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Topiramate or valproate in patients with juvenile myoclonic epilepsy: A randomized open-label comparison

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Abstract

Few randomized, controlled trials evaluating antiepileptic drug (AED) efficacy and tolerability have focused solely on patients with juvenile myoclonic epilepsy (JME). We conducted a pilot, randomized controlled trial comparing topiramate ($N = 19$) and valproate ($N = 9$) in adolescents/adults with JME to evaluate clinical response when these broad-spectrum agents are titrated to optimal effect. Rating scales were used to systematically assess tolerability. Among patients completing 26 weeks of treatment, 8 of 12 (67%) in the topiramate group and 4 of 7 (57%) in the valproate group were seizure-free during the 12-week maintenance period. Median daily dose was 250 mg topiramate or 750 mg valproate. Two (11%) topiramate-treated patients and one (11%) valproate-treated patient discontinued due to adverse events. Systemic toxicity scores, but not neurotoxicity scores, differed substantially between the two groups; greater systemic toxicity was associated with valproate. Our preliminary findings that topiramate may be an effective, well-tolerated alternative to valproate warrant validation in a double-blind trial.

Keywords: Topiramate; Juvenile myoclonic epilepsy; Primary generalized epilepsy; Valproate

1. Introduction

Juvenile myoclonic epilepsy (JME) is one of the most common epilepsy syndromes. Yet data from well-controlled trials of antiepileptic drugs (AEDs) as monotherapy in JME are very limited, a deficiency noted in various efforts to develop evidence-based guidelines for epilepsy [1,2]. Based on open-label studies and nearly 30 years of clinical experience, valproate is widely regarded as the drug of choice in JME.

Evidence has accumulated that topiramate may also be effective in JME. Its multiple mechanisms of action [3–5] and activity in animal models of genetically determined generalized epilepsy [6] support clinical observations. Results from double-blind, randomized controlled trials have documented the efficacy of topiramate monotherapy in primary generalized tonic-clonic seizures (PGTCS) [7,8], with effects comparable to those of valproate [8]. In double-blind, placebo-controlled trials of topiramate as adjunctive therapy in treatment-resistant PGTCS [9], topiramate was effective in a subset of patients with JME [10]. However, the number of patients was too small to assess its effects on myoclonus, although it appeared that myoclonus was not aggravated.

We conducted an exploratory trial with blind randomization of adolescents/adults with JME to 26 weeks of open-label treatment with valproate or topiramate titrated to optimal response. Because these two agents have different

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side effect profiles, the relative side effect burden was quantified with toxicity rating scales patterned after those in the Veterans' Administration (VA) Cooperative Study [11].

2. Methods

Patients eligible for this 26-week randomized, parallel-group, open-label study were adolescents/adults (12–65 years old, ⩾25 kg) with a confirmed diagnosis of JME. Diagnostic criteria included myoclonic jerks, seizure onset at 8–26 years of age, and coexistent generalized tonic-clonic seizures with generalized epileptiform abnormalities on EEG consistent with JME. Patients had to have active epilepsy in the form of myoclonus or ⩾1 PGTCS in the 3 months before study entry. Topiramate or valproate could be initiated as monotherapy or as an adjunct to another AED (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy. Females of childbearing potential had to be premenarchal, physically incapable of bearing children, or practicing an acceptable method of contraception.

Exclusion criteria included previous discontinuation of topiramate or valproate due to an adverse event; abnormal cranial CT or MRI scan; dementia or mental retardation; progressive myoclonic epilepsy; clinically unstable medical conditions; history of nephrolithiasis; SGOT and/or SGPT levels greater than two times the upper limit of the normal range; co-therapy with a carbonic anhydrase inhibitor or barbiturate AED; and use of an experimental medication or device within 30 days of study entry.

A 14-week titration phase was followed by a 12-week maintenance phase. After blinded randomization in 2:1 ratio to topiramate or valproate, the assigned agent was titrated according to clinical response. Blinded randomization was achieved by providing study sites with individual envelopes containing medication assignments generated by computer. The patient, investigator, and pharmacist remained blinded to medication assignment until screening was completed and the envelope was opened.

The topiramate target dosage was 3–4 mg/kg/day (maximum, 9 mg/kg/day) for patients 12–16 years of age and 200 mg/day (maximum, 600 mg/day) for patients >16 years of age. Valproate target dosages were 10 mg/kg/day in patients 12–16 years of age and 750 mg/day in those >16 years (overall maximum, 60 mg/kg/day). Medications were titrated at 1- to 2-week intervals according to clinical response and were administered in divided doses. Topiramate was provided as 25- or 100-mg TOPAMAX tablets; valproate was provided as 125-, 250-, or 500-mg Depakote tablets.

Seizure counts were captured with seizure diaries maintained by patients and were reviewed at each study visit. Seizure data were used to calculate reduction from baseline monthly seizure frequency. Patient and investigator global evaluations of improvement (i.e., marked, moderate, minimal, none, or worse) in overall outcome, alertness, activities of daily living, seizure severity, interaction with patient's environment, and response to verbal requests were obtained at the final study visit.

Questionnaires assessing drug-related systemic toxicity and neurotoxicity (Table 1) were adapted from those used in the VA Cooperative Study [11] to reflect adverse effects commonly associated with valproate and topiramate treatment, as well as nonspecific central nervous system effects with AEDs in general. The questionnaires were completed at each post-baseline visit (4, 8, 14, and 26 weeks). For both scales, signs/symptoms were scored relative to the patient's prestudy condition, with higher scores corresponding to greater frequency/severity of treatment-emergent toxicity. The highest possible severity score for individual parameters was 50. Total scores ⩾10 were considered clinically significant. With respect to side effect scores: 10 indicated occasional vomiting, moderate weight gain/loss (7–12 pounds), mild tremor, occasional sleepiness during the day, or moderate impairment of cognitive function; 20–25, frequent vomiting, large weight gain/loss (18–18 pounds), moderate tremor, or difficulty staying awake; and 50, severe tremor, severe gait disturbance requiring assistance, stuporous, or severe cognitive impairment that interferes with all daily activities. Median scores for both scales were calculated at 4, 8, 14, and 26 weeks for each treatment group. The proportion of patients for whom toxicity scores were zero at each time interval was determined.

Table 1
Systemic toxicity and neurotoxicity assessment[a]

Systemic toxicity
Nausea, vomiting
Reduced platelet or white blood cell count
Hypersensitivity reactions
Impotence (libido or potency)
Hyponatremia
Liver disease/abnormal liver function tests
Weight gain/loss
Hair loss, texture changes, hirsutism
Neurotoxicity
Diplopia
Nystagmus
Dysarthria
Ataxia
Tremor
Sedation
Affect and mood
Attention/concentration
Language
Dizziness
Headache

[a] The questionnaires assessing drug-related systemic toxicity and neurotoxicity were patterned after those in the Veterans' Administration Cooperative Study [11].

3. Results

Baseline characteristics for patients randomized to topiramate and valproate are summarized in Table 2. Contrary to the protocol, two patients were receiving valproate at dosages that investigators considered suboptimal at study entry. One patient was randomized to topiramate; the other was randomized to valproate. Despite randomization, the topiramate group had a higher proportion of females as well as patients with PGTCS, and fewer patients receiving AED therapy at study entry. At study entry, 5 of 19 (26%) in the group assigned to topiramate and 2 of 9

Table 2
Baseline characteristics of randomized patients ($N = 28$)

	Topiramate ($N = 19$)	Valproate ($N = 9$)
Age	15 (9–42)[a]	16 (12–34)
Gender, female	13 (68%)	4 (44%)
Weight (kg)	66 (32–116)	72 (55–109)
Baseline seizure type		
Myoclonic	14 (74%)	9 (100%)
PGTCS	12 (63%)	4 (44%)
Absence	2 (11%)	2 (22%)
Baseline AED		
None	12 (63%)	4 (44%)
Carbamazepine	3 (16%)	0
Oxcarbazepine	1 (5%)	0
Phenytoin	1 (5%)	2 (22%)
Lamotrigine	1 (5%)	1 (11%)
Valproate	1 (5%)	1 (11%)
Ethosuximide	0	1 (11%)

[a] Data are given as median (range) or N (%).

(22%) of those assigned to valproate were receiving AEDs (carbamazepine, oxcarbazepine, phenytoin) that could be considered inappropriate for patients with JME. All patients were converted to topiramate or valproate monotherapy, except for one patient in the topiramate group who continued oxcarbazepine, although the dose was reduced from 600 to 75 mg/day by study end.

Overall, 12 of 19 (63%) topiramate-treated and 7 of 9 (78%) valproate-treated patients completed 26 weeks of treatment. In the topiramate group, 2 (11%) patients discontinued treatment due to adverse events, 2 (11%) because of inadequate seizure control, and 1 (5%) due to patient choice; 2 (11%) patients were lost to follow-up. One (11%) valproate-treated patient discontinued due to adverse events and one (11%) discontinued for other reasons. Among study completers, the median topiramate dosage was 250 mg/day (range, 100–500 mg/day); the median valproate dosage was 750 mg/day (range, 500–1000 mg/day).

Table 3
Seizure reduction from baseline

Seizure reduction	Number (%) of patients	
	Topiramate	Valproate
Intent-to-treat[a]	19	9
Myoclonic		
<50%	2/14 (14%)	0
50 to <75%	0	1/9 (11%)
75 to <100%	3/14 (21%)	1/9 (11%)
100%	9/14 (64%)	7/9 (78%)
PGTCS		
<50%	1/12 (8%)	1/4 (25%)
50 to <75%	1/12 (8%)	0
100%	10/12 (83%)	3/4 (75%)
No seizures in preceding 12 weeks	8 (42%)	4 (44%)
Study completers	12	7
Myoclonic		
<50%	1/11 (9%)	0
50 to <75%	0	1/7 (14%)
75 to <100%	3/11 (27%)	0
100%	7/11 (64%)	6/7 (86%)
PGTCS		
<50%	1/10 (10%)	1/4 (25%)
50 to <75%	1/10 (10%)	0
100%	8/10 (80%)	3/4 (75%)
No seizures in preceding 12 weeks	8 (67%)	4 (57%)

[a]Last observation carried forward.

Response rates for all randomized patients (intent-to-treat, $N = 28$) and for study completers ($N = 19$) are listed in Table 3. Seizure control improved in both patients who had been receiving valproate at the baseline visit. Of the two patients in each group who had absence seizures at baseline, one in the valproate group continued to have absence seizures; neither of the patients in the topiramate group reported absence seizures during the 12-week maintenance period. Reductions in myoclonic seizure frequency were clinically significant ($\geqslant 50\%$ reduction from baseline) in the majority ($\geqslant 85\%$) of patients. Two topiramate-treated patients did not experience a clinically significantly reduction in myoclonic seizure frequency. Of those completing the study, 8 of 12 (67%) in the topiramate group and 4 of 7 (57%) in the valproate group had no seizures during the 12-week maintenance period.

Results of physician and patient evaluations of improvement are illustrated in Fig. 1. Physicians reported that 73% of patients experienced marked/moderate global improvement with topiramate or valproate treatment, whereas 56% of patients felt that they had experienced marked/moderate improvement. According to physicians and patients, 43% of topiramate-treated patients and 14% ($N = 1$) of valproate-treated patients experienced marked/moderate improvement in alertness. Alertness worsened in one valproate-treated patient.

Systemic toxicity and neurotoxicity scores at 4, 8, 14, and 26 weeks are listed in Table 4, with higher scores corresponding to greater frequency/severity. At each evaluation point, systemic toxicity scores were higher in

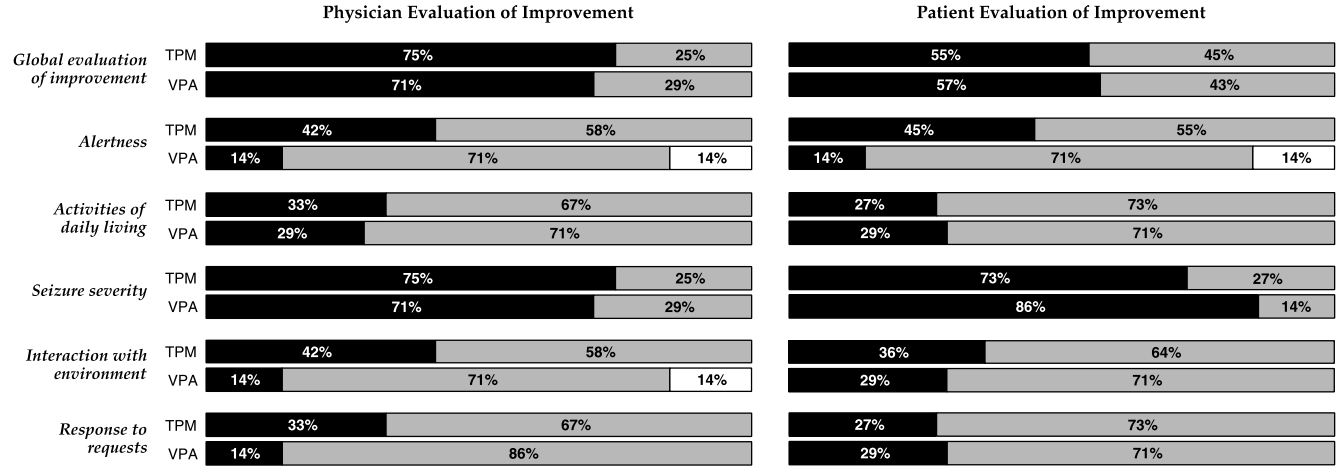

Fig. 1. Physician and patient evaluation of improvement. ■, Marked/moderate; ▒, minimal/none; □, worse.

Table 4
Systemic toxicity and neurotoxicity scores

	Week 4		Week 8		Week 14		Week 26	
	TPM	VPA	TPM	VPA	TPM	VPA	TPM	VPA
Systemic toxicity								
N	13	8	13	7	14	7	15	7
Median	3	4	3	10	3	10	3	10
Range	0–23	0–58	0–10	3–45	0–25	3–25	0–25	0–70
Patients scoring 0	5 (38%)	1 (13%)	5 (38%)	0	4 (29%)	0	4 (27%)	1 (14%)
Neurotoxicity								
N	12	8	11	7	12	6	14	6
Median	0	0	0	0	0	0	0	0
Range	0–85	0–25	0–10	0–60	0–20	0–35	0–20	0–10
Patients scoring 0	10 (83%)	7 (88%)	8 (73%)	5 (71%)	8 (67%)	5 (83%)	10 (71%)	4 (67%)

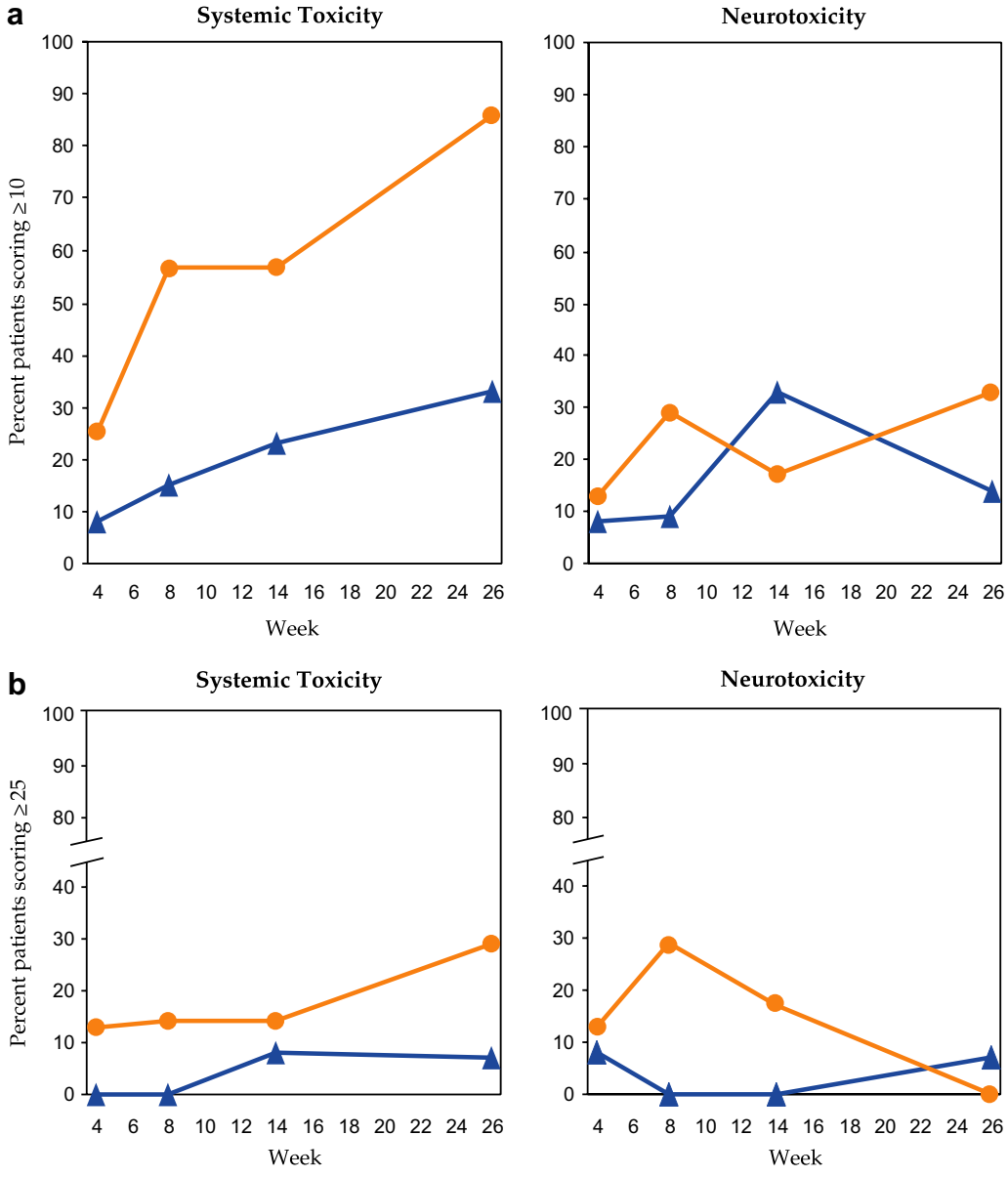

Fig. 2. Systemic toxicity and neurotoxicity scales grouped according to the proportion of patients scoring ⩾10 (a) and ⩾25 (b). ▲, Topiramate; ●, valproate.

Table 5
Most common adverse events[a] during randomized treatment

	Number (%) of patients	
	Topiramate ($N = 19$)	Valproate ($N = 9$)
Headache	5 (26%)	1 (11%)
Concentration/attention difficulty	3 (16%)	1 (11%)
Fatigue	2 (11%)	3 (33%)
Alopecia	2 (11%)	3 (33%)
Dizziness	2 (11%)	1 (11%)
Weight loss	2 (11%)	0
Paresthesia	2 (11%)	0
Psychomotor slowing	2 (11%)	0
Somnolence	2 (11%)	0
Nausea	1 (5%)	3 (33%)
Weight gain	0	2 (22%)
Appetite increase	0	2 (22%)
Insomnia	0	2 (22%)
Abnormal vision	0	2 (22%)
Rash	0	2 (22%)

[a] Events occurring in two or more patients.

valproate-treated patients, with fewer valproate-treated patients reporting the lowest score (zero). Neurotoxicity scores did not substantially differ between treatment groups. A similar pattern was observed when systemic toxicity and neurotoxicity scores were stratified according to the proportion of patients scoring $\geqslant 10$ and $\geqslant 25$ on each toxicity scale (Fig. 2).

The most common adverse events are reported in Table 5. Of the topiramate-treated patients with treatment-limiting adverse events, one patient reported language problems, psychomotor slowing, and concentration/attention difficulty; the other patient reported dizziness, mood problems, and concentration/attention difficulty. One valproate-treated patient discontinued treatment due to increased appetite, insomnia, nausea, fatigue, and concentration/attention difficulty.

Among study completers, mean weight change from baseline was −4.1 kg (range, −9.1 to +1.2 kg) in 12 topiramate-treated patients (mean baseline weight, 70.8 kg), compared with +5.0 kg (range, −3.6 to +16.7 kg) in seven patients receiving valproate (mean baseline weight, 75.2 kg). The change in baseline body weight differed significantly ($P \leqslant 0.001$) between the treatment groups.

4. Discussion

This exploratory study suggests that, when titrated to response, moderate dosages of valproate and topiramate may be similarly effective in JME in terms of patients seizure-free during the 12-week maintenance period. However, topiramate and valproate had qualitatively different side effect profiles. At doses providing similar therapeutic effects, valproate had a higher side effect burden as measured with systemic toxicity scales.

This study illustrates the challenges of conducting randomized, controlled trials in JME. Despite randomization, treatment groups were not balanced with respect to seizure types present at baseline. A larger proportion of patients in the topiramate group than in the valproate group had PGTCS as a baseline seizure type. Efficacy assessments were based on seizure data recorded by patients/families and were analyzed as reductions from baseline seizure frequency. Not only are PGTCS easier to count than myoclonic seizures and PGTCS data therefore less variable, PGTCS tend to be infrequent in most patients with JME. Without a placebo group, an extended interval free of PGTCS could reflect a true treatment effect or the natural history of PGTCS occurrence. In our study, the observation that PGTCS appeared more responsive than myoclonic seizures to topiramate could be attributable to the phenomenon of infrequent seizures or it may reflect relatively greater effectiveness of topiramate against PGTCS than myoclonus. Further confounding interpretation of these data is the fact that double-blind, randomized, controlled nonequivalence trials have demonstrated that topiramate is effective in PGTCS [7,9], but similar Class I evidence is not available for topiramate in myoclonus or absence seizures.

No study of an agent as monotherapy in JME meets criteria for Class I evidence of AED efficacy, although levetiracetam was recently approved by the US Food and Drug Administration for use as adjunctive therapy in controlling myoclonic seizures in patients with JME. Based on an overwhelming body of evidence from open-label studies and retrospective case series, valproate monotherapy is presumed to be effective in JME.

Linkage studies, however, have shown that JME is a genetically heterogeneous disorder in which there may be multiple subsyndromes with subtle differences in phenotype, for example, seizure type combination, age at seizure onset, and EEG patterns [12]. Such differences are likely to reflect differences in pathophysiology and underlying molecular defects in ion channels that could influence response to AED therapy. Approximately 60% of patients with classic JME were reported to be seizure-free with AED therapy, including valproate, compared with less than 10% of patients with JME that had evolved from childhood absence epilepsy [12]. Efficacy evaluations of AED therapy in JME may benefit from genotyping in the future. In the meantime, our experience points to the need for more homogeneous populations or the need for very large sample sizes to accommodate genetic heterogeneity. Stratified randomization based on possible prognostic factors may minimize the chance occurrence of between-group imbalances that may confound data interpretation. Video/EEG would allow for more accurate evaluations of treatment effects on myoclonic and absence seizures, reducing data variability and increasing statistical power. An alternative endpoint, such as myoclonus-free days, could also reduce variability and improve data quality.

To increase the pool of eligible patients, inclusion criteria allowed patients with JME who were receiving an AED other than valproate or topiramate. The baseline AED was

then withdrawn to achieve valproate or topiramate monotherapy. At study entry, one-fourth (7/28) of patients entering the study were receiving phenytoin, carbamazepine or oxcarbazepine, which are known to aggravate myoclonic and/or absence seizures in JME [12–16]. Reductions in seizure frequency may reflect the effects of withdrawing these agents and/or the therapeutic effects of valproate or topiramate.

As others have demonstrated [8], topiramate and valproate have qualitatively different side effect profiles, as demonstrated by the specific adverse events reported to investigators, as well as the toxicity scale scores. These scores, which quantify the overall side effect burden of drug therapy, suggest that valproate is associated with a higher burden of systemic effects than topiramate. However, the two agents share a similarly low burden in terms of neurotoxicity. In both groups, neurotoxicity scores were unchanged from baseline in two-thirds or more of patients. The toxicity scales in our pilot study were derived from validated scales, but need to be validated on their own. However, this study illustrates the potential usefulness of toxicity rating scales for evaluating agents with different adverse event profiles.

An interesting observation is the difference between investigators and patients in their assessments of improvement. This difference is most notable in global improvement, with investigators' ratings being more positive than patients' self-ratings, regardless of treatment assignment. Both patients and investigators reported greater improvement in alertness with topiramate compared with valproate. In ratings of seizure severity improvement, interaction with patient's environment, and response to verbal requests, investigators tended to underestimate the degree of improvement with valproate that patients perceived. These findings underscore the importance of patients' perspective in assessing a therapy's success clinically.

The findings reported here reflect the limitations inherent in pilot studies with small sample sizes and point to the challenges of designing future studies to evaluate monotherapy AED efficacy in patients with JME. However, such studies are clearly needed. Although highly effective in JME, valproate is not appropriate nor is it well tolerated by all patients. Other effective, well-tolerated options with fewer long-term systemic effects need to be identified.

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