Evolving Antiepileptic Drug Treatment in Juvenile Myoclonic Epilepsy

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Background: In the face of availability of newer antiepileptic drugs (AEDs) such as lamotrigine and topiramate, there is need to reassess the role of older AEDs in the treatment of juvenile myoclonic epilepsy (JME).

Objectives: To explore whether lamotrigine and topiramate monotherapy or polytherapy can be effective options in the treatment of JME, and to determine whether older AEDs, such as phenytoin and carbamazepine, have a role in the treatment of JME.

Design: A retrospective cohort study.

Setting: A large academic teaching hospital.


Methods: We compared the efficacy of valproic acid, lamotrigine, and topiramate monotherapy or polytherapy in the control of different seizure types of JME, and compared their efficacy and tolerability with the efficacy and tolerability of phenytoin and carbamazepine.

Results: Seizure outcome did not differ when patients receiving valproic acid monotherapy (n=36) were compared with those receiving lamotrigine monotherapy (n=14), and when patients receiving valproic acid polytherapy (n=22) were compared with those receiving lamotrigine polytherapy (n=21) or topiramate polytherapy (n=15) (P>.05 for all). The combined data of myoclonic seizure control by all 3 AEDs were poorer when compared with the combined data of generalized tonic-clonic seizure control by all 3 AEDs (P=.03), but not when compared with the combined data of absence seizure control by all 3 AEDs (P=.43). Valproic acid, lamotrigine, and topiramate, when compared with phenytoin or carbamazepine, demonstrated significantly better control of myoclonic seizures (P<.01 for all), but not of generalized tonic-clonic seizures (P>.11 for all).

Conclusions: Lamotrigine and topiramate are effective alternative options to valproic acid in the treatment of JME. Lamotrigine is an effective option as monotherapy and polytherapy. Topiramate is an effective option as polytherapy, but more data are needed to determine if it is an effective option as monotherapy. More effective therapy is needed to improve myoclonic seizure control. Older AEDs, such as phenytoin and carbamazepine, may not be indicated in JME patients.

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**Valproic Acid** is the drug of choice for the treatment of juvenile myoclonic epilepsy (JME). Different series1-4 report good to excellent control of seizures in 70% to 85% of patients treated with valproic acid monotherapy or polytherapy. Standard handbooks5 and textbooks3,5 of epilepsy published up to 2000 recommend adding phenytoin or carbamazepine in exceptional cases in which additional control of generalized tonic-clonic (GTC) seizures is required.6,8 However, recent reports8 suggest that carbamazepine and phenytoin may worsen seizure control. As a result, and because of the purported broad spectrum of activity against all seizure types associated with JME, during the past few years, lamotrigine and topiramate have been suggested as alternative options.5

In several small and large case series,10-13 lamotrigine monotherapy resulted in a 40% to 83% seizure-free rate for patients with JME, but little is known about its tolerability in patients with JME. Little is also known about the efficacy and tolerability of topiramate in the treatment of JME.14,15 The outcomes of the 3 individual seizure types (GTC, myoclonic, and absence) were studied with the use of valproic acid4-6 and lamotrigine,11 and essentially no major differences were found. Nevertheless, some studies have found
suboptimal myoclonic seizure control with valproic acid\textsuperscript{16} and worsening of myoclonic seizures with lamotrigine.\textsuperscript{17}

We compared the efficacy of valproic acid, lamotrigine, and topiramate in seizure control when used as monotherapy or polytherapy in patients with JME. We also assessed their efficacy in GTC, myoclonic, and absence seizure control and evaluated their tolerability. Finally, we compared the efficacy and tolerability of valproic acid, lamotrigine, and topiramate with the efficacy and tolerability of phenytoin and carbamazepine to assess whether the currently preferred drugs offer substantial advantages.

### METHODS

#### PATIENT IDENTIFICATION

Consecutive JME patients treated at the University of Alabama at Birmingham Epilepsy Center were identified. Only those patients who received valproic acid, lamotrigine, topiramate, phenytoin, or carbamazepine between April 1, 1991, and March 31, 2001, were included in this study. Patients were excluded if they (1) had associated nonepileptic seizures either clinically or diagnosed on videotape-electroencephalogram, (2) had associated semiological features suggestive of partial seizures, (3) persistently did not comply with the medications, (4) had not attended the clinic during the past 3 years, or (5) had less than 1 year of follow-up.

#### EVALUATION OF EFFICACY AND TOLERABILITY OF ANTIEPILEPTIC DRUGS

Efficacy was defined as control of GTC, myoclonic, and absence seizures. The criteria for classification of seizure control were as follows: GTC, good (<1 seizure per year), moderate (1-4 seizures per year), or poor (>4 seizures per year); myoclonic, good (<5 single seizures or clusters per month, rare seizures, or occasional seizures), moderate (5-14 single seizures or clusters per month, several seizures, or frequent seizures), or poor (>13 single seizures or clusters per month or daily seizures); and absence, good (<5 seizures per month, rare seizures, or occasional seizures), moderate (5-14 seizures per month, several seizures, or frequent seizures), or poor (>15 seizures per month, frequent seizures, or daily seizures). When seizure control for any specific seizure type was not documented in the medical record, the seizure control was assessed as unknown and was excluded from evaluation. Seizures due to provoking factors were excluded from evaluation. The GTC seizure outcome for an antiepileptic drug (AED) was evaluated only if the duration of effective therapy was more than 6 months, whereas myoclonic and absence seizure outcomes were evaluated only if the duration of effective therapy, excluding the period of titration, was more than 1 month.

If the first AED failed and the second AED subsequently added to the regimen controlled the seizures, the outcome was classified as poor for the first AED monotherapy and good for the second AED polytherapy. Likewise, if the first AED monotherapy and the second AED polytherapy failed and the third AED subsequently added to the regimen controlled the seizures, the outcome was classified as poor for the first AED monotherapy and the second AED polytherapy and good for the third AED polytherapy. If an AED was added for control of a specific type of seizure, such as a GTC seizure, the outcome was evaluated in relationship only to that type of seizure.

Tolerability was defined as the withdrawal rate of AEDs per patient-year of treatment. The reasons for AED withdrawal were assessed in relationship to inefficacy or the presence of adverse effects. Inefficacy was defined as the need to change the AED because of inability to control or worsening seizures. Although inappropriateness of the medication and planned pregnancy were criteria for withdrawal of an AED, this was not included in our assessment of tolerability if the seizure control was satisfactory.

All follow-ups were noted from the medical records. Few important missing data were supplemented by telephone calls.

#### STATISTICAL ANALYSIS

All statistical tests were performed with computer software (InStat software 3.0; GraphPad Software Inc, San Diego, Calif). A 2-tailed Fisher exact test or a \( \chi^2 \) test was used to analyze dichotomized variables. Antiepileptic drug efficacy, in relationship to monotherapy and polytherapy and individual seizure type control, was assessed by comparing good seizure control data with the combined data of moderate and poor control. The tolerability data of valproic acid, lamotrigine, topiramate, phenytoin, and carbamazepine compared the number of patients withdrawn from individual therapies per patient-year of treatment. The \( \alpha \) level was set at \( \leq .05 \).

#### PATIENT DEMOGRAPHIC CHARACTERISTICS

Seventy-two patients (45 women and 27 men), aged 21-55 years, received valproic acid, lamotrigine, topiramate, phenytoin, or carbamazepine treatment for JME between April 1, 1991, and March 31, 2001. The median age of first GTC or myoclonic seizure was 15 years (range, 4-37 years). The first seizure type was absence in 19 patients, GTC in 28 patients, myoclonic in 26 patients, photoconvulsion in 1 patient, and unknown in 3 patients. Magnetic resonance imaging and computed tomographic scans of the head were performed in 41 and 4 patients, respectively. Two patients had abnormal findings on imaging: shunted hydrocephalus (1), and venous angioma (1). They did not have partial seizures. An electroencephalogram showed only focal findings in 5 patients, and the result was normal in 10 patients. The remaining patients showed 3 Hz or more of generalized spike- or polyspike-wave complexes.

#### AED THERAPY

Thirty-seven (51\%) of the patients received monotherapy during the entire course of the treatment; 12 (17\%) received a single AED (valproic acid \( n=10 \), lamotrigine \( n=1 \), or phenytoin \( n=1 \)), and 25 (35\%) received several AEDs but always as monotherapy. The remaining 35 (49\%) patients received polytherapy (that included AEDs other than those evaluated in this study, such as clonazepam, levetiracetam, and zonisamide) at some time during the treatment. Phenytoin, carbamazepine, and valproic acid were commonly used as the first, second, or third AED; lamotrigine as the second, third, or fourth AED; and topiramate as the third, fourth, or fifth AED.

The GTC, myoclonic, and absence seizure outcome with valproic acid, lamotrigine, and topiramate...
monotherapy and polytherapy is given in Table 1. Table 2 shows the total number of patient-years of AED treatment and GTC, myoclonic, and absence seizure outcome. The number of patients withdrawn from AED therapy and the reasons are given in Table 3. The mean follow-up of all patients was 5.9 years.

<table>
<thead>
<tr>
<th>Antiepileptic Drug*</th>
<th>Minimum Effective Dose in Monotherapy/Polytherapy, mg</th>
<th>Patients Withdrawn</th>
<th>Reason for Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. (%)†</td>
<td>Per Patient-year of Treatment</td>
</tr>
<tr>
<td>Valproic acid (n = 58)</td>
<td>875/1260</td>
<td>23 (40)</td>
<td>6</td>
</tr>
<tr>
<td>Lamotrigine (n = 35)</td>
<td>350/390</td>
<td>9 (26)</td>
<td>9</td>
</tr>
<tr>
<td>Topiramate (n = 19)</td>
<td>230/250</td>
<td>9 (47)</td>
<td>24</td>
</tr>
<tr>
<td>Phenytoin (n = 28)</td>
<td>260/420</td>
<td>16 (57)</td>
<td>16</td>
</tr>
<tr>
<td>Carbamazepine (n = 18)</td>
<td>850/800</td>
<td>14 (78)</td>
<td>22</td>
</tr>
</tbody>
</table>

*Data in parentheses are number of patients.
†The number of patients mentioned in this column may not match the sum of the numbers given in columns 5, 6, and 7 because both inefficacy and adverse effects may have been the reason for withdrawal.

### AED EFFICACY

There were 3 major efficacy outcomes in our study. First, seizure control did not differ when patients receiving valproic acid (n = 36) and lamotrigine (n = 14) monotherapy were compared, and when patients receiving val-

<table>
<thead>
<tr>
<th>Antiepileptic Drug*</th>
<th>Type of Seizure†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>GTC</td>
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<td>G</td>
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Abbreviations: ABS, absence; G, good; GTC, generalized tonic-clonic; M, moderate; MCL, myoclonic; P, poor.
*Data in parentheses are number of patients. The sum according to individual seizure types may be different from the number in parentheses because a particular seizure type may not be active at the time of therapy or the outcome may be unknown.
†Data are given as number (percentage) of patients with each outcome. Percentages are based on the total for each type of seizure and type of drug, and may not total 100 because of rounding.
proic acid (n=22), lamotrigine (n=21), and topiramate (n=15) polytherapy were compared (P>0.05 for all) (Table 1). Topiramate monotherapy was not included in the comparison because of an inadequate number of patients (n=4). Second, valproic acid, lamotrigine, and topiramate did not differ significantly (P>0.2 for all) in GTC, myoclonic, and absence seizure control; however, the combined data of myoclonic seizure control by all 3 AEDs were poorer when compared with the combined data of GTC seizure control by all 3 AEDs (P=0.03), but not when compared with the combined data of absence seizure control by all 3 AEDs (P=0.43) (Table 2). Third, valproic acid, lamotrigine, and topiramate, when compared with phenytoin or carbamazepine, demonstrated significantly better control of myoclonic seizures (P<0.01 for all), but not GTC seizures (P>0.11 for all). Valproic acid, lamotrigine, and topiramate absence seizure control was not compared with that of phenytoin or carbamazepine because of the small number of patients (Table 2).

AED TOLERABILITY

The withdrawal rate (per patient-year of treatment) of valproic acid was significantly lower compared with the rates of topiramate (P=0.003), phenytoin (P=0.02), and carbamazepine (P=0.001), but not with the rate of lamotrigine (P=0.12) (Table 3); for phenytoin and carbamazepine, this finding was independent of inappropriateness of therapy. Lack of acceptable seizure control and adverse effects each accounted for nearly half of the withdrawals from valproic acid, lamotrigine, and topiramate treatment, whereas the former contributed to nearly three fourths of withdrawal from phenytoin and carbamazepine treatment. Worsening of seizure control was seen in 6 of the 18 patients treated with carbamazepine, 2 of the 35 patients treated with lamotrigine, and 1 of the 19 patients treated with topiramate. While carbamazepine worsened myoclonic and absence seizures, lamotrigine and topiramate worsened only myoclonic seizures.

CURRENTLY PREFERRED AEDs

Monotherapy vs Polytherapy Efficacy Outcome

In our small sample of JME patients, lamotrigine monotherapy and lamotrigine and topiramate polytherapy were effective options to valproic acid therapy. Data from several small and large series support these findings. In these series, lamotrigine was used as monotherapy or polytherapy in JME patients, while topiramate was used as polytherapy and aimed primarily at GTC seizures in patients with primary generalized epilepsy, including some JME patients. Kustra et al, in an open-label prospective design, treated 92 JME patients who underwent lamotrigine monotherapy. The total duration of maintenance therapy was 8 weeks. The GTC and absence seizures were controlled in nearly 80% of the patients, and myoclonic seizures were controlled in 72%. Other smaller case series, composed of 32 JME patients treated with lamotrigine monotherapy or polytherapy and followed up for 6 to 22 months, observed similar findings. Topiramate adjunctive therapy was studied in a double-blind placebo-controlled design in patients with primary generalized epilepsy, including 22 JME patients. Topiramate was highly effective for GTC seizures, although for myoclonic seizures, differences were statistically insignificant. In the researchers' opinion, lack of a difference in myoclonic seizure control between topiramate and placebo could have been because of the small number of patients. The number of JME patients treated with topiramate monotherapy in our series was too few to make a definitive comment about whether topiramate monotherapy can be an effective option.

It is questionable whether a larger sample size may have shown a clinically significant superiority of valproic acid over lamotrigine and topiramate or vice versa. Obtaining significant differences in our study in few other outcome comparisons indicates that the data size is probably meaningful, at least for more frequent events such as myoclonic seizure control and tolerability, if not adequate. In addition, it may be argued that a true comparison of efficacy between these AEDs is not valid because patients were not randomized, resulting in a selection bias. Interestingly, lamotrigine was used as the second, third, or fourth AED and topiramate as the third, fourth, or fifth AED in our series, in contrast to valproic acid, which was used as the first AED in many patients. Demonstration of lamotrigine and topiramate efficacy at par with the gold standard valproic acid, despite their use in patients refractory to valproic acid, reinforces the validity of comparison.

Our finding of lamotrigine and topiramate as effective options in the treatment of JME patients matches the recommendations of a large group of expert epileptologists based on their knowledge of medical literature and personal experience. In this consensus report, valproic acid, lamotrigine, and topiramate were ranked as the first, second, and fourth drugs of choice, respectively. Clonazepam, which was ranked third, is useful for myoclonic seizures and has a minor role in the treatment of GTC seizures.

GTC vs Myoclonic vs Absence Seizure Efficacy Outcome

In our series, valproic acid, lamotrigine, and topiramate treatment individually did not demonstrate any significant difference in the seizure outcome of GTC, myoclonic, and absence seizures. All 3 AEDs produced good control of GTC seizures in 19 (68%) of 28 to 12 (80%) of 15 patients, absence seizures in 3 (50%) of 6 to 18 (78%) of 23 patients, and myoclonic seizures in 18 (58%) of 31 to 32 (59%) of 54 patients. However, the combined data of myoclonic seizure control by all 3 AEDs were suboptimal when compared with that data of GTC seizure control. Most series describe good to excellent myoclonic seizure outcome in JME patients. Obeid and Panayiotopoulos, in a prospective open-label study, reported control of myoclonic seizures in all 17 patients treated with clonazepam, 12 of whom also received other AEDs. We failed to achieve similar results despite use of clonazepam in nearly three fourths of the patients with a suboptimal outcome. Neurotoxic effects and tolerance were the major limitations of clonazepam. Our criteria for myoclonic
seizure control were liberal. Good outcome included patients who were not only seizure free but also patients who had up to 5 single seizures or clusters of jerks a month. Therefore, our classification should have had improved chances of obtaining a better outcome.

Two studies20,21 reported that 20% to 30% of JME patients are truly resistant to AEDs (excluding factors such as noncompliance and inadequate treatment). These studies did not report difficulty in controlling or worsening of myoclonic seizures. However, in keeping with our results, Sagild and Alving22 found that 69% (48/74) of JME patients taking valproic acid or primidone did not have GTC seizures but continued to have myoclonic seizures. There are several reports of lamotrigine-induced worsening of myoclonic seizures in the literature. Bira-ben et al13 describe worsening of myoclonic seizures in all 7 JME patients treated with lamotrigine. Similar worsening of myoclonic seizures was noted in at least some patients in 4 other series.13,22-24 Conversely, other small and larger series10,12 did not record this complication at all. Considering that some investigators reported such a complication and some did not, it is more likely that the incidence of this complication is low and difficult to accurately assess in relatively small case series.

A question arises about whether patients in our series failed to achieve good to excellent myoclonic seizure control because of (1) undetected drug-induced worsening of seizure control or (2) intrinsic pharmacoresistance of myoclonic seizures. Fifty-four (75%) of 72 patients in our series received 2 new AEDs, such as lamotrigine and topiramate. At least one of these, lamotrigine, is known to produce worsening of myoclonic seizure control. It is thought that lamotrigine-induced worsening probably arises from its sodium channel blocking action, similar to that of phenytoin and carbamazepine, which are known to worsen control of absence and myoclonic seizures in patients with primary generalized epilepsy and JME.17 In a retrospective study, if the treating physician was not vigilant in documenting an accurate count of seizures at follow-up, worsening of seizure control may mimic poor control. Because of the retrospective nature of our series, an undetected worsening of seizures cannot be entirely excluded. However, equally poor control of myoclonic seizures with valproic acid and topiramate, which are not known to produce worsening of seizures, suggests intrinsic resistance of myoclonic seizures, probably from genetic heterogeneity. A well-conducted prospective trial may clarify this issue.

Tolerability Outcome

We found that tolerability was significantly poorer for topiramate compared with valproic acid. Lamotrigine tolerability was nonsignificantly different from that of valproic acid and topiramate. The following factors may explain the lower tolerability for topiramate. First, during the early years of lamotrigine and topiramate use, the titration rate was relatively rapid, and it is possible that treating physicians were more cautious in titrating lamotrigine rather than topiramate. Second, topiramate was approved by the Food and Drug Administration in 1996, compared with valproic acid in 1978 and lamotrigine in 1994. Assuming a high efficacy of valproic acid, lamotrigine, and topiramate in JME patients, serial commercial availability of the drugs probably provided valproic acid with the most preferred status, lamotrigine with the intermediate preferred status, and topiramate with the least preferred status. An example of such a preferred status is that some patients, despite having adverse effects from valproic acid, did not want to switch to newer AEDs because of the fear of losing control of seizures. Furthermore, valproic acid and to a lesser extent lamotrigine exploited the advantages of lack of effective alternative options for longer periods compared with topiramate. All these factors probably resulted in the graded decremental withdrawal rate for topiramate, lamotrigine, and valproic acid seen in our series. In one study,23 medically refractory patients receiving a starting dosage of 25 mg/d of topiramate showed improved tolerability compared with patients receiving a starting dosage of 50 mg/d. Therefore, it is likely that slow titration of topiramate and lamotrigine may improve the tolerability of these AEDs in JME patients.

CURRENTLY PREFERRED VS OLDER AEDs: EFFICACY AND TOLERABILITY OUTCOMES

The treatment regimen of JME is evolving from the older AEDs, such as phenytoin and carbamazepine, to the currently preferred AEDs, such as valproic acid, lamotrigine, and topiramate. Phenytoin and carbamazepine have not been completely discarded from the treatment of JME; and lamotrigine and topiramate have not been approved by the Food and Drug Administration for primary generalized epilepsy. In our series, the efficacy outcome of phenytoin and carbamazepine for myoclonic seizure control was poorer compared with the efficacy outcome of valproic acid, lamotrigine, and topiramate, but the GTC seizure outcome was not significantly different between the 2 groups. Other researchers4,5,25 have reported similar findings. The effectiveness of phenytoin and carbamazepine for controlling GTC seizures in JME patients has tempted physicians to use these AEDs in JME patients with difficult to control GTC seizures. Interestingly, in our series, the tolerability of phenytoin and carbamazepine, independent of inappropriateness of therapy, was poorer only when compared with valproic acid, and not lamotrigine or topiramate. Our data suggest that older AEDs, such as phenytoin and carbamazepine, may not be indicated in JME patients because newer AEDs, such as lamotrigine and topiramate, offer advantages with regard to improved myoclonic seizure control. With the rapid titration schedule, lamotrigine or topiramate does not differ in tolerability when compared with phenytoin and carbamazepine. Whether a slow titration schedule will achieve improvement in tolerability remains to be seen.

RETROSPECTIVE VS PROSPECTIVE STUDY IN JME PATIENTS

Randomized controlled trials are expensive and usually involve short-duration treatment. They are designed pri-
marily to satisfy licensing requirements, and often diverge considerably from clinical practice. Because of market pressures, they rarely compare 2 or more active treatments directly. A randomized controlled trial of drugs used in JME patients may be difficult to conduct because only 20% to 30% of such patients are refractory to treatments directly. A randomized controlled trial of drugs

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