical practice (ie, combined with other AEDs for intractable epilepsy cases), may be associated with cognitive decline. However, other factors that may have contributed to cognitive changes during zonisamide therapy include changes in concomitant therapy and interactions between zonisamide and the other AEDs. The wide variation in timing of neuropsychological testing also may have influenced the patients’ results on the range of tests. Future investigations focusing on the effects of zonisamide monotherapy—with specific attention to dosage, titration, and therapy duration—should elucidate the cognitive impacts of this AED in the epilepsy population. Monitoring patients’ subjective complaints of cognitive change will provide further relevant information.

REFERENCES