Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures

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ABSTRACT

Objective: To evaluate the efficacy and safety of adjunctive topiramate (sprinkle capsules or oral liquid) in reducing daily rates of partial-onset seizures (POS) in infants with refractory POS.

Methods: In this double-blind, placebo-controlled, parallel-group, international study, infants ($n = 149$) with clinical or EEG evidence of refractory POS were randomly allocated (1:1:1:1) to receive adjunctive topiramate 5, 15, or 25 mg/kg/d or placebo for 20 days. The primary variable was the median percentage reductions in daily POS rate from baseline to final assessment as recorded on a 48-hour video-EEG.

Results: Of the 149 infants (mean age 12 months) included in the intent-to-treat analysis set, 130 completed the study. Median percentage reduction from baseline in daily POS rate was not significantly different ($p = 0.97$) between topiramate 25 mg/kg (20.4%) and placebo (13.1%). Lower doses were not formally tested, but nominal p values for comparisons with placebo were not significant (15-mg/kg/d dose: $p = 0.97$; 5-mg/kg/d dose: $p = 0.91$). Treatment-emergent fever, diarrhea, vomiting, anorexia, weight decrease, somnolence, and viral infection occurred more frequently ($\geq 10\%$ difference) with topiramate than with placebo.

Conclusion: In infants aged 1–24 months, topiramate 5, 15, or 25 mg/kg/d was not effective as adjunctive treatment for refractory partial-onset seizures. No new safety concerns associated with topiramate use were noted.

Classification of evidence: This interventional study provides Class I evidence that topiramate 5, 15, or 25 mg/kg/d compared with placebo does not significantly reduce seizure rates in infants aged 1 month to 2 years with refractory partial-onset seizures. *Neurology*® 2010;74:714–720

GLOSSARY

AED = antiepileptic drug; **ANCOVA** = analysis of covariance; **ITT** = intent-to-treat; **MITT** = modified intent-to-treat; **POS** = partial-onset seizures; **TEAE** = treatment-emergent adverse event; **vEEG** = video-EEG.

The incidence of newly diagnosed epilepsy is highest in the first year of life and includes many syndromes that are unique and are difficult to diagnose and classify.^{1,2} Also, seizure types and epilepsy syndromes evolve with age, making accurate diagnoses difficult or retrospectively incorrect in up to 25% of cases.^{3,4} Contributing to the treatment challenges, many randomized controlled trials of newer antiepileptic drugs (AEDs) did not assess efficacy in children, and most available AEDs have not been rigorously investigated in infants, leaving physicians with incomplete data on which to base treatment decisions.⁵ A sizeable number of epilepsy syndromes are significantly different from those in adults. Therefore, clinical trial design in this population requires careful evaluation and must be different from adult trials.⁶ Drug dosing is also more difficult in children and often requires adjustment as the child matures.⁷

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Investigators and institutions at which trials were performed are listed in appendix e-1 on the *Neurology*® Web site at www.neurology.org. From the University of Washington (E.N.), Seattle, WA; Child Neurology Center (B.R.), Gulf Breeze, FL; Department of Pediatrics (N.Y.), K.E.M. Hospital, Pune, Maharashtra, India; Children's Memorial Hospital (D.N.), Chicago, IL; Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (S.N., S.W., T.W., C.L.K., E.Y., J.S.N., L.F.), Raritan, NJ; Johnson & Johnson Pharmaceutical Research & Development (M.E.), Division of Janssen Pharmaceutica, N.V., Beerse, Belgium; and SIRO Clinpharm Pvt. Ltd. (L.V.), Mumbai, India.

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Supplemental data at
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Preliminary evidence from prospective open-label studies in children,⁸ and retrospective review of patient records in infants with epilepsy⁹ and refractory epilepsy,¹⁰ indicated topiramate (Topamax[®]; Ortho-McNeil-Janssen Pharmaceuticals, Inc., Titusville, NJ) to be efficacious and well-tolerated as monotherapy or adjunctive therapy. A few case reports also suggested efficacy and tolerability of topiramate in infants with partial seizures.^{11,12} The current prospective, placebo-controlled, double-blind study assessed the efficacy, safety, and tolerability of adjunctive topiramate in infants with refractory partial-onset seizures (POS).

METHODS **Infants.** Infants of either sex, aged 1–24 months, inclusive, of at least 41 weeks of gestational age, weighing ≥ 3.5 kg and < 15.5 kg, length ≥ 49 cm, and receiving regular enteral feeding were enrolled. At enrollment, infants needed to have a diagnosis of POS, based on clinical or EEG evidence, with or without secondary generalization (at least 1 month before for infants older than 6 months, and at least 2 weeks before for infants aged 6 months or younger), a CT or MRI scan to confirm the absence of a progressive lesion (lesions of tuberous sclerosis and Sturge-Weber syndrome were allowed), and an EKG with no “abnormal, clinically significant” interpretations as made by the central reader. Infants must have been receiving at least 1 concurrent marketed AED other than topiramate for 1 month or more for infants older than 6 months and for more than 2 weeks for infants aged 6 months or younger. The existing treatment was concluded by the investigator to be inadequate in controlling seizures if infants, at optimized doses of the AEDs, had at least 1 seizure in the 4 weeks before screening. In addition, the AED must have been unchanged for at least 5 half-lives before screening.

Infants were excluded if they could not take oral medications; had a surgically implanted and functioning vagus nerve stimulator; had epilepsy surgery within 3 months before screening; or had febrile seizures, seizures due to an acute medical illness, or nonepileptic seizures within 2 weeks before the first day of screening. Infants with progressive neurologic disorders, uncontrolled medical illness, disturbances of autonomic function, inborn errors of metabolism, and known hypersensitivity to topiramate were also excluded. Infants with status epilepticus (defined as 30 minutes of continuous motor seizures) in the 2 weeks before, infants who had received more than 4 courses of rescue treatments (such as diazepam) in the month before the first day of screening, and infants using 3 or more concurrent AEDs were excluded from the double-blind phase.

Infants who met all inclusion criteria and had in addition at least 4 seizures in the 2 weeks before the first day of screening were qualified for baseline 48-hour vEEG. Infants with evidence of at least 2 countable electroclinical POS seizures in the 48-hour vEEG were eligible for entry into the double-blind phase.

Standard protocol approvals, registrations, and patient consents. The independent ethics committee or institutional review board at each study site approved the protocol, and the study was conducted in accordance with the ethical principles

that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. All parents (or their legally acceptable representatives) of infants provided written informed consent. This study is registered at ClinicalTrials.gov (NCT00113815).

Study design. This vEEG rater-blinded, parallel-group, 4-arm study was conducted from September 2005 to June 2007 in 52 centers across 19 countries in Asia, the European Union, Latin America, and the United States.

The study consisted of 4 phases: a 3-day screening phase during which the 48-hour baseline vEEG was performed, a 20-day double-blind treatment phase, a 1-year open-label extension, and a follow-up visit 30 days after the last treatment visit. The results of the double-blind phase are reported here.

Double-blind phase. Infants were randomly allocated (1:1:1:1) by an Interactive Voice Response System to topiramate 5, 15, or 25 mg/kg/d or placebo (randomization was performed centrally using randomly permuted blocks, stratified by infants’ age at randomization, but not by center). Investigators, study staff, infants’ parents (or their legally acceptable representatives), and the sponsor were blinded to study medication identity and final dosage.

Infants received topiramate and matching placebo orally (as either the liquid or the sprinkle capsule formulation), twice daily, in addition to their existing regimen of AEDs. The liquid formulation was given to all infants weighing < 9 kg; to heavier infants who could not take solid foods; and to any infant with agreement of parents or legally acceptable representatives, the investigator, and the sponsor’s medical monitor. All other infants received the sprinkle capsule. Topiramate was started at 3 mg/kg/d, with upward titration every 3 days until the final target dosage of 5, 15, or 25 mg/kg/d or the maximum tolerated dose had been achieved (table e-1 on the *Neurology*[®] Web site at www.neurology.org). The topiramate dose strengths were 5 mg/mL for oral liquid and 25 mg per sprinkle capsule. The formulations were likely bioequivalent, based on available data.

A single dose reduction of study medication was allowed for safety or tolerability concerns. Infants then continued at the reduced dose. A pause in upward titration was also permitted. The number and doses of concomitant AEDs remained constant (except in case of elevated AED levels or adverse effects, when dose reductions were permitted). A course of rescue treatment for seizure exacerbation or status epilepticus was permitted twice (infants were withdrawn from the study if the status epilepticus was not controlled by a single course of rescue treatment). Compliance to study medication was ensured by maintaining a log of all study drug dispensed, ensuring return of blister packages and bottles (used and unused), ensuring completion of take-home record by parents and recording of that information in the case report form by investigator or designated study personnel.

Efficacy assessment. A 48-hour vEEG was recorded during screening (baseline) and at end of the double-blind phase or at early withdrawal and was read by a blinded central reader. Seizure events were counted on the vEEG only if qualifying EEG changes were accompanied by clinical evidence of a seizure manifestation. The criteria for qualifying EEG changes were a duration ≥ 10 seconds, involvement of at least 2 adjacent electrodes, and clearly focal or asymmetric changes that had a recognizable evolution. At a minimum of once a day, each infant’s parent (or legally acceptable representative) recorded the date, type, and number of seizures for each seizure type; adverse events seen and action taken; and study drug information (daily dosing details

Figure 1 Patient disposition in the double-blind phase (intent-to-treat analysis set)

"Other" reasons for withdrawal included meeting the escape criterion, doubling of seizure rate, multiple seizures, more than 1 dose reduction, incorrect dosing, withdrawal of consent, and unknown. AE = adverse event.

including regimen, vomited doses, and action taken) in the take-home records that were provided at screening and at each subsequent visit.

Table 1 Patient demographics and baseline characteristics (intent-to-treat analysis set)

	Placebo (n = 37)	Topiramate		
		5 mg/kg/d (n = 38)	15 mg/kg/d (n = 37)	25 mg/kg/d (n = 37)
Age, mean (SD), mo	12 (5.9)	13 (7.6)	12 (6.2)	10 (5.2)
Sex, n (%)				
Boys	14 (38)	22 (58)	19 (51)	23 (62)
Race, n (%)				
White	26 (70)	25 (66)	19 (51)	21 (57)
Black or African American	1 (3)	1 (3)	1 (3)	2 (5)
Asian	9 (24)	7 (18)	11 (30)	7 (19)
Other ^a	1 (3)	5 (13)	6 (16)	7 (19)
Weight, mean (SD), kg	9 (2.4)	9 (2.5)	9 (2.5)	8 (2.2)
Length, mean (SD), cm	73 (8.9) ^b	74 (11.2)	74 (8.5)	71 (8.3)
Length (percentile)				
Mean (SD)	41 (33.9)	35 (35.1)	42 (31.2)	37 (33.3)
Median (range)	29 (1–99)	19 (0–100)	41 (0–98)	41 (0–98)
Head circumference, mean (SD), cm	42 (3.8)	43 (4.0)	42 (3.6)	42 (3.6) ^b
Head circumference (percentile)				
Mean (SD)	21 (30.2)	22 (31.3)	15 (26.0)	18 (29.9)
Median (range)	3 (0–98)	3 (0–96)	1 (0–93)	1 (0–94)
Days since first seizure, median (range)	247 (35–704)	260 (34–712)	247 (42–666)	261 (32–679)
Days since epilepsy diagnosis, median (range)	197 (22–602)	196 (8–683)	157 (9–635)	187 (9–618)

^a"Other" includes all Indian (from India) except 1 Thai in the topiramate 5-mg/kg/d group.

^bn = 36.

The primary efficacy variable was the percentage reduction in daily POS rate (for all dosage groups tested) as recorded on 48-hour vEEG. The secondary efficacy variables included percentage of treatment responders (defined as $\geq 50\%$ reduction in seizure rate for POS and all seizure types as recorded on 48-hour vEEG); and percentage reduction in seizure rates for all seizure types as recorded on 48-hour vEEG, and for POS and all seizure types as recorded on infant take-home records.

Safety assessments. Safety assessments included monitoring and recording all treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital sign measurements, anthropometric measurements, physical and neurologic examination results, renal ultrasounds, 12-lead EKGs, and evaluations for oligohydrosis, hyperthermia, and rash.

Study population. Data from infant take-home records were analyzed using the intent-to-treat (ITT) population, which included infants who were randomized, received at least 1 dose of study medication, and had at least 1 postbaseline efficacy measurement. Data from vEEG recordings were analyzed using the modified ITT (MITT) population, which included infants who had provided evaluable (interpretable, obtained before the first dose of study medication and within 2 days of the last dose of study medication, and not obtained within 48 hours after a dose of rescue treatment or immediately after a significant change in maintenance AEDs) vEEG data at baseline and at the end of the double-blind phase. Safety data were analyzed using the safety population, which included infants who were randomized and received at least 1 dose of study medication.

Statistical methods. The primary efficacy analysis compared each topiramate group with placebo, using a step-down procedure at a 2-sided type I error of 0.05 for each step. The percentage reduction in POS rate based on vEEG data was analyzed using an analysis of covariance (ANCOVA) on ranks, including age group (< 6 months vs ≥ 6 months on day 1) and treatment group as factors, and baseline POS seizure rate as a covariate. Effect of additional factors, such as sex, baseline AED category (inducer, noninducer), and number of AEDs (≤ 1 , 2, > 2), were also analyzed using the same ANCOVA model. Percentage reduction in seizure rates for POS and all seizure types based on vEEG data and infant take-home records were also analyzed using the same ANCOVA model. The proportions of responders were summarized by treatment group and compared with those for placebo at a 2-sided significance level of 0.05, using Mantel-Haenszel statistics stratified by age group.

Sample size determination. A sample size of 30 infants per group (a total of 120 infants for the 4 arms) was required to have an 80% power to detect a 37% treatment difference, based on previous studies in adults,¹³ assuming that the treatment effects would be similar and the standard deviation would be no greater than 50%.

RESULTS Of the 149 infants enrolled, 130 completed the study (figure 1). In the ITT (n = 149) and MITT (n = 130) analysis sets, the most common reasons for study discontinuation across all treatment groups were discontinuations due to "other" reasons.

Demographics and baseline characteristics of infants in the 4 treatment groups were generally similar in the ITT and MITT analysis sets. The study population was

Figure 2 Percentage reduction in partial-onset seizures from baseline to the end of double-blind treatment period

Based on modified intent-to-treat analysis set; $n = 28$ (placebo), 34 (topiramate [TPM] 5 mg/kg/d), 34 (TPM 15 mg/kg/d), 34 (TPM 25 mg/kg/d). Based on video-EEG data; for infants who had 0 baseline seizures and the postseizure number was greater than 0, value $-8,999$ was imputed as the percent reduction in accordance with the worst-rank analysis. Differences in interpretation of the baseline video-EEG between the investigator and the blinded central reader resulted in infants with 0 baseline seizures per the central reader entering the study. The lower and higher boundaries of the boxes are the 25th and 75th percentiles. Whiskers below and above indicate the 10th and 90th percentiles. The solid lines within the boxes mark the medians. Outlying data points are extreme values. 25-mg/kg/d dose: $p = 0.97$; 15-mg/kg/d dose: $p = 0.97$; 5-mg/kg/d dose: $p = 0.91$ vs placebo.

52% boys, 61% white, with a mean (SD) age of 12 (6.3) months (table 1). Based on seizure log data, the percentage of infants with both partial and generalized seizures was low (overall rate of 13%); 36% of infants had partial secondarily generalized seizures. vEEG patterns consistent with profound epileptogenic encephalopathy were observed in 29% of infants.

At baseline, 55% of infants were using 1 AED and 44% were using 2 AEDs. The most frequently used AEDs at baseline were valproic acid (56%), phenobarbital (29%), and carbamazepine (17%). Rescue medications (phenobarbital, diazepam, lorazepam) were needed by 9 of 112 infants (8%) in the combined topiramate groups and 4 of 37 infants (11%) in the placebo group. The median treatment duration was 20 days in each treatment group. The double-blind phase was completed at the target topiramate dosage by 95% infants on 5 mg/kg/d, 76% on 15 mg/kg/d, and 84% on 25 mg/kg/d.

Primary efficacy. There was no difference ($p = 0.97$) in median percentage reduction from baseline in daily POS rate between topiramate 25 mg/kg (20.4%) and placebo (13.1%). Lower doses, though not formally tested, were also not significantly differ-

ent from placebo (figure 2). Similar results were obtained when the analysis was additionally adjusted for sex ($p = 0.28$), category (inducer, noninducer) of AEDs used at baseline ($p = 0.59$), or number of AEDs at baseline ($p = 0.93$).

Secondary efficacy. The percentages of treatment responders in the topiramate groups (27% [$n = 9$] in the 5-mg/kg/d group, 38% [$n = 13$] in the 15-mg/kg/d group, and 44% [$n = 15$] in the 25-mg/kg/d group) were not different from placebo (36% [$n = 10$], $p > 0.4$ for all topiramate groups compared with placebo). The median percentage reduction in seizure rate for all seizure types based on vEEG data, or for POS or all seizure types based on infant take-home records, was also not different between any of the topiramate groups and placebo ($p > 0.2$ for all comparisons) (table 2).

Safety. The incidence of TEAEs was higher in the combined topiramate groups (81%) vs the placebo group (51%). Incidences of anorexia and weight decrease in the topiramate groups were dose related (figure 3). Status epilepticus was observed in 1 infant each on topiramate 5 mg/kg/d and placebo. Similar per-

Table 2 Percent reduction in seizure frequency by seizure type at end of double-blind phase (modified intent-to-treat and intent-to-treat analysis sets)^a

Seizure type	Placebo	Topiramate		
		5 mg/kg/d	15 mg/kg/d	25 mg/kg/d
Based on vEEG data (MITT analysis set)	n = 28	n = 34	n = 34	n = 34
All seizure types, median (range)				
Baseline	6.39 (0.0 to 148.7)	6.75 (0.0 to 158.6)	8.33 (0.0 to 176.4)	10.00 (0.0 to 148.1)
Change from baseline ^b	15.68 (–8,999.0 to 100.0)	23.83 (–8,999.0 to 100.0)	5.53 (–8,999.0 to 100.0)	20.40 (–8,999.0 to 100.0)
p Value ^c		0.99	0.94	0.97
Based on infant take-home records (ITT analysis set)	n = 36	n = 37	n = 37	n = 37
POS, median (range)				
Baseline	6.00 (0.0 to 240.0)	7.50 (0.0 to 175.0)	5.00 (0.0 to 78.5)	8.00 (0.0 to 100.0)
Change from baseline ^b	9.87 (–8,999.0 to 97.7)	29.63 (–8,999.0 to 100.0)	0.08 (–8,999.0 to 100.0)	15.79 (–8,999.0 to 100.0)
p Value ^c		0.45	0.97	0.68
All seizure types, median (range)				
Baseline	8.75 (0.0 to 250.0)	13.50 (0.0 to 457.5)	6.50 (0.0 to 151.5)	11.00 (0.0 to 299.5)
Change from baseline ^b	9.87 (–8,999.0 to 97.7)	22.22 (–8,999.0 to 100.0)	5.69 (–8,999.0 to 100.0)	25.00 (–8,999.0 to 100.0)
p Value ^c		0.27	0.50	0.22

Abbreviations: ITT = intent-to-treat; MITT = modified intent-to-treat; POS = partial-onset seizures; vEEG = video-EEG.

^aThe baseline seizure frequencies for the MITT and ITT analysis sets are based on daily seizure rates. One infant in the placebo group and 1 infant in the topiramate 5-mg/kg/d group (ITT analysis set) did not have the baseline seizure information in their seizure logs and hence have not been included in the analysis.

^bFor patients who had 0 baseline seizures and the postseizure number is greater than zero, value –8,999 was imputed as the percent reduction in accordance with the worst-rank analysis. Differences in interpretation of the baseline vEEG between the investigator and the blinded central reader resulted in infants with 0 baseline seizures per the central reader entering the study.

^cTest for no difference between treatments based on an analysis of covariance model using ranked data with factors for treatment group, age stratification at randomization (<6 vs 6–24 months), and baseline POS rate as covariate.

centages of infants on topiramate (4%) and placebo (5%) discontinued the study because of a TEAE.

Treatment-emergent serious adverse events were reported in 3 infants each in the 4 treatment groups. No deaths occurred during the double-blind phase. The only death reported (staphylococemia) occurred on an unknown date after early discontinuation of topiramate 5 mg/kg/d and was considered by the investigator to have a doubtful relationship with topiramate.

Markedly low serum CO₂ level (<17 mmol/L or decrease of >5 mmol/L from baseline) was the only clinically significant laboratory abnormality with a higher incidence (≥5% difference) in the combined topiramate groups (6%, n = 7) compared with placebo (0%). A dose-related mean decrease in serum CO₂ levels was observed with topiramate (–3.31 mmol/L in the 5-mg/kg/d group, –4.07 mmol/L in the 15-mg/kg/d group, and –5.15 mmol/L in the 25-mg/kg/d group) vs placebo (0.72 mmol/L). Indications of metabolic acidosis (low serum CO₂ values, adverse event, or need for alkali therapy) were observed in 9% (n = 10) of infants on topiramate vs none on placebo. There was no clinically meaningful effect of topiramate on mean change in liver function

tests or ammonia. Hyperammonemia (ammonia levels >128 μmol/L and >1.5 times increase from baseline) was reported in 1 infant on topiramate and concomitant valproate treatment. There were no reports of increased intraocular pressure, acute myopia, or acute secondary angle-closure glaucoma. No renal or hepatic safety concerns were raised, and nephrolithiasis was not detected. There were no reports of oligohydrosis or oligohydrosis-related hyperthermia. Rash was reported in 3 infants on topiramate (study discontinuation resulted for 1 infant) and 2 on placebo.

No clinically meaningful changes in vital signs, EKG variables, or laboratory values (other than CO₂ and ammonia) were observed. The mean percentage increase in body weight from baseline to end of the double-blind phase was less in the topiramate groups (≤1.76%) compared with placebo (3.39%). Seven infants on topiramate had an adverse event of decreased weight vs 1 infant on placebo.

DISCUSSION In this double-blind trial, topiramate at all doses tested was not effective in the reduction in seizures in infants with refractory POS. The completion rate, extent of exposure, and target doses

Figure 3 Treatment-emergent adverse events experienced by $\geq 5\%$ of patients in any of the topiramate groups

Based on safety analysis set ($n = 149$). For each of the treatment-emergent adverse events, data for all treatment groups are shown, but there were many points of overlap among groups. TPM = topiramate.

achieved were robust and adequate for all topiramate dose groups. The results of all analyses were highly consistent with each other. The population exposed in this controlled study was also similar to that of earlier uncontrolled studies.⁸ Thus, the lack of efficacy is likely not attributable to study methodology or conduct factors.

The lack of efficacy for topiramate observed in this study differs from results obtained in adults and children older than 2 years with refractory POS,¹⁴⁻¹⁸ suggesting fundamental differences in refractory POS experienced by infants. Topiramate, at dosages ranging from 1 to 24 mg/kg/d, was effective in controlling multiple seizure types and was well tolerated in pediatric patients (aged 1–18 years) with refractory epilepsy in an open-label study.⁸

The infants in this study included a heterogeneous population from 52 centers worldwide. Although the focus was on refractory POS, infants with a diversity of other seizure types were also enrolled. Pediatric epileptology literature consistently documents that seizure disorders in very young children follow a dichotomous course and are either benign and inconsequential or catastrophic, i.e., difficult to control and usually associated with adverse long-term outcomes such as mental retardation.^{19,20} Early in their course, it is often difficult to distinguish the children with catastrophic epilepsy from those whose epilepsy will ultimately be medically controlled.⁴ Many children with catastrophic epilepsies also

have seizures as a result of clinically important underlying brain abnormalities^{21,22} and are very pharmacoresistant.^{23,24} The results suggest that infants are a particularly treatment-resistant patient population. By contrast, seizures associated with epilepsies of later onset in patients older than 2 years, which usually have different underlying causes, are more readily treatable with AEDs.

Topiramate at dosages up to 25 mg/kg/d was generally well tolerated as adjunctive therapy, and there were no new or unexpected safety findings in the infants in this study compared with previous results for adults and older children. There was a dose-related increase in the incidence of anorexia and weight decrease in the topiramate groups. The cognitive and neuropsychiatric events that occurred for at least 5% of topiramate-treated patients were ataxia, somnolence, and nervousness. Metabolic acidosis was reported in 10 infants, of whom 7 were from Asian countries (mainly India).

The double-blind period was necessarily short compared with trials in adults because of the ethical concerns in designing longer placebo-controlled trials in this vulnerable patient group. Coupled with the requirement to up-titrate topiramate, infants were only exposed for a few days to the higher doses. In addition, use of 48-hour vEEGs made the efficacy parameter dependent on an extremely short sample window compared with trials in adults where seizure rates are sampled over weeks. This may have increased variability

and the likelihood of failure to distinguish treatment differences. However, the use of vEEG monitoring led to unambiguous detection of seizures and demonstrated the heterogeneity of seizure types and the occurrence of epileptic encephalopathies in nearly one-third of the infants with vEEG recordings.

In this well-controlled, randomized, double-blind study, topiramate 5, 15, or 25 mg/kg/d was not effective as adjunctive treatment for refractory POS in infants aged 1–24 months. Topiramate treatment was well tolerated, and no new safety concerns appeared.

AUTHOR CONTRIBUTIONS

Dr. Wang and Ms. Weber, employees of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., are responsible for the statistical analyses.

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DISCLOSURE

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