SWITCHING FROM IMMEDIATE-RELEASE TO EXTENDED-RELEASE CARBAMAZEPINE: EVALUATION OF SAFETY, EFFICACY, AND TOLERABILITY IN ADOLESCENTS WITH EPILEPSY

Based on a poster presented by Wheless J
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Carbamazepine (CBZ) is a well-established, effective first-line treatment for partial and generalized tonic-clonic seizures. Poor patient compliance with 3- and 4-times daily medication regimens increases the risk of large fluctuations in plasma concentrations of CBZ, which may vary as much as 2.5-fold from peak to trough. Low trough levels can also potentially increase the risk of breakthrough seizures. CBZ extended-release capsules (CBZ-ERC) consist of 3 different types of beads (uncoated immediate release, polymer-coated extended release, and pH-sensitive coated enteric release) designed to deliver CBZ beyond 12 hours. The objective of this study was to measure efficacy, safety, tolerability, and quality-of-life (QOL) data in adolescents switched from treatment with immediate-release CBZ (IR-CBZ) to an equal total daily dose (TDD) of CBZ-ERC at a minimum of 400 mg/d.

All patients enrolled in the study were aged 2 to 17 years, had a history of partial epilepsy, and had been prescribed IR-CBZ at a TDD of 400 mg or more for at least 3 months before screening. Enrolled patients could not take more than 1 concomitant antiepileptic drug during the course of the study. Upon initiation of the study, subjects switched from their prior IR-CBZ product to an equal TDD of CBZ-ERC administered twice daily. Assessment performed at baseline (month 0) and at end of study (month 3) included seizure diary, Hague side effects (HASES) and seizure severity (HASS) scales, and the QOL in Epilepsy Inventory–Adolescents (QOLIE-AD-48).

Subjects, physicians, and parents completed a treatment satisfaction instrument using a 6-point Likert scale with responses ranging from “strongly agree” to “strongly disagree” to evaluate benefits of the medication switch, and a 3-point scale with a choice of the responses “new medication,” “previous medication,” and “equal preference” used to evaluate medication preference.

Thirty-nine patients were enrolled in the study. Mean age of the subject group was 14.4 ± 1.7 years (mean ± SD). Thirty-six percent of subjects were female, with 61.5% reporting white ethnicity, 20.5% African American, and 18% of Latin or other ethnicity. The intent-to-treat population (n = 38) included only subjects with 1 or more seizure diary cards completed post-baseline. A decrease in monthly seizure count was noted over the 3-month study period among patients switched from IR-CBZ to CBZ-ERC therapy, although this decrease was not statistically significant.

Significant improvements occurred in the sedation and confusion subscales and total score of the HASES at study endpoint (P < .01). Mild improvements also occurred in vertigo, ataxia, and diplopia subscales of the HASES and in ictal and predominantly postictal categories of the HASS, but they did not reach statistical significance. Improvement was seen in all 8 multi-item QOLIE-AD-48 scales at the end of the study period, although statistical significance was achieved only in epilepsy impact (P < .05) and health perception (P < .01). Overall results from the medication satisfaction questionnaires indicate that most patients, parents, and physicians were satisfied with the patient’s medication at endpoint compared to baseline, with CBZ-ERC preferred by each of the 3 subpopulations (adolescents 79% vs 9% [P < .0001]; parents 79% vs 3% [P < .001]; physicians 87% vs 3% [P < .001]).

Quality-of-life scores indicate that switching from IR-CBZ to CBZ-ERC resulted in a greater QOL attrib-
utable to decreased frequency of seizures and reduced side effects. The ease of a twice-daily regimen compared to the more frequent dosing of IR-CBZ formulations is also a benefit that may lead to increased medication compliance. All of these factors contributed to improved patient, parent, and physician satisfaction with CBZ-ERC versus IR-CBZ.

REFERENCES

CONVERSION TO LAMOTRIGINE MONOTHERAPY FROM VALPROATE MONOTHERAPY IN ADOLESCENTS WITH EPILEPSY

Based on a poster presented by Fakhoury T, Baumann R, Vuong A, Hammer A, Mesenheimer J
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Valproic acid (VPA) slows the rate of lamotrigine (LTG) clearance from the body. During treatment for epilepsy, some patients treated with VPA may undergo conversion to LTG monotherapy, although no controlled clinical trials conducted to date have explored LTG plasma concentrations during this conversion process. This investigation sought to describe the outcome of clinical use of an algorithm for conversion to LTG from VPA during treatment of adolescent patients with epilepsy.

The conversion algorithm used in this study was recently approved by the US Food and Drug Administration (FDA). This investigation was conducted as an open-label evaluation of patients age 16 years or older and was composed of the following 4 phases: initial screening; an 8-week LTG escalation period; a VPA withdrawal phase (≤6 weeks); and a 4-week LTG monotherapy phase. The algorithm used for the conversion from LTG to VPA was composed of the following steps: (Continued...)
**Efficacy of Zonisamide in Juvenile Myoclonic Epilepsy**

*Based on a poster presented by Kothare S, Valencia I, Khurana D, Hardison H, Melvin J, Legido A*

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Juvenile myoclonic epilepsy (JME) occurs in 5% to 11% of patients with epilepsy and is considered an hereditary idiopathic generalized epilepsy syndrome. Characteristic features of this syndrome include myoclonic jerks (100%), generalized tonic-clonic (GTC) seizures (80%), absence seizures (25%), and abnormal photoparoxysmal response (40%). The recommended treatment for JME is valproate (VPA). Recently, topiramate and lamotrigine also have proven effective in treating JME. Zonisamide (ZNS) is a new antiepileptic drug with multiple mechanisms of action, including an effect on voltage-dependent T-type calcium channels. Existing medical literature suggests that ZNS may be efficacious in primary generalized epilepsy. The objective of this study was to evaluate the efficacy of ZNS in the treatment of JME.

Investigators retrospectively evaluated medical records of patients diagnosed with JME and treated with ZNS at St. Christopher’s Hospital for Children in Philadelphia between 2001 and 2003. Diagnosis of JME was based on International Classification of Epilepsies criteria and supporting electroencephalogram (EEG) findings. Patients with GTC, myoclonic, and absence seizures were evaluated. Seizure counts were recorded from patient diaries at baseline and during treatment to assess GTC incidence and early morning myoclonic seizures. Subjects included 3 males and 12 females age 11 to 20 years receiving ZNS doses ranging from 200 to 500 mg/day (2.0–8.5 mg/kg/day). Patients’ treatment doses were increased by 50 to 100 mg every 2 weeks during the study period until maximum therapeutic effect was attained. Thirteen patients received ZNS monotherapy and 2 patients received ZNS adjunctively with VPA in cases in which ZNS was added after VPA failed to control seizures. Follow-up continued for an average of 12 months (range 2–24 months). Seizure reduction was as follows: 100% in 6 (40%), 75% in 3 (20%), 50% in 1 (7%), and 25% or less in 3 (20%) patients.

Overall, 80% of patients on ZNS monotherapy demonstrated good control (>250% seizure reduction). Sixty-nine percent, 62%, and 38% of patients were free of GTC, myoclonic, and absence seizures, respectively. Seizure control was achieved within 4 to 8 weeks of attaining the maintenance dose. One of 2 patients on polytherapy demonstrated a 75% reduction in seizure frequency, whereas the other patient demonstrated no response. One patient discontinued ZNS and was switched to VPA because of poor seizure control. No significant side effects or ZNS-VPA interactions were noted during the study.

Zonisamide was effective and well tolerated in the treatment of these patients. Ease of titration, good safety profile, once-daily dosing, lack of significant interaction with VPA, and short latency for onset of efficacy make ZNS an attractive therapeutic alternative for patients with JME.

**REFERENCES**


**Treatment with Topiramate versus Valproate in Juvenile Myoclonic Epilepsy**

*Based on a poster presented by Levisohn R,* Holland K,† Hulihan J,‡ Fisher A§

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Juvenile myoclonic epilepsy (JME) is an idiopathic epilepsy syndrome that is associated with a lifelong risk of seizures. Thus, patients with JME face indefinite treatment with antiepileptic medication. Commonly, valproate (VPA) is used for treatment of JME based on
a long history of effectiveness, although no evidence-based studies exist to support its use. Some patients do not tolerate VPA and some continue to have seizures while on this agent, thus alternative treatment is needed. This investigation explores whether topiramate (TPM) offers a useful therapeutic alternative to VPA in the treatment of patients with JME.

In this pilot study, patients with JME (untreated or on an antiepileptic agent other than TPM or VPA) were randomized to receive open-label treatment with TPM or VPA. In each instance, the study drug dosage was titrated to effective levels over a 14-week period, then maintained for an additional 12 weeks.

Overall, 28 patients were included in the study. The median age of participants was 15 years (range 9–42 years) for patients treated with TPM, and 16 years (range 12–34 years) for those patients treated with VPA. Seven patients in the TPM treatment group and receiving VPA dropped out of the trial for various reasons. Adverse events (AEs) were the identified cause of study discontinuation for 2 patients treated with TPM and 1 patient treated with VPA. Among patients completing the study, the median final dose administered was 250 mg/day (TPM: range 100–500 mg/day) and 750 mg/day (VPA: range 500–1000 mg/day). During the 12-week maintenance period, 9 of 19 patients treated with TPM and 3 of 9 patients treated with VPA were seizure-free. Baseline myoclonic, primary generalized tonic-clonic, and absence seizures were completely controlled in 7 of 14, 8 of 12, and 2 of 2 patients treated with TPM, respectively. Complete control of these 3 seizure types was attained in 6 of 9, 3 of 4, and 1 of 2 patients treated with VPA, respectively. Headache (n = 5) and concentration/attention difficulty (n = 3) were the most common AEs observed during the study (ie, occurring in more than 2 patients). The most common AEs reported among patients treated with VPA were fatigue (n = 3), nausea (n = 3), and alopecia (n = 3). Patients treated with TPM lost an average of 4 kg of body weight during the study, whereas those patients receiving VPA gained an average of 5 kg (P ≤ 0.001). Neurotoxicity scores did not differ substantially between patient groups, but systemic toxicity scores were significantly higher among subjects treated with VPA.

These preliminary findings suggest that TPM and VPA are similarly effective in the treatment of JME but have different AE profiles. These conclusions should be confirmed in a larger population of patients with JME in the setting of a randomized clinical trial.

**Efficacy and Tolerability of Topiramate in Children Younger than 2 Years of Age**

*Based on a poster presented by del Carmen Fons M, Valencia I, Kothare S, Khurana D, Yum S, Hardison H, Legido A
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Topiramate (TPM) is a new antiepileptic drug (AED) that has demonstrated efficacy and tolerability in older children and adults. Experience in children younger than 2 years is limited, and long-term efficacy and side effects in this age group have not been well established. The objective of this study was to evaluate the efficacy and tolerability of TPM as an alternative antiepileptic treatment in a pediatric population younger than 2 years of age.

Investigators retrospectively reviewed medical records of children with epilepsy younger than 2 years treated at St. Christopher’s Hospital for Children in Philadelphia between 2001 and 2003. All the relevant demographic and clinical data were entered into a database and subsequently analyzed.

Thirteen children with epilepsy (5 boys and 8 girls) were treated with TPM during the study period. Seventy-six percent of these enrolled patients demonstrated some degree of developmental delay. Seizure types diagnosed in the study group included partial seizures (n = 5), generalized tonic-clonic seizures (n = 3), myoclonic seizures (n = 1), and infantile spasms (n = 4). Mean age at seizure onset was 9.7 months (range 0–23 months). TPM therapy was initiated at a mean age of 11.8 months (range 4–24 months). The number of previous AEDs before TPM therapy was 0 in 4 children, 1 in 6 children, 2 in 2 children, and 4 in 1 child, and 1 child had been previously treated with the ketogenic diet. TPM was used as monotherapy in 7 children, and as adjunctive therapy in 6 children (range of concomitant AEDs, 1–4). Mean duration of clinical follow-up was 10 months. The mean dose of TPM was 8.8 mg/kg/day (range 2.5–18 mg/kg/day).

The degree of seizure reduction was as follows: greater than 95% in 4 children (31%), 75% in 1 child (7.5%), 50% to 75% in 4 children (31%), 50% in 1 child (7.5%), and less than 25% in 3 children (23%). Overall, 77% of patients showed good seizure control (>50% reduction), including 85% of those children on monotherapy and 65% of children on...
polytherapy. Three of 4 patients (75%) with infantile spasms (1 cryptogenic and 1 symptomatic) attained complete seizure control. Adverse effects, including lethargy, hyperthermia, and anorexia, occurred in 2 children. These side effects improved after dosage decreases in both cases. TPM treatment was discontinued in 1 patient because of lack of efficacy.

In children younger than 2 years, TPM was an efficacious and safe option for treatment of diverse seizure disorders. Further prospective studies in larger groups of patients are necessary to evaluate the long-term efficacy and tolerability of TPM in the infant population.

REFERENCES


EFFECTS OF ANTICONVULSANT THERAPY ON COGNITION AND ATTENTION IN CHILDREN WITH NEW-ONSET, IDIOPATHIC EPILEPSY: A PROSPECTIVE STUDY

Based on a poster presented by Mandelbaum D,* Barack G,† Bhise V‡

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Epilepsy is associated with difficulties in cognitive and behavioral performance in children. These problems have been attributed to an interplay of genetics, ongoing seizures, subclinical epileptiform discharges, postictal states, psychosocial issues, underlying brain abnormalities, and the use of antiepileptic drugs (AEDs).

Results of a prior study by these investigators indicate that children with generalized seizures demonstrate lower cognitive scores at baseline than children with focal seizures, and children with nonconvulsive seizure disorders score lower on tests of cognitive ability than those children with convulsive seizures.¹ Last year, the investigators presented data from baseline assessments of children with new-onset, idiopathic epilepsy on cognitive, behavioral, and motor function using an assessment battery to evaluate skills thought to be more vulnerable to effects of epilepsy and/or AEDs than those assessed in the initial study.² As in their previous study, children with focal seizures demonstrated better performance than those children with generalized seizures, although children from both groups did poorly on the Test of Variables of Attention (TOVA) at baseline. The present study prospectively explored cognitive effects of AED therapy in children with new-onset idiopathic epilepsy.

Investigators evaluated children age 6 to 17 years diagnosed with new-onset, idiopathic generalized convulsive, generalized nonconvulsive, or focal seizures based on electroencephalography and clinical findings. Focal seizures were classified as unilateral or bilateral (independent foci found on both hemispheres) and by the presence or absence of secondary generalization. Three cases could not be classified with regard to seizure focus. Neuropsychologic testing was administered before beginning AED therapy, with follow-up evaluation after 6 and 12 months of treatment. Each child underwent tests of cognitive function evaluating new learning, memory, and attention after initiation of AED therapy, including the Kaufmann Brief Intelligence Test, Wide Range Assessment of Memory and Learning, the Stroop Color and Word Test, the TOVA, the Trial Making Test, the Grooved Pegboard Test, the Child Behavior Checklist, the Children’s Depression Inventory, and the Revised Children’s Manifest Anxiety Scale.

Fifty-seven children were evaluated between 1997 and 2002, 6 (n = 45) and 12 months (n = 31) after initiating AED therapy. For the group evaluated after 12 months, a composite cognitive score was stable from baseline to 6 months, but it improved after 12 months of treatment with AEDs. Children with focal seizures demonstrated a steady increase in performance, whereas those children exhibiting generalized seizures performed less well after 6 months of therapy, but they improved beyond baseline measurements after 12 months of treatment with AEDs. Attention scores, as measured by the TOVA test, were also stable between baseline and 6 months, but they improved between 6 and 12 months of AED treatment. Again, among children with generalized seizures, a performance decrease was noted after 6 months of therapy, followed by improvement after 12 months.
Among the 11 children with generalized seizures, 10 had nonconvulsive seizures, and 7 of 10 were treated with ethosuximide monotherapy (the child with generalized convulsive seizures was on carbamazepine, 1 child with absence seizures was on valproate [VPA] plus ethosuximide, and 2 children with absence seizures were on VPA plus topiramate). Children with focal seizures showed a worsening in the reaction time (RT) and reaction time variability (RTV) components of the TOVA over time. Of the 19 children in this subset, 12 (65%) were on carbamazepine monotherapy, 2 were on VPA, 1 was on gabapentin, 1 was on tiagabine, 1 was on ethosuximide, 1 was on lamotrigine plus topiramate, and 1 child was on levetiracetam plus carbamazepine.

Treatment with anticonvulsant medications had a net positive effect on cognitive functioning of children after 12 months of treatment. Patients with generalized epilepsies performed poorly compared to those with focal seizures. The transient drop observed in the performance of children with generalized seizures at 6 months may be a function of the seizure disorder or the drugs (predominantly ethosuximide) used to treat it.

REFERENCES


WORST FEAR WHEN ANTIEPILEPTIC DRUG TREATMENT IS DISCONTINUED IS THAT SEIZURES RECUR AND ARE INTRACTABLE—FORTUNATELY THIS “RECURRENT” NIGHTMARE IS RARE

Based on a platform session presented by Camfield P, Camfield C

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When daily medication treatment induces several years of remission, most children with epilepsy are encouraged to stop daily antiepileptic drug (AED) treatment. In approximately 70% of cases, these children remain seizure-free, although there is always a concern that children who have stopped AED therapy will have recurrent seizures that do not come back under control when AED treatment is resumed. To identify the incidence of intractable epilepsy among children after AED discontinuation, the authors prospectively evaluated the incidence of seizure recurrence and subsequent intractable epilepsy after AED discontinuation among children in the Nova Scotia epilepsy cohort.

All of the children included in this investigation developed epilepsy between 1977 and 1985 and underwent clinical follow-up for at least 5 years after their first seizure. Seizure intractability was defined as occurrence of at least 1 seizure during each 2-month period throughout the past year of follow-up, after treatment with 3 or more AEDs at maximum tolerated doses failed to control seizures.

Records from 389 children were evaluated during the investigation. Among these children, 73% \( n = 282 \) became seizure-free for periods of time ranging from 1 to 4 years before stopping AED treatment. Of this group, 70% \( n = 197 \) remained seizure-free after AED therapy was discontinued, whereas 30% \( n = 85 \) experienced subsequent recurrent seizures. Of this subgroup of children with recurrent seizures, only 3 patients (1% of the initial subject cohort) ultimately developed intractable epilepsy. One of these patients with intractable epilepsy underwent successful temporal lobectomy, but the other 2 patients continue to have frequent seizures 14 and 20 years after diagnosis.

The results of this investigation indicate that approximately 1% of children with epilepsy who become seizure-free and discontinue AED therapy subsequently develop recurrent seizures that cannot again be controlled with medication. The authors were unable to predict this outcome based on patient characteristics. It remains unclear whether this small group of patients with intractable epilepsy after AED discontinuation would have eventually developed intractable seizures even if AED therapy had been continued.