Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures

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Abstract—*Objective:* To evaluate the efficacy and tolerability of levetiracetam (LEV) as adjunctive therapy in children (4 to 16 years) with treatment-resistant partial-onset seizures. *Methods:* This multicenter, randomized, placebo-controlled trial consisted of an 8-week baseline period followed by a 14-week double-blind treatment period. During the treatment period, patients received either placebo or LEV add-on therapy and were up-titrated to a target dose of 60 mg/kg/day. *Results:* One hundred ninety-eight patients (intent-to-treat population) provided evaluable data. The reduction in partial-onset seizure frequency per week for LEV adjunctive therapy over placebo adjunctive therapy was significant (26.8%; $p = 0.0002$; 95% CI 14.0% to 37.6%). A 50% or greater reduction of partial seizure frequency per week was attained in 44.6% of the LEV group (45/101 patients), compared with 19.6% (19/97 patients) receiving placebo ($p = 0.0002$). Seven (6.9%) LEV-treated patients were seizure-free during the entire double-blind treatment period, compared with one (1.0%) placebo-treated patient. One or more adverse events were reported by 88.1% of LEV-treated patients and 91.8% of placebo patients. The most common treatment-emergent adverse events were somnolence, accidental injury, vomiting, anorexia, hostility, nervousness, rhinitis, cough, and pharyngitis. A similar number of patients in each group required a dose reduction or withdrew from the study as a result of an adverse event. *Conclusion:* Levetiracetam adjunctive therapy administered at 60 mg/kg/day is efficacious and well tolerated in children with treatment-resistant partial seizures.

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Partial seizures are the most common seizure type in children.[1,2] All new antiepileptic drugs (AEDs) approved worldwide during the past decade have rigorously demonstrated efficacy against partial seizures in adults in adjunctive placebo-controlled trials.[3] Four newer anticonvulsants (oxcarbazepine, topiramate, lamotrigine, and gabapentin) have completed adjunctive placebo-controlled trials in children with treatment-resistant partial seizures.[4-7] More than 25% of adults and children with epilepsy experienced treatment-resistant seizures or intolerable side effects.[8] Even with the newer agents, many children continue to have inadequate seizure control.[9] This indicates a need for new AEDs to help this cohort of patients achieve better seizure control, or seizure control without intolerable side effects.

Levetiracetam (Keppra®, (*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide) is an AED with linear pharmacokinetics, minimal metabolism, an incompletely described mechanism of action, and a unique preclinical profile.[10] The mechanism of action of levetiracetam seems to be unrelated to known mechanisms of neurotransmission. Levetiracetam seems to partially inhibit N-type high-voltage–activated Ca^{2+} currents and reduces the Ca^{2+} release from intraneuronal stores.[11-14] It reverses the effects of negative allosteric modulators of γ-aminobutyric acid (GABA)– and glycine-gated currents.[15] Recently, the identification of the levetiracetam binding site was revealed as the

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synaptic vesicle protein 2A (SV2A).[16] Levetiracetam has demonstrated efficacy and a favorable tolerability profile as adjunctive therapy in treatment-resistant partial seizures in adults,[17,18] while two open-label studies[19,20] and a retrospective case study[21] suggest it is likely to be efficacious and well tolerated in children as well. The combination of pharmacokinetic and pharmacodynamic properties, coupled with the need for additional proven therapies in children with treatment-resistant partial seizures, signifies the need for a randomized controlled trial. In this study, we evaluated the efficacy and tolerability of levetiracetam as adjunctive therapy in children aged 4 to 16 years with inadequately controlled partial seizures.

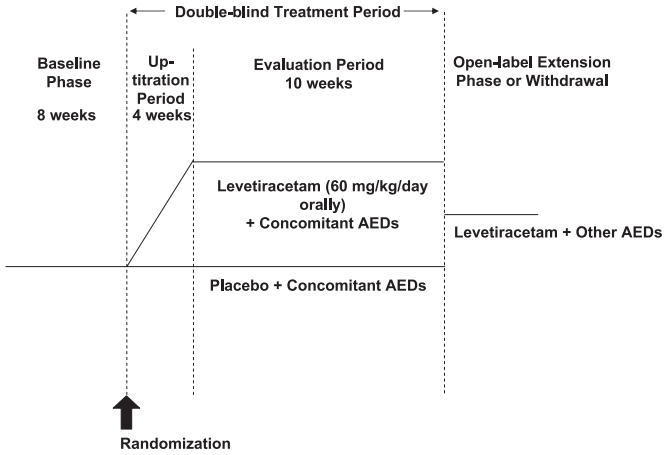

Figure 1. Trial design. AED = antiepileptic drug.

Methods. *Patients.* Children aged 4 to 16 years, inclusive, and weighing 13.5 to 80 kg (30 to 177 lb) were eligible for randomization into the study if they had partial seizures (including the subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures) that at the time of enrollment were inadequately controlled with one or two concomitant AEDs. The diagnosis of epilepsy with uncontrolled partial seizures, whether or not secondarily generalized, had to be made at least 6 months before the screening visit. This diagnosis was based on the International League Against Epilepsy Classification.[22,23] To qualify for randomization, patients were required to have at least four partial seizures during the 4 weeks preceding the screening visit and to have at least four partial seizures during each 4-week interval of the 8-week baseline period.

During the 2 weeks before the screening visit, the addition or deletion of AEDs was not permitted, although minor adjustments to current AED dosages were allowed. AED dosages had to remain unchanged during the study's baseline and treatment periods (including the up-titration and evaluation periods). Intermittent benzodiazepines (≤1 administration per week) were allowed; routine benzodiazepine use was allowed as one of the two AEDs. Vagal nerve stimulation implanted more than 6 months before the screening visit, and with stable settings for the 2 months preceding that visit, was allowed and considered one of the two AEDs. Female patients were required to be premenarchal, surgically sterile, or practicing a medically acceptable method of contraception. Females of childbearing potential were required to have a negative pregnancy test at the screening visit.

Pregnant or nursing females or those trying to conceive were excluded from the study. Patients were excluded if there was evidence or a history of any of the following: a treatable seizure etiology; epilepsy secondary to a progressive cerebral disease or any other progressively neurodegenerative disease; seizures too close together to accurately count; status epilepticus that required hospitalization during the 3 months before the screening visit; history of or the presence of pseudoseizures; current diagnosis of Lennox-Gastaut syndrome; a cardiovascular, respiratory, hepatic, renal, gastrointestinal, hematologic, oncologic, psychiatric, or progressive neurologic disorder likely to have an impact on the outcome of the trial; any disorder or condition that might have interfered with the absorption, distribution, or excretion of drugs; current or past allergy to pyrrolidone derivatives or a history of multiple drug allergies; clinically significant deviations from reference range values for laboratory parameters as determined by the investigator; any medication (other than a concomitant AED) acting on the CNS that had not been on a stable regimen for more than 1 month before the screening visit; felbamate use for less than 18 months before the screening visit; use of any investigational drug or device during the 30 days before the screening visit; participation in any previous levetiracetam study; or use of a ketogenic diet within 30 days before the screening visit.

The study was conducted at 60 centers in the United States and Canada; data from 1 of these centers were excluded (see Results, Patient characteristics), and 7 centers enrolled no patients. The study's protocol and consent forms were approved by institutional review boards at each center, and the study was conducted in accordance with the Declaration of Helsinki. Before enrollment, all study protocol aspects were reviewed with all parents or legal guardians (and patients if appropriate), and written informed consent was obtained.

Study design. The study was a randomized, placebo-controlled, double-blind, parallel-group trial consisting of an 8-week baseline period (figure 1) followed by a 14-week double-blind treatment period. At the conclusion of the double-blind treatment period, patients could either withdraw study drug over 6 weeks or enter a blinded conversion period leading to an open-label extension study. Only results from the double-blind treatment period are reported here. The baseline period began with a screening visit during which investigators obtained informed consent, assessed entry criteria, and performed screening procedures. These procedures included a complete physical and neurologic history and examination (pulse, blood pressure, and body weight) and laboratory testing (blood chemistry, hematology, urinalysis, and pregnancy test if appropriate). During the 8-week baseline period, patients were maintained on a stable dose of their AED(s), and, throughout the baseline and treatment periods, patients or their parents or legal guardians maintained a diary in which they recorded seizure type and frequency. These diaries were reviewed, and the seizures were coded by the investigators.

Patients who completed the baseline period and still met eligibility criteria entered into the double-blind treatment period. The treatment period was composed of a 4-week up-titration period and a 10-week evaluation period. At the start of the up-titration period, patients were randomized to receive placebo or levetiracetam at an initial dose of 20 mg/kg/day, increasing every 2 weeks to a final target dose of 60 mg/kg/day. If a patient could not tolerate 60 mg/kg/day, the dose could be reduced to 40 mg/kg/day and maintained at that dose for the remainder of the evaluation period. Patients exited the trial if they could not tolerate 40 mg/kg/day. All study medications were administered orally in two divided doses approximately 12 hours apart.

Randomization used a computer-generated schedule with patients allocated sequentially. The randomization schedule was performed by center using a permuted block size of 4.

Blinding was maintained through the use of matching levetiracetam and placebo tablets of identical appearance for oral administration; these tablets were packaged in blister cards to be dispensed to the patient. All patients, investigators, site personnel, study personnel from the contract research organization responsible for the monitoring and conduct of the trial, and study sponsor personnel were blinded to the identity of each patient's specific study drug. Except in cases of emergency, specific patients' trial drug identity codes and plasma concentrations of levetiracetam were not available to study personnel until after trial completion and final data review. No unblinding occurred during the study.

During the 10-week evaluation period, patients continued the total daily dose of study medication achieved at the conclusion of the 4-week up-titration period and maintained that dose throughout the study unless a dose reduction was required for safety concerns. Patients returned to the clinic for evaluations of efficacy and tolerability at 2-week intervals for the first 6 weeks of the

treatment period (visits at weeks 10, 12, and 14, with the screening visit as week 0) and at 4-week intervals for the remaining 8 weeks (visits at weeks 18 and 22). During the treatment period, investigators conducted interim physical examinations, documented treatment-emergent adverse events and concomitant medication/nondrug therapy use, performed routine laboratory tests, and measured plasma concentrations of concomitant AEDs. Treatment-emergent adverse events were collected through parental spontaneous reporting, parental responses to open-ended general health questions, and investigator observation. Formal side effect questionnaires were not used to identify adverse events.

Potential reasons for premature discontinuation from study medication during the double-blind treatment period included intolerable adverse events; decision by parent, guardian, or investigator that it was in the patient's best interest; or any major trial protocol violation.

Efficacy and safety variables. The primary efficacy variable was partial seizure frequency (including simple, complex, and secondarily generalized partial seizures) per week during the treatment period. Secondary efficacy variables included responder rates (defined as the percentage of patients experiencing a ≥50% reduction from baseline in partial seizure frequency during the treatment period), percentage reduction from baseline in partial seizure frequency, percent reduction from baseline in seizure frequency by category (>25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%), absolute change from baseline in partial seizure frequency, cumulative percentage of seizure-free patients since beginning of the evaluation period, and partial seizure frequency per week during the up-titration and evaluation periods. The tolerability of levetiracetam was evaluated by comparing rates of spontaneously reported treatment-emergent adverse events in the two treatment groups, together with results of physical and neurologic examinations, laboratory tests, vital signs, and EKGs for each treatment group.

Statistical analyses. A sample size of 120 patients (60 per treatment arm) was initially chosen to provide 80% power to detect a difference in mean log-transformed seizure frequency per week of 0.223, assuming that the common SD was 0.43 using a two-group t test with a 0.050 two-sided significance level. This common SD value was taken from previous adult epilepsy trials. A difference of 0.223 in log-transformed data corresponded to a reduction from placebo of 20% in seizure frequency per week. All statistical analyses were planned before the unblinding of the trial drug code and were performed using the intent-to-treat (ITT) patient population.

In January 2001, a blinded review of the seizure frequency per week for the first 64 evaluable patients was performed to assess whether the pretrial SD assumption of 0.43 was valid. The blinded review determined the SD to be 0.55 rather than 0.43. Accordingly, the study's sample size was increased to 97 patients per group, using this new common SD of 0.55 in the above sample size calculation. The initial randomization list had been developed for 40 sites. When the sample size, and consequently the number of sites, increased, a randomization extension list was generated according to the same specifications as the original randomization.

The ITT population consisted of all randomized patients who took at least one dose of levetiracetam or placebo and for whom at least one postrandomization data point was available. Efficacy and tolerability analyses were conducted by treatment group using descriptive methods for all variables. The two methods of presenting the data descriptively were 1) a frequency distribution containing the numbers of observations and the corresponding percentages for dichotomous and categorical variables (whether ordered or not); and 2) the number of available observations, mean, SD, median, first and third quartiles, minimum, and maximum for continuous variables.

The primary efficacy variable was analyzed using analysis of covariance (ANCOVA). The partial seizure frequency per week during the treatment period (up-titration and evaluation periods) was computed. Because the data for seizure frequency per week were not normally distributed, the ANCOVA model was applied on the $\log_e (x + 1)$ transformed data (seizure frequency per week), including treatment as a factor and the $\log_e$ transformed baseline seizure frequency as a covariate. The difference in treatment least squares mean with a two-sided 95% CI was computed and expressed as a percentage reduction over placebo, i.e., $100 \times [1 - \exp(\text{least squares mean (levetiracetam)} - \text{least squares mean (placebo)})]$. For absolute change and percent of partial seizure frequency per week from baseline, the Kruskal–Wallis test was used for between-treatment comparisons.

A logistic regression model was used to compare treatment groups with respect to responder rates over the treatment period. An odds ratio with a 95% CI was also computed.

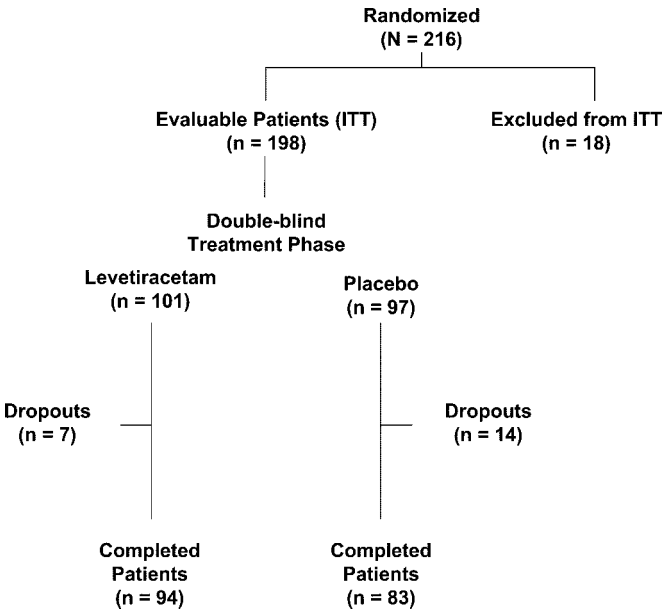

Figure 2. Patient disposition. ITT = intent-to-treat.

Results. *Patient characteristics.* Eligible patients were enrolled between September 1999 and March 2003 (42 months). Overall, 282 patients were screened, and 216 were randomized (figure 2). Before breaking the blind, 18 patients were excluded, including all 16 patients at one site who were excluded because of extensive violation of the protocol and consequent unreliability of the data, and 2 patients because they discontinued before taking any study medication. Therefore, 198 evaluable patients were identified and considered the ITT population for data analysis. These patients were randomized to double-blind treatment with levetiracetam (n = 101) or placebo (n = 97).

Baseline demographic and seizure characteristics are summarized in table 1. The levetiracetam and placebo treatment groups were similar with respect to age (mean 10.2 years and 9.8 years, respectively), sex (male 54% and 47%), and race (white 73% and 67%). The two groups were also similar with regard to mean duration of epilepsy (7.4 vs 6.8 years), mean age at diagnosis (2.9 vs 3.1 years), and percentage of patients taking one (30.7% vs 37.1%) or two (60.4% vs 55.7%) concomitant AEDs during the 8-week baseline period. During the 8-week baseline period, the median partial seizure frequencies per week in the levetiracetam and placebo groups were 4.7 and 5.3, respectively, whereas the mean (± SD) partial seizure frequencies per week were 19.6 ± 71.6 and 18.5 ± 50.9.

Of the 198 patients (ITT), 177 (89.4%) completed the treatment period, and 21 (10.6%) discontinued treatment prematurely (7 patients in the levetiracetam group and 14 patients in the placebo group). The most common reason for discontinuation was adverse events: 5 patients (5.0%) in the levetiracetam group and 9 patients (9.3%) in the

Table 1 *Demographic and baseline characteristics (intent-to-treat population)*

Variable	Levetiracetam, n = 101	Placebo, n = 97
% Male	53.5	47.4
% White	73.3	67.0
Age, median (range), y	10.4 (4–17)	9.7 (3–17)
% Receiving concomitant AEDs (in >10% of patients)		
Carbamazepine	34.7	38.1
Topiramate	28.7	32.0
Valproate	25.7	28.9
Lamotrigine	22.8	20.6
Oxcarbazepine	12.9	10.3
Partial seizure frequency, median (range)	4.7 (0–696)	5.3 (0–467)

AED = antiepileptic drug.

placebo group. Other reasons for discontinuation included unsatisfactory therapeutic effect (no levetiracetam patients vs 2 placebo patients), patient lost to follow-up (1 levetiracetam patient vs 2 placebo patients), and other (1 each in the levetiracetam and placebo groups).

Efficacy. Levetiracetam adjunctive therapy resulted in a reduction in partial-onset seizure frequency per week, and percent reduction over placebo during the treatment period was 26.8% ($p = 0.0002$; 95% CI 14% to 37.6%). Median partial-onset seizures per week by visit with last observation carried forward are presented in figure 3, and each median, with the respective Quartile 1 and Quartile 3 values, is presented in table E-1 (on the *Neurology* Web site at www.neurology.org). Significant differences between levetiracetam and placebo treatment were initially observed at the first time point of data analysis, 2 weeks after randomization. The median percentage reduction from baseline during the treatment period in weekly partial seizure frequency was higher in the levetiracetam group compared with the placebo group (43.3% vs 16.3%; Kruskal–Wallis, $p < 0.0001$; figure 4). Similar results were found for the evaluation period and the up-titration period. The categorical summary of percent reduction from baseline in partial seizure frequency during treatment favored levetiracetam over placebo (Mantel–Haenszel, $p < 0.001$), with 24.8% and 12.9% of levetiracetam-treated patients achieving reductions of 50% to less than 75% and 75% to less than 100%, compared with 14.4% and 4.1%, for placebo. The median absolute change from baseline in seizure frequency per week during the treatment period was −1.6 seizures/week in the levetiracetam group vs −0.7 seizures/week for placebo (Kruskal–Wallis, $p = 0.003$).

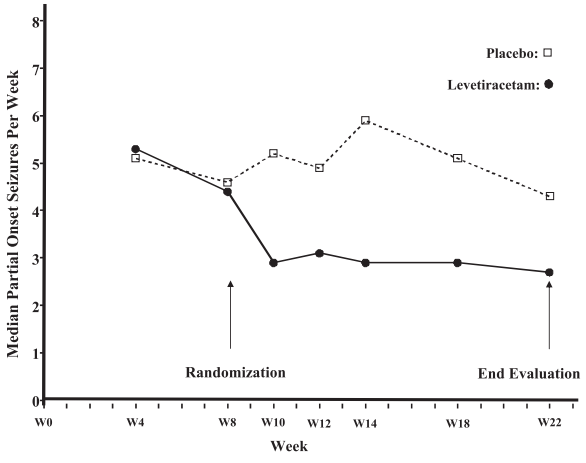

Figure 3. Median partial-onset seizure frequency (per week) by visit/week (intent-to-treat population, last observation carried forward).

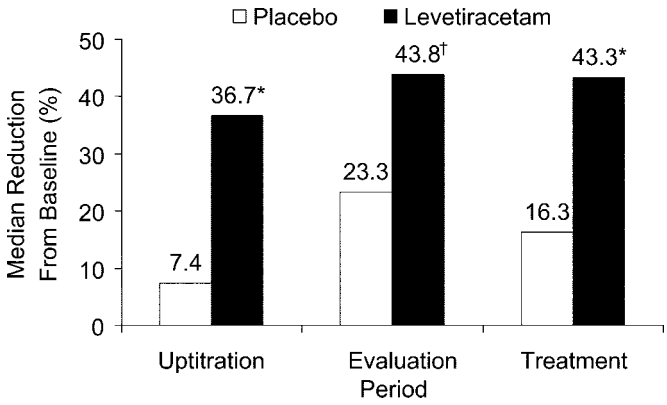

*Figure 4. Median percent change from baseline in weekly partial seizure frequency. * $p < 0.0001$ vs placebo. † $p < 0.01$ vs placebo.*

Overall, during the treatment (titration + evaluation) period, 44.6% of levetiracetam-treated patients were responders (i.e., they experienced a ≥50% reduction from baseline in weekly partial seizure frequency), compared with 19.6% of placebo patients (figure 5, left). The odds ratio generated from logistic regression was 3.3 ($p = 0.0002$, with 95% CI 1.75 to 6.24), indicating that the odds of response (at least a 50% reduction in partial seizure frequency) was 3.3 times as great in the levetiracetam group as in the placebo group. Seven levetiracetam-treated patients (6.9%) were seizure-free during the treatment (titration + evaluation) period, compared with one placebo patient (1.0%) (figure 5, right).

Tolerability. Treatment-emergent adverse events, summarized by body system and by specific adverse event in table 2, were comparable between the levetiracetam and placebo groups. At least one treatment-emergent adverse event was experienced by 88.1% (n = 89) of levetiracetam-treated patients and 91.8% (n = 89) of placebo patients. At least one treatment-emergent adverse event considered to

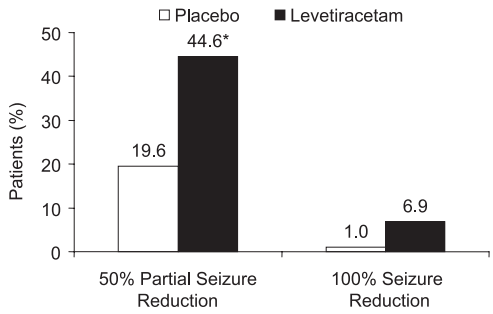

*Figure 5. Responder rate (≥50% partial seizure reduction from baseline and 100% seizure reduction) for levetiracetam and placebo adjunctive therapy. * $p = 0.0002$ vs placebo.*

Table 2 *Incidence (%) of treatment-emergent adverse events by COSTART body system and by individual adverse event**

	Levetiracetam, % (n = 101)	Placebo, % (n = 97)
COSTART body system†		
Body as a whole	58.4	64.9
Digestive	36.6	38.1
Hematologic and lymphatic	5.9	2.1
Metabolic and nutritional	4.0	10.3
Nervous	58.4	47.7
Respiratory	30.0	28.9
Skin and appendages	9.9	13.4
Special senses	12.9	9.3
Urogenital system	9.9	9.3
Specific adverse event		
Somnolence	23	11
Accidental injury	17	10
Vomiting	15	13
Anorexia	13	8
Rhinitis	13	8
Hostility	12	6
Cough increased	11	7
Pharyngitis	10	8
Nervousness	10	2
Asthenia	9	3
Diarrhea	8	7
Personality disorder	8	7
Dizziness	7	2
Emotional lability	6	4
Pain	6	3
Agitation	6	1

* Adverse events had to occur in at least 5% of levetiracetam-treated patients and be more frequent than in placebo patients.

† Investigator term describing each adverse event was coded to a body system and preferred term using the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) dictionary (version 5).

be related to study drug was reported in 56 levetiracetam-treated patients (55.4%) and 39 placebo patients (40.2%). The occurrence of treatment-emergent adverse events by body system was similar between the two groups. The most common treatment-emergent adverse events that occurred in at least 10% of the levetiracetam-treated patients and more frequently than placebo patients were somnolence, accidental injury, vomiting, anorexia, rhinitis, hostility, increased cough, pharyngitis, and nervousness (see table 2). The majority of these events were rated as mild to moderate in severity.

Five patients randomized to levetiracetam (5.0%) discontinued treatment because of an adverse event; 2 of them had a dose reduction for the same event before discontinuation. An additional 11 levetiracetam-treated patients, for a total of 13 patients (12.9%), required a dose reduction. Discontinuations and dose reductions due to adverse events were more common in the placebo group, including nine patients (9.3%) who discontinued because of an adverse event, four of whom had had a dose reduction for the same event. Ten additional placebo patients, for a total of 14 patients (14.4%), also required a dose reduction.

Psychiatric and behavioral treatment-emergent adverse events occurring in more than 5% of the patients were, in decreasing order of incidence, hostility (11.9% levetiracetam, 6.2% placebo), nervousness (9.9% levetiracetam, 2.1% placebo), personality disorder (7.9% levetiracetam, 7.2% placebo), emotional lability (5.9% levetiracetam, 4.1% placebo), and agitation (5.9% levetiracetam, 1.0% placebo).

Eight patients (7.9%) in the levetiracetam group and nine patients (9.3%) in the placebo group experienced a serious adverse event. None were considered by the investigator to be possibly related to study drug, except for one case of convulsion in a patient randomized to placebo. There were no deaths in this study.

Changes from baseline in laboratory values—blood chemistry, hematology, and urinalysis—were minor and comparable between treatments. Although between-treatment differences were significant (Kruskal–Wallis) for white blood cell count ($p = 0.0366$), relative percent ($p = 0.0006$) and absolute ($p = 0.0007$) neutrophil count and relative percent lymphocytes ($p = 0.0003$), no laboratory changes were considered clinically significant by any study investigator. No changes in vital signs or EKG parameters were considered clinically significant by any study investigator.

Discussion. This is the first double-blind, randomized, placebo-controlled trial of levetiracetam in a pediatric population. The results demonstrated that levetiracetam was efficacious and well tolerated at a target dose of 60 mg/kg/day when given as adjunctive therapy in pediatric patients with inadequately controlled partial seizures. Levetiracetam 60 mg/kg/day significantly improved seizure control compared with placebo. The primary analyses demonstrated that compared with placebo, adjunctive levetiracetam had a statistically greater reduction in the log partial seizure frequency per week between the baseline and treatment periods ($p = 0.0002$; percent reduction = 26.8%, 95% CI 14% to 37.6%). The median percent reduction in weekly partial seizure frequency was higher for levetiracetam-treated patients compared with placebo-treated patients ($p < 0.0001$). Assessment of secondary efficacy parameters demonstrated better efficacy with levetiracetam therapy than with placebo therapy: 44.6% of levetiracetam patients vs 19.6% of placebo patients were responders who experienced a reduction of 50% or more from baseline in weekly partial seizure frequency ($p = 0.0002$). Seven (6.9%) patients who received levetiracetam and one patient (1.0%) who received placebo were seizure-free during the treatment (titration + evaluation) period (see figure 5).

The addition of levetiracetam to existing AED therapy at doses up to 60 mg/kg/day was well tolerated and associated with a pattern and incidence of treatment-emergent adverse events similar to those observed with placebo. Fewer levetiracetam than placebo patients discontinued therapy prematurely because of treatment-emergent adverse events (5.0% vs 9.3%). The incidence of serious treatment-emergent adverse events was similar between the two treatment groups. No clinically significant (as judged by investigators) laboratory abnormalities occurred in either group.

The incidence of many of the common adverse

events including infection, fever, abdominal pain, nausea, diarrhea, increased cough, rhinitis, and otitis media that were seen in both the levetiracetam and placebo groups are consistent with the expected incidence for school-age children. Of the accidental injuries, many (8 of 17 levetiracetam and 6 of 10 placebo patients) were clearly attributable to causes other than seizure or other CNS-related events.

Patients were recruited over 42 months; prolonged enrollment is often seen in expanded indication trials of marketed drugs. The change in sample size was done after a blinded review of the seizure frequency per week for the first 64 evaluable patients to be able to evaluate variability. The sample size was refined subsequently. This is an acceptable clinical practice and did not jeopardize the blind in any way. There was no interim analysis of efficacy of the drug, and there were no stopping rules used.

The study was designed to confirm the short-term tolerability of levetiracetam in patients aged 4 to 16 years. The pharmacokinetics of levetiracetam in children[24] are similar to those in adults,[25] although clearance is approximately 30% to 40% higher. The compound is eliminated almost entirely in the urine, with approximately two-thirds appearing unchanged and most of the rest appearing as a simple hydrolysis product.[25] Levetiracetam pharmacokinetics are linear with dose.[26] In studies in adult patients, there were no significant pharmacokinetic interactions with other AEDs or with digoxin, warfarin, probenecid, or an oral contraceptive.[27]

This trial demonstrated the efficacy and tolerability of levetiracetam in children with treatment-resistant partial seizures, suggesting a therapeutic profile that is different from that of both the traditional and newer AEDs used as concomitant therapy. The results of this trial provide clinicians with additional options for improving the overall management of epilepsy in children as young as 4 years of age.

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Neuro*Images*

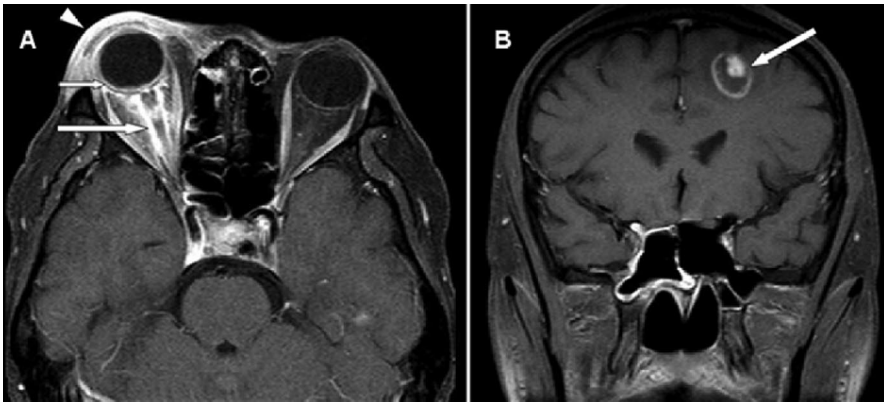

Figure. (A) Swelling of the right optic nerve and contrast enhancement of the nerve sheath (large arrow) compatible with optic neuritis. Abnormal swelling and enhancement of the retina and choroid indicates retinochoroiditis (small arrow). There is extrascleral extension of the inflammation into the retrobulbar fat but no evidence of cavernous sinus thrombosis. Furthermore, the preseptal soft tissues and eyelids are inflamed, in keeping with orbital cellulitis (arrowhead). (B) A large, ring-enhancing lesion (arrow) in the left frontal lobe, with an eccentric "targetoid" appearance. Multiple nodular enhancing lesions were also noted in the corticomedullary junction of both cerebral hemispheres (not shown).

MRI of ocular toxoplasmosis

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A 46-year-old man presented with progressive loss of vision and chemosis and proptosis of the right eye. On examination, there was no perception of light. Fundoscopy revealed marked swelling of the optic disc, macular edema, and retinal hemorrhages. A clinical diagnosis of central retinal vein occlusion was made, and a magnetic resonance (MR) study of the orbits and brain (figure, A and B) was performed to exclude cavernous sinus thrombosis. The MR findings of optic neuritis, retinochoroiditis, and multiple enhancing lesions in the brain led to a diagnosis of ocular and cerebral toxoplasmosis. Less likely differential diagnoses of lymphoma, tuberculosis, and sarcoidosis were also considered. Subsequent serologic testing for HIV was positive. A PCR assay of a vitreous sample confirmed the presence of *Toxoplasma gondii.* Following treatment with oral pyrimethamine and sulfadiazine, the patient's chemosis and proptosis resolved. However, visual acuity remained poor; the patient had no perception of light 9 months after treatment. In HIV-positive patients, ocular toxoplasmosis is a much less common opportunistic infection than cytomegalovirus (CMV) retinitis. Unlike CMV retinitis, however, toxoplasmosis can cause a progressive intraocular infection, panophthalmitis, and orbital cellulitis.[1]

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1. Moorthy RS, Smith RE, Rao NA. Progressive ocular toxoplasmosis in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 1993;115:742–747.

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