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CME

Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy

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Abstract—*Objective:* We report the results of a prospective study of the efficacy and tolerability of levetiracetam, a new antiepileptic drug with a unique mechanism of action, in comparison with controlled-release carbamazepine as first treatment in newly diagnosed epilepsy. *Methods:* Adults with ≥2 partial or generalized tonic–clonic seizures in the previous year were randomly assigned to levetiracetam (500 mg twice daily, n = 288) or controlled-release carbamazepine (200 mg twice daily, n = 291) in a multicenter, double-blind, noninferiority, parallel-group trial. If a seizure occurred within 26 weeks of stabilization, dosage was increased incrementally to a maximum of levetiracetam 1,500 mg twice daily or carbamazepine 600 mg twice daily. Patients achieving the primary endpoint (6-month seizure freedom) continued on treatment for a further 6-month maintenance period. *Results:* At per-protocol analysis, 73.0% (56.6%) of patients randomized to levetiracetam and 72.8% (58.5%) receiving controlled-release carbamazepine were seizure free at the last evaluated dose (adjusted absolute difference 0.2%, 95% CI −7.8% to 8.2%) for ≥6 months (1 year). Of all patients achieving 6-month (1-year) remission, 80.1% (86.0%) in the levetiracetam group and 85.4% (89.3%) in the carbamazepine group did so at the lowest dose level. Withdrawal rates for adverse events were 14.4% with levetiracetam and 19.2% with carbamazepine. *Conclusions:* Levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy at optimal dosing in a setting mimicking clinical practice. This trial has confirmed in a randomized, double-blind setting previously uncontrolled observations that most people with epilepsy will respond to their first-ever antiepileptic drug at low dosage.

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Selecting the most appropriate antiepileptic drug (AED) for a patient with newly diagnosed epilepsy remains a significant challenge.[1] Although some of the newer agents may show better tolerability than older generation AEDs, no comparative study has demonstrated improved efficacy for any of these over carbamazepine, phenytoin, or valproic acid.[2] There is still an unmet need for mechanistically unique, broad-spectrum, safe and well tolerated, easy-to-use AEDs, particularly because more than 30% of patients are refractory to existing treatments.[3]

Levetiracetam (LEV), the *S*-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide, is currently used as adjunctive therapy for partial-onset seizures in adults and children aged ≥4 years. It has a novel mode of action in that it is the only AED that binds to synaptic vesicle protein 2A.[4] Preliminary studies have suggested that LEV may provide effective seizure control when used as monotherapy.[5]

We report the results of a randomized, double-blind trial comparing LEV and controlled-release carbamazepine (CBZ-CR) given as first treatment at optimized dosages in patients with newly diagnosed epilepsy. This is the first study to comply with European regulations for the evaluation of new AEDs for this indication, which recommend a noninferiority trial showing at least a similar benefit–risk balance for the test product compared with an acknowledged standard at individually optimized dosages using clinically relevant endpoints.[6] The guidelines stipulate that the primary outcome measure should be the proportion of patients remaining seizure free for at least 6 months on either drug during the evaluation period with maintenance of efficacy for at least a year.

*See the appendix for the list of investigators.

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Methods. This randomized, double-blind, parallel-group, positive-controlled monotherapy trial had the primary objective of demonstrating that monotherapy with LEV (1,000 to 3,000 mg/day) was noninferior to monotherapy with CBZ-CR (400 to 1,200 mg/day) in adults (≥16 years) with newly diagnosed epilepsy experiencing partial or generalized tonic–clonic seizures. The study was conducted at 85 centers in 12 European countries and in South Africa in accordance with Good Clinical Practice guidelines. An independent ethics committee at each center approved the protocol before patient enrolment commenced. All participants provided written informed consent before entering the study.

Patients. Patients aged ≥16 years with newly diagnosed partial or generalized seizures with clear focal origin or generalized tonic–clonic seizures without clear focal origin were eligible for inclusion if they had experienced ≥2 unprovoked seizures separated by at least 48 hours during the past year with at least 1 seizure during the previous 3 months. Exclusion criteria included pseudoseizures, seizures occurring only in clusters, and clinical or electroencephalographic findings suggestive of idiopathic generalized epilepsy.

Study design. After a 1-week screening period, patients were randomly assigned to enter a 2-week titration period during which they received either LEV 500 mg daily or CBZ-CR 200 mg daily before reaching the first target dose (dose level 1: LEV 500 mg twice daily, CBZ-CR 200 mg twice daily). This was followed by 1-week stabilization and a 26-week evaluation period. Patients who remained seizure free for 6 months entered an additional 26-week maintenance period. Patients completing the trial continued to receive the allocated treatment under double-blind conditions until the database was locked.

Patients experiencing a seizure during the first evaluation period had their AED dose increased (over 2 weeks with intermediate daily doses of LEV 1,500 mg and CBZ-CR 600 mg) to dose level 2 (LEV 1,000 mg twice daily, CBZ-CR 400 mg twice daily) followed by the same stabilization, evaluation, and maintenance periods as before. These stages were repeated for patients experiencing a seizure at dose level 2, with progression to dose level 3 (LEV 1,500 mg twice daily, CBZ-CR 600 mg twice daily, via respective intermediate daily doses of 2,500 mg and 1,000 mg). To ensure blinding, LEV (Keppra, UCB SA) and CBZ-CR tablets (Tegretol-CR, Novartis) were identically encapsulated.

Patients who reported poor tolerability at dose levels 2 or 3 could revert to an intermediate dose with blinding maintained and continue in the study. However, they were not permitted to resume treatment at the previous poorly tolerated dose or to undergo further increases if another seizure occurred. Those who reported a seizure at dose level 3 or during the maintenance period were withdrawn from the study.

Assessments. All patients recorded number and type of any seizures and adverse events (AEs) using daily record cards. AEs were also assessed at each visit using a nonstructured interview. Blood samples were collected for the measurement of study drug plasma concentrations to ensure correct assignment and to confirm adherence, without standardization of sampling times. To preserve blinding, these were not made available to the treating physician. Adherence was also assessed by counting returned capsules and was defined as an apparent capsule consumption within 80% to 120% of the prescribed amount.

Statistics. As required by the noninferiority design,[7] the primary efficacy analysis was based on the per-protocol (PP) population, which excluded patients deviating from the protocol. Efficacy analyses were also performed for the intention-to-treat (ITT) population, i.e., patients who took at least one dose of study drug. Safety analyses were performed on the ITT population only.

In calculating the sample size and defining the noninferiority limit, data from all published monotherapy trials in newly diagnosed epilepsy were considered (see recent detailed review[8]). These revealed 6-month seizure freedom rates in ITT analyses ranging from 38% to 51%. Therefore, it was estimated that 45% of participants randomly assigned to CBZ-CR would remain seizure free for 6 months. Based on the only identified placebo-controlled study in untreated patients, which demonstrated a 3-month seizure freedom rate of 11.5% in participants randomly assigned to placebo,[9] the seizure freedom rate on placebo was conservatively set at 15%. Halving the difference between what CBZ-CR was expected to yield (45%) and the estimate for placebo (15%), a 15% absolute difference in seizure freedom rates was selected for the noninferiority threshold.

The required sample size was calculated by the method described by Lin[10] and Jones et al.[11] to detect noninferiority between populations using two proportions. With 232 patients in each treatment group, the two-sided 95% CI of the difference in 6-month seizure freedom was expected to have a lower boundary superior to −15% with 90% power, assuming that the CBZ-CR seizure freedom rate was 45% and that the true difference between LEV and CBZ-CR was 0. Overall, 290 patients were required for each treatment group on the assumption that 20% would be excluded from the PP analysis due to protocol violations.

Patients were randomly assigned to CBZ-CR or LEV at Visit 2 using an IVRS system and following a central 1:1 randomization scheme with a statistical block size of 2 and stratified by seizure category (seizures with clear focal origin vs tonic–clonic seizures without clear focal origin). The primary efficacy endpoint was the proportion of PP patients achieving at least 6-month seizure freedom at the last evaluated dose, with analyses being performed over the dose period during which the patient completed the study. A logistic regression model was used to analyze the data, including treatment and last assessed seizure category as factors. The parameters estimated from this model were used to derive an adjusted absolute difference (LEV − CBZ-CR) and its 95% two-sided CI. Secondary efficacy endpoints included 1-year seizure freedom rates and 6-month and 1-year seizure freedom rates by dose level. The influence of baseline seizure frequency on the 6-month seizure freedom rate was also explored. The time to study withdrawal was described using the Kaplan–Meier method.

Results. *Patient populations.* Patient recruitment began in June 2002, and the last patient completed the study in July 2005. The trial profile is illustrated in figure 1. A total of 288 and 291 patients were randomly assigned to LEV and CBZ-CR. The ITT population (all randomized patients who took at least one dose of either study medication) consisted of 285 LEV and 291 CBZ-CR patients. The PP population (subset of ITT patients who had no major protocol deviations affecting efficacy variables during the study period) for 6-month (1-year) seizure freedom comprised 237 (228) LEV and 235 (224) CBZ-CR patients.

Patient demographics. The demographic and epilepsy characteristics did not differ between the two groups (table 1). The etiology of the epilepsy was not apparent in approximately two-thirds of patients in both groups but, where known, previous head trauma or cerebrovascular disease were the most frequently identified causative factors (combined, 22% of the overall population). The distribution by seizure type at randomization was similar in both treatment groups (LEV: 80% partial seizures, 20% tonic–clonic seizures without clear focal origin; CBZ-CR: 79.7% partial seizures, 20.3% tonic–clonic seizures without clear focal origin). At their last assessment, the number of patients classified as reporting tonic–clonic seizures without clear focal origin decreased to 11.9% and 13.4% in the LEV and CBZ-CR groups.

Study discontinuations. In total, 66.7% of patients in both the LEV (190/285) and CBZ-CR (194/291) groups completed the 6-month evaluation period. A similar proportion of patients in each group reached the end of the 6-month maintenance period, thereby completing the study (LEV 54.0%; CBZ-CR 53.6%). Mean adherence to study medication was estimated at 96.0% and 95.4% in the LEV and CBZ-CR groups, respectively.

Efficacy. Primary endpoint. In the PP population, 73.0% (173/237) of patients in the LEV group and 72.8% (171/235) in the CBZ-CR group were seizure free for ≥6 months at the last evaluated dose. The adjusted absolute difference between LEV and CBZ-CR (95% two-sided CI)

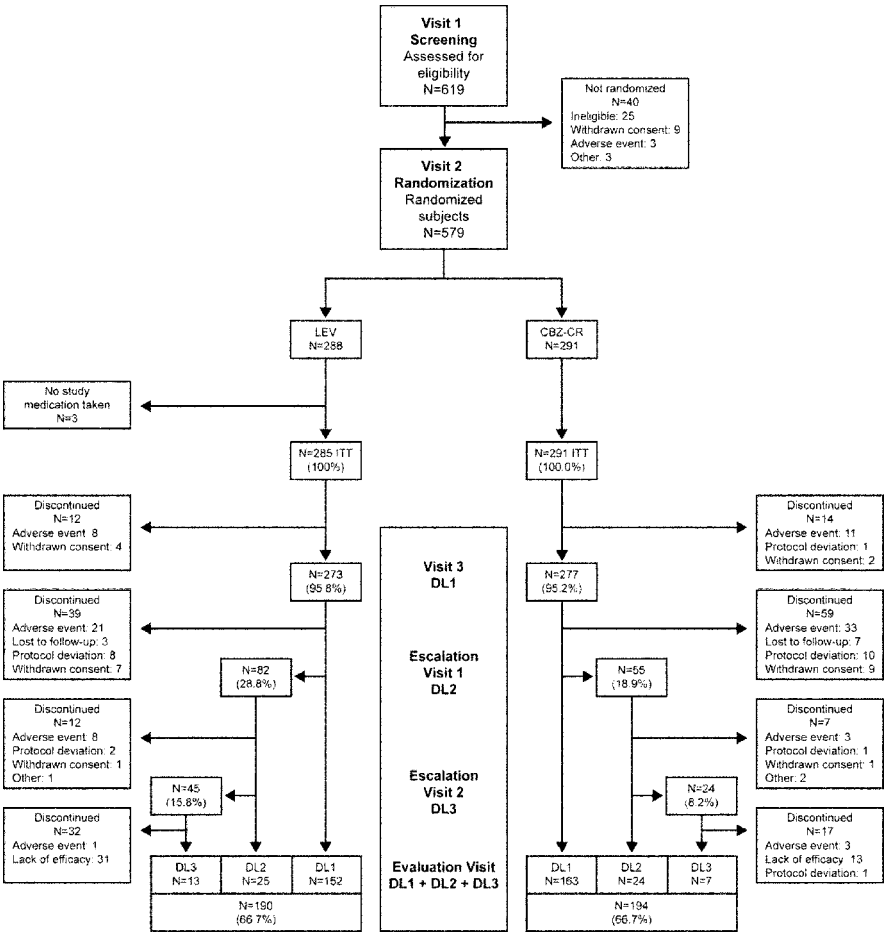

Figure 1. Trial profile. LEV = levetiracetam; CBZ-CR = controlled release carbamazepine; ITT = intention to treat; DL = dose level; DL1 = LEV 500 mg twice daily or CBZ-CR 200 mg twice daily; DL2 = LEV 1,000 mg twice daily or CBZ-CR 400 mg twice daily; DL3 = LEV 1,500 mg twice daily or CBZ-CR 600 mg twice daily.

obtained from the logistic regression model (including a factor for seizure category as last assessed) was 0.2% (95% CI −7.8% to 8.2%). Because the lower limit of the CI was above the noninferiority limit set by the study protocol (−15%), LEV could be considered noninferior to CBZ-CR (figure 2).

Secondary endpoints. Similar proportions of patients in the LEV and CBZ-CR groups were seizure free for 6 months on the last evaluated dose in the ITT analysis (LEV 66.7%, 190/285; CBZ-CR 66.7%, 194/291). For both the ITT and PP populations, LEV was noninferior to CBZ-CR for this endpoint (figure 2). There was no significant difference between treatment groups with regard to 1-year seizure freedom rates in both the PP (LEV 56.6%, 129/228; CBZ-CR 58.5%, 131/224) and ITT (LEV 49.8%, 142/285; CBZ-CR 53.3%, 155/291) populations. Time to withdrawal in both patient groups (PP and ITT populations) is illustrated in figure 3. Patients reporting ≥3 seizures in the 3 months before randomization in the combined groups were less likely ($p < 0.001$) to achieve 6-month seizure freedom (LEV 74/116, 63.8%; CBZ-CR 61/97, 62.9%) than those experiencing ≤2 seizures over the same period (LEV 99/121, 81.8%; CBZ-CR 110/138, 79.7%).

Seizure freedom by dose level. Dose level 1 (LEV 500 mg twice daily or CBZ-CR 200 mg twice daily) was sufficient to achieve seizure freedom for ≥6 months (figure 4) in the majority of patients in the PP population (LEV 140/237, 59.1%; CBZ-CR 146/235, 62.1%). This amounted to 80.1% and 85.4% of all responders to either drug. An additional 13.9% and 10.7% patients in the LEV and CBZ-CR groups reached this endpoint at higher doses, which corresponds to 52.4% of the LEV-treated patients and 58.1% of the CBZ-CR–treated patients who tested dose level 2 or 3.

Similarly, dose level 1 was sufficient to achieve seizure freedom for ≥1 year in the majority of patients in the PP population (LEV 111/228, 48.7%; CBZ-CR 117/224, 52.2%). This amounted to 86.0% and 89.3% of all patients seizure free ≥1 year whatever the dose levels (figure 4). An additional 7.9% and 6.3% patients in the LEV and CBZ-CR groups attained this endpoint at higher drug doses, which corresponds to 29.5% of the LEV-treated patients and 32.6% of the CBZ-CR–treated patients who tested dose level 2 or 3.

Tolerability. A similar proportion of patients in the LEV (79.6%) and CBZ-CR groups (80.8%) experienced at least one AE during the treatment period, with most events being of mild or moderate intensity. Overall, there was no substantial difference in the adverse events reported between the treatment groups (table 2). However, selecting those AEs with a significant difference at the 5% level, depression and insomnia were reported more often with LEV, whereas back pain was experienced more frequently by CBZ-CR–treated patients. Fewer patients in the LEV group (14.4%, 41/285) discontinued therapy because of AEs than those randomly assigned to CBZ-CR (19.2%, 56/291), although this difference did not reach significance (table 3). More patients gained weight (≥7% of

Table 1 *Demographic and epilepsy characteristics in the ITT and PP populations of patients randomly assigned to levetiracetam or controlled-release carbamazepine*

		ITT population		PP population	
	Statistic	LEV (n = 285)	CBZ-CR (n = 291)	LEV (n = 237)	CBZ-CR (n = 235)
Age, years	Mean (SD)	39.8 (16.6)	39.0 (15.8)	39.5 (16.5)	39.6 (16.2)
Sex					
Male	n (%)	146 (51.2)	171 (58.8)	121 (51.1)	141 (60.0)
Female	n (%)	139 (48.8)	120 (41.2)	116 (48.9)	94 (40.0)
Ethnicity					
White	n (%)	262 (91.9)	268 (92.1)	223 (94.1)	218 (92.8)
Black	n (%)	5 (1.8)	10 (3.4)	4 (1.7)	7 (3.0)
Asian	n (%)	1 (0.4)	4 (1.4)	0	3 (1.3)
Other	n (%)	17 (6.0)	9 (3.1)	10 (4.2)	7 (3.0)
Height, cm	Mean (SD)	170.0 (9.7)	171.1 (9.7)	170.0 (9.7)	171.0 (9.7)
Weight, kg	Mean (SD)	73.7 (16.8)	73.6 (15.2)	73.6 (16.7)	73.5 (15.4)
BMI, kg/m^2	Mean (SD)	25.5 (5.2)	25.1 (4.6)	25.4 (5.2)	25.1 (4.6)
No. of seizures in past year	Median	4.0	3.0	4.0	3.0
	Q1–Q3	2.0–10.0	2.0–10.5	2.0–10.0	2.0–10.0
No. of seizures in past 3 months	Median	2.0	2.0	2.0	2.0
	Q1–Q3	1.0–4.5	1.0–5.0	1.0–4.0	1.0–4.0
Epilepsy duration, years	Median	0.8	0.8	0.7	0.7
	Q1–Q3	0.3–2.4	0.3–2.7	0.3–2.2	0.3–2.4
Age at onset, years	Median	34.7	31.9	34.8	32.3
	Q1–Q3	21.5–49.5	20.7–47.4	21.6–49.2	20.6–49.1
Time since last seizure, days	Median	9.0	11.0	9.0	10.0
	Q1–Q3	3.0–23.0	4.0–28.0	3.0–23.0	4.0–28.0

ITT = intention-to-treat; PP = per-protocol; LEV = levetiracetam; CBZ-CR = controlled-release carbamazepine.

baseline) on CBZ-CR than on LEV (37/276, 13.4% vs 21/269, 7.8%; $p = 0.038$, two-sided Fisher exact test).

Discussion. No drug has shown superior efficacy to CBZ in a randomized, head-to-head comparison in newly diagnosed epilepsy patients with partial or generalized tonic–clonic seizures.[12-18] Second-generation AEDs such as lamotrigine, gabapentin, and oxcarbazepine have demonstrated a tendency toward better tolerability.[13,18,19] However, these studies did not use an extended-release formulation of CBZ, the preferred formulation for minimizing side effects.[20,21] CBZ-CR, therefore, can be regarded as the best standard comparator for these seizure types.

The difficulties in designing monotherapy AED trials that satisfy regulatory requirements and demonstrate utility in everyday clinical practice are well known.[22] "Conversion to monotherapy" studies in refractory epilepsy provide proof of efficacy, but these data have limited clinical applicability.[22,23] The use of suboptimal comparators in some of these trials remain a cause of ethical concern.[24] On the other hand, studies comparing novel AEDs with established agents in newly diagnosed patients have been criticized for small sample sizes, fixed dosage schedules, inflexible exit criteria, and inadequate follow-up times.[22,25]

The noninferiority monotherapy study presented here is the first that conforms to the new European guidelines, which recommend that comparisons must be made with an acknowledged standard at optimized dosage.[6] In this regard, a controlled-release formulation of CBZ was used, with a modest starting dose, slow titration, and the possibility for patients to remain on the lowest effective dose. This design mimics clinical practice in tailoring dosage to balance efficacy with tolerability.

In this study involving more than 500 patients with newly diagnosed epilepsy, LEV was shown to be noninferior to CBZ-CR. For the PP population, 73% of patients in each group remained seizure free for at least 6 months at the last evaluated dose level. Noninferiority was also demonstrated for the ITT population. One-year seizure freedom rates with LEV were comparable to those with CBZ-CR in the PP (56.6% vs 58.5%) and ITT (49.8% vs 53.3%) populations. LEV was also noninferior to CBZ-CR by the more stringent criteria discussed recently by the International League against Epilepsy.[8] These set at

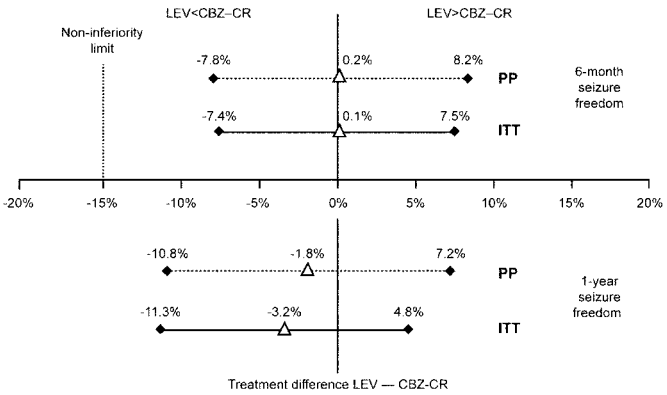

Figure 2. Adjusted treatment differences with two-sided 95% CIs in 6-month and 1-year seizure freedom rates at the last evaluated dose for the per-protocol (PP) and intention-to-treat (ITT) populations randomly assigned to levetiracetam (LEV) or controlled-release carbamazepine (CBZ-CR). The noninferiority limit was not defined for 1-year seizure freedom.

≤20% the relative difference in seizure freedom or retention rate that can be regarded as clinically insignificant. No other newer AED has been shown to be equivalent to an older generation reference agent, partly because previous studies[15,16,26-30] were not sufficiently powered to demonstrate noninferiority.[8]

The great majority of PP patients (59.1% LEV; 62.1% CBZ-CR) remained seizure free at 6 months on the lowest dose of either drug, with only a few

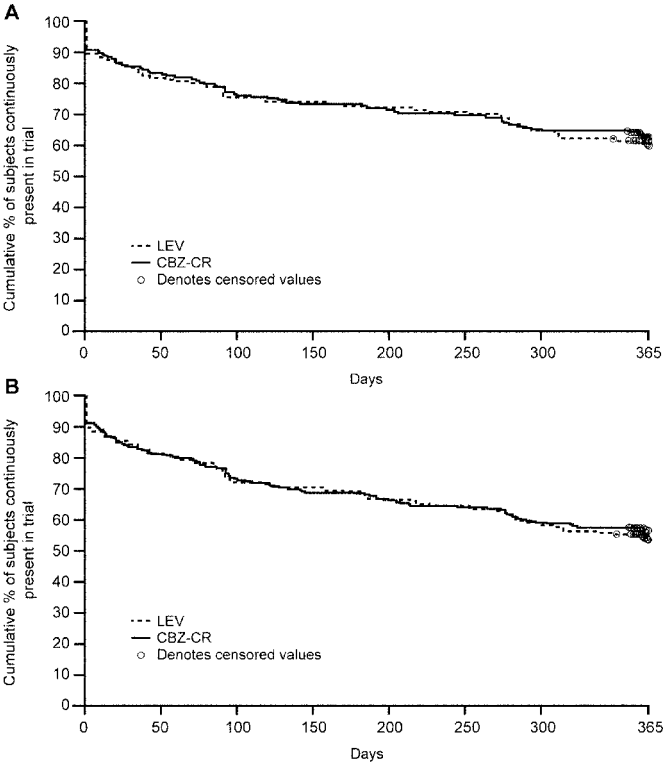

Figure 3. Time to discontinuation in patients randomized to levetiracetam (LEV) or controlled-release carbamazepine (CBZ-CR) in the per-protocol (A) and intention-to-treat (B) populations.

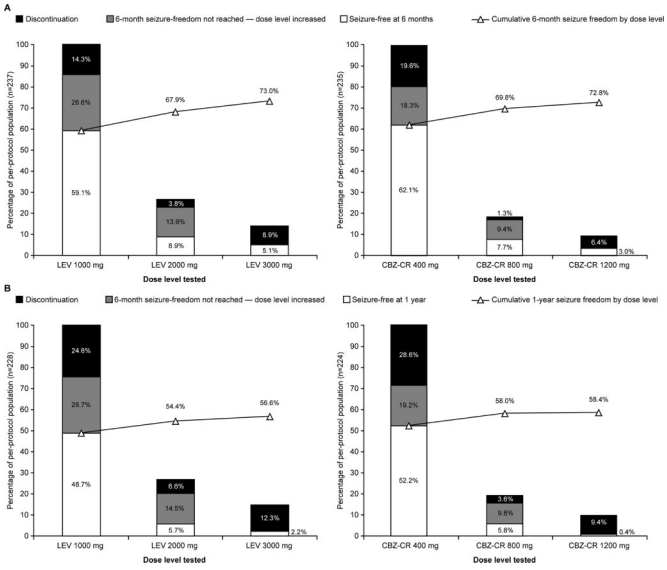

Figure 4. Proportions of patients in levetiracetam (LEV) and controlled-release carbamazepine (CBZ-CR) treatment groups who were seizure-free for ≥6 months (A) and ≥1 year (B) at each dose level in the per-protocol population.

additional patients responding to the intermediate (LEV 8.9%; CBZ-CR 7.7%) or highest (LEV 5.1%; CBZ-CR 3.0%) doses, representing more than 50% of the patients who tested dose level 2 or 3. A similar proportion of patients in the LEV (27.0%) and CBZ-CR (27.2%) groups remained refractory to treatment. Overall, 80.1% (86.0%) and 85.4% (89.3%) of patients becoming seizure free for 6 months (1 year) on LEV and CBZ-CR did so on dose level 1, i.e., LEV

Table 2 *Most common adverse events (%) reported by patients in the levetiracetam and controlled-release carbamazepine groups during the randomized treatment period in the intention-to-treat population*

Preferred term	LEV (n = 285)	CBZ-CR (n = 291)	Relative risk LEV/CBZ-CR (95% CI)
Headache	20.7	25.4	0.81 (0.60 to 1.10)
Fatigue	16.5	14.1	1.17 (0.80 to 1.72)
Somnolence	11.2	9.3	1.21 (0.74 to 1.97)
Dizziness	10.9	13.7	0.79 (0.51 to 1.23)
Nasopharyngitis	9.1	9.6	0.95 (0.57 to 1.58)
Influenza	8.4	8.6	0.98 (0.57 to 1.67)
Diarrhea	7.4	6.5	1.13 (0.62 to 2.05)
Nausea	7.0	10.7	0.66 (0.38 to 1.13)
Depression	6.3	2.1	3.06 (1.23 to 7.61)
Insomnia	6.0	2.4	2.48 (1.04 to 5.89)
Vertigo	5.3	4.5	1.18 (0.57 to 2.43)
Weight gain	3.2	6.5	0.48 (0.22 to 1.05)
Back pain	2.8	6.9	0.41 (0.18 to 0.91)
Rash	2.8	5.5	0.51 (0.22 to 1.17)

LEV = levetiracetam; CBZ-CR = controlled-release carbamazepine.

Table 3 *Incidence of adverse events experienced by at least 1% of patients in the levetiracetam and controlled-release carbamazepine groups leading to study drug discontinuation during the randomized treatment period in the intention-to-treat population*

System/organ class/preferred term	LEV (n = 285), n (%)	CBZ-CR (n = 291), n (%)
Ear and labyrinth disorders		
Vertigo	6 (2.1)	2 (0.7)
Gastrointestinal disorders		
Nausea	0	3 (1.0)
General disorders		
Asthenia	0	3 (1.0)
Fatigue	5 (1.8)	4 (1.4)
Nervous system disorders		
Ataxia	0	3 (1.0)
Dizziness	2 (0.7)	3 (1.0)
Somnolence	6 (2.1)	2 (0.7)
Psychiatric disorders		
Aggression	0	3 (1.0)
Anxiety	3 (1.1)	1 (0.3)
Depression	5 (1.8)	2 (0.7)
Skin		
Rash	4 (1.4)	9 (3.1)

LEV = levetiracetam; CBZ-CR = controlled-release carbamazepine.

500 mg twice daily or CBZ-CR 200 mg twice daily, the majority of whom never had another seizure after entering the trial. Outcome was poorer in patients reporting three or more seizures in the 3 months before starting treatment. This pattern of response supports, in a randomized, double-blind setting, similar observations made in unselected patients[31,32] and supports the assertion that optimal dosages of AEDs identified from randomized adjunctive studies in refractory epilepsy are not applicable to monotherapy trials in a newly diagnosed population.[22]

The selection of treatment for a patient with newly diagnosed epilepsy must take side effects and long-term safety into consideration.[1] More CBZ-CR treated patients discontinued treatment because of AEs (19.2% vs 14.4% for LEV), although this difference was not significant. Patients taking LEV were more likely to report depression and insomnia, whereas those assigned to CBZ-CR reported back pain more often. The fast and sustained efficacy and good tolerability of LEV in adults and children with partial-onset seizures,[33-38] together with its favorable pharmacokinetic profile, lack of enzyme-inducing properties, and low potential for pharmacokinetic interactions,[39,40] make it a promising AED for use as initial monotherapy in newly diagnosed epilepsy.

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Appendix

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