Levetiracetam Efficacy in Idiopathic Generalized Epilepsy: Long Suspected and Now Confirmed in Randomized Clinical Trials

Placebo-Controlled Study of Levetiracetam in Idiopathic Generalized Epilepsy. Berkovic SF, Knowlton RC, Leroy RF, Schiemann J, Falter U; On behalf of the Levetiracetam N01057 Study Group. *Neurology*. 2007;68 [Epub ahead of print]. OBJECTIVE: To assess the efficacy and tolerability of adjunctive levetiracetam in patients with uncontrolled generalized tonic-clonic (GTC) seizures associated with idiopathic generalized epilepsies (IGE). METHODS: This multicenter, randomized, double-blind, placebo-controlled, parallel-group study enrolled adults and children (4 to 65 years) with IGE experiencing 3 GTC seizures during the 8-week baseline period (4-week retrospective and 4-week prospective), despite receiving stable doses of one or two antiepileptic drugs (AEDs). Patients were randomized to levetiracetam (target dose 3,000 mg/day for adults; 60 mg/kg/day for children) or placebo and a 4-week titration period was followed by a 20-week evaluation period. RESULTS**:** Of 229 patients screened, 164 were randomized (levetiracetam, n = 80; placebo, n = 84). Levetiracetam produced a greater mean reduction in GTC seizure frequency per week over the treatment period (56.5%) than placebo (28.2%; $p = 0.004$). The percentage of patients who had 50% reduction of GTC seizure frequency per week (responders) during the treatment period was 72.2% for levetiracetam and 45.2% for placebo ($p < 0.001$; OR 3.28; 95% CI 1.68 to 6.38). During the first 2-week treatment 64.6% of patients on levetiracetam and 45.2% on placebo ($p = 0.018$) were classified as responders. During the evaluation period the percent of patients free of GTC seizures (34.2% vs 10.7%; $p < 0.001$) and all seizure types (24.1% vs 8.3%; $p = 0.009$) was greater for levetiracetam than placebo. Levetiracetam was well tolerated with 1.3% of patients discontinuing therapy due to adverse events vs 4.8% on placebo. CONCLUSION**:** Adjunctive levetiracetam is an effective and well-tolerated antiepileptic drug for treating generalized tonic-clonic seizures in patients with idiopathic generalized epilepsies.

COMMENTARY

Idiopathic generalized epilepsy is more responsive to antiepileptic drug (AED) therapy than partial epilepsy (1). This circumstance is fortunate considering that few AEDs are approved for idiopathic generalized epilepsy. Among the older AEDs marketed in the United States, ethosuximide is specifically approved for generalized absence seizures, while valproate and clonazepam are the only two wide-spectrum agents indicated for idiopathic generalized epilepsy. The ethosuximide analog, methsuximide, is a wide-spectrum AED that is indicated only as a second-line agent for absence seizures and is not widely known or used. All the new AEDs were approved initially for partial epilepsy. Two agents, topiramate and

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lamotrigine, were later approved for treatment of primary generalized tonic–clonic seizures as add-on therapies, based on class I evidence (2,3). Levetiracetam now joins these two drugs as a Food and Drug Administration (FDA) approved adjunctive treatment for idiopathic generalized epilepsy, thanks to the study of Berkovic and colleagues.

In the study by Berkovic and colleagues, there were also significant differences between the levetiracetam and placebo groups in several variables relating to all seizure types combined. These variables included responder rate (59.5% vs 29.8%), seizure-free rate (24.1% vs 8.3%), and median reduction of seizure days for all seizures (62.8% vs 24.7%). However, the investigators provided specific outcomes only for generalized tonic–clonic seizures, even though myoclonic seizures were reported in 33.8% of patients randomized to levetiracetam and in 41.7% of patients randomized to placebo, and absence seizures were reported in 38.8% of levetiracetam patients and 56% of placebo patients.

Levetiracetam also has demonstrated class I evidence of efficacy as an adjunctive therapy for refractory generalized myoclonic seizures (4) and is the only AED with FDA approval for treatment of this seizure type. Topiramate, zonisamide, and lamotrigine have only class IV evidence of efficacy for generalized myoclonic seizures. The new AEDs have more limited evidence of efficacy for the treatment of generalized absence seizures. Lamotrigine shows class II–III evidence of efficacy (5,6) but does not have formal FDA indication for treatment of generalized absence seizures. No other new AED has better than class IV evidence of efficacy for generalized absence seizures, although there are reports that topiramate, zonisamide, and levetiracetam may be effective (7–9). In the study by Berkovic and colleagues, the authors did indicate that levetiracetam did not aggravate absence seizures. One study of refractory idiopathic generalized epilepsy demonstrated that absence seizures were less likely to respond to levetiracetam than were tonic–clonic or myoclonic seizures (10). This observation cannot be extrapolated to idiopathic generalized epilepsy as a whole, because refractory idiopathic generalized epilepsy represents only a fraction of the total patients with this condition. The absence of data highlights the need to evaluate levetiracetam and the other new wide-spectrum AEDs for first-line treatment of all the idiopathic generalized epilepsy seizure types.

Of the newer AEDs, only topiramate has an FDA indication as a first-line treatment for primary generalized tonic–clonic seizures in idiopathic generalized epilepsy. Valproate, the most widely accepted drug of choice for idiopathic generalized epilepsy, can have limiting adverse effects and risks, particularly for women of childbearing potential. Because of these risks and potential adverse effects, other wide-spectrum AEDs are often used off-label as first-line treatment (11,12). A recent large unblinded, randomized, controlled trial found that valproate was significantly better than lamotrigine and topiramate in time to drug failure and better than lamotrigine in time to 1-year remission, in patients with idiopathic generalized epilepsy (13). This trial did not include levetiracetam or zonisamide and was not sufficiently powered to analyze the relative efficacy of the drugs for individual seizure types. A future well-powered randomized study is indicated to compare levetiracetam and valproate in idiopathic generalized epilepsy. There currently is encouraging class IV evidence for the use of levetiracetam as first-line monotherapy in generalized epilepsy, particularly in juvenile myoclonic epilepsy (12), however, this evidence has to be confirmed in a class I study.

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