

LACOSAMIDE: WHAT CAN BE EXPECTED FROM THE NEXT NEW ANTIPILEPTIC DRUG?

Adjunctive Lacosamide for Partial-Onset Seizures: Efficacy and Safety Results from a Randomized Controlled Trial. Halász P, Kälviäinen R, Mazurkiewicz-Beldzińska M, Rosenow F, Doty P, Hebert D, Sullivan T; SP755 Study Group. *Epilepsia* 2009;50(3):443–453. **PURPOSE:** To evaluate the efficacy and safety of lacosamide (200 and 400 mg/day) when added to one to three concomitant antiepileptic drugs (AEDs) in patients with uncontrolled partial-onset seizures. **METHODS:** This multicenter, double-blind, placebo-controlled trial randomized patients (age 16–70 years) with partial-onset seizures with or without secondary generalization to placebo, lacosamide 200, or lacosamide 400 mg/day. The trial consisted of an 8-week baseline, a 4-week titration, and a 12-week maintenance period. **RESULTS:** Four hundred eighty-five patients were randomized and received trial medication. Among these, 87% were taking two or more concomitant AEDs. Median percent reduction in seizure frequency per 28 days from baseline to maintenance period (intent-to-treat, ITT) was 20.5% for placebo, 35.3% for lacosamide 200 mg/day ($p = 0.02$), and 36.4% for 400 mg/day ($p = 0.03$). In the per protocol population, the reductions were 35.3% for lacosamide 200 mg/day ($p = 0.04$) and 44.9% for 400 mg/day ($p = 0.01$) compared to placebo (25.4%). The 50% responder rate for lacosamide 400 mg/day (40.5%) was significant ($p = 0.01$) over placebo (25.8%), but was not for 200 mg/day (35.0%). In the per protocol population, the 50% responder rate for lacosamide 400 mg/day (46.3%) was significant ($p < 0.01$) compared with the placebo responder rate (27.5%). Dose-related adverse events (AEs) included dizziness, nausea, and vomiting. Clinically relevant changes in the mean plasma concentrations of commonly used AEDs were not observed. **DISCUSSION:** Results of this trial demonstrated the efficacy and tolerability of adjunctive lacosamide 200 and 400 mg/day and support that lacosamide may be an advantageous option for the treatment of partial-onset seizures in patients with epilepsy.

COMMENTARY

Lacosamide was recently approved as an antiepileptic drug for adjunctive therapy of partial onset seizures in the United States and the European Union. Lacosamide's most clinically relevant mechanism appears to be the enhancement of slow inactivation of voltage-gated sodium channels (1); thus, the mechanism is reportedly different from the sodium channel effect of phenytoin and carbamazepine, which enhance the fast inactivation of voltage-gated sodium channels (2). Although this characteristic appears to make lacosamide somewhat unique, the clinical implications of the mechanistic differences are unknown. Lacosamide is rapidly and completely absorbed, has a half-life of 13 hours, and demonstrates linear kinetics in the dose range of 100–800 mg. Ninety-five percent of the drug is eliminated in the urine, 40% unchanged. The major metabolic pathway is demethylation, which is dependent on cytochrome P450 CYP2C19. Inducers of P450 CYP2C19 would be expected to increase lacosamide metabolism, but preliminary data failed to show an effect of carbamazepine and phenytoin on lacosamide plasma concentrations (2). Lacosamide does not induce or inhibit cytochrome P450 enzymes and is unlikely to have clinically significant interactions when added to other medications (3). A low protein binding of less than 15% is another feature that reduces the potential for interaction.

In a previous study by Ben-Menachem and colleagues, efficacy of lacosamide as an adjunctive therapy was examined at three doses, 200, 400, and 600 mg/day, administered twice daily (4). The two higher doses were significantly better than placebo in reducing seizure frequency. The dose of 200 mg/day was superior to placebo in decreasing seizure frequency for the “per protocol” population, but the difference did not reach significance in the intent-to-treat analysis. The responder rates were very similar in the current study by Halász et al. when compared with the prior Ben-Menachem et al. study, with approximately 40% responder rate at the 400 mg/day dose and 33 to 35 percent responder rate at the 200 mg/day dose. The median percent seizure reduction for 200 mg/day was slightly higher (35.3%) in the Halász et al. study in comparison with the earlier study (26%), but there was also a greater median percent seizure reduction in the placebo group (20.5% vs 10%). The study by Halász and colleagues confirmed efficacy for the 400-mg/day dose and found that while the 200-mg/day dose was superior to placebo in seizure reduction, it was not significantly better than placebo in 50% responder rate. However, a pooled analysis of the two studies found that 200 mg/day was significantly better than placebo in both the median percent in seizure reduction and the 50% responder rate (2). The pooled analysis was even able to demonstrate that lacosamide was superior to placebo in reducing seizure frequency at a dose of 100 mg/day during titration.

A dose of 600 mg/day was not included in the current study by Halász et al. but was evaluated in a third study by Chung et al., which was published only in abstract form (5). The Chung

et al. study compared 400 mg and 600 mg of lacosamide to placebo in a patient population that is very similar to that in the study by Halász et al. Both doses were superior to placebo and close to each other in efficacy measures, with around 37 to 38 percent seizure reduction and 38 to 41 percent responder rates. In general, the 600-mg/day dose was not significantly better than 400 mg/day either in seizure reduction or the 50% responder rate, but it was associated with a greater incidence of adverse effects. As a result, both European and U.S. regulatory agencies approved lacosamide at doses of 200 and 400 mg/day. Nevertheless, individual patients may tolerate and benefit from a higher dose.

With respect to seizure freedom, which is the ultimate target of any epilepsy therapy, 3.6% and 2.4% of patients who completed the maintenance period were seizure-free at the 200-mg and 400-mg daily doses, with 2.1% of placebo patients also seizure-free in the Halász et al. study. In the previous published study by Ben-Menachem et al., 0%, 1.2%, 6.2%, and 1.6% of patients who completed the study were seizure-free with placebo, 200, 400, and 600 mg/day of lacosamide, respectively (4). The seizure-free numbers were 0%, 2.5%, and 8.1% for placebo, 400, and 600 mg/day, respectively, in the third study by Chung et al. (5).

The most common adverse effects were fairly consistent between the Halász et al. and Ben-Menachem et al. lacosamide trials. The adverse experiences of dizziness, headache, and nausea were noted in both published studies, but the most common adverse experience, dizziness, occurred less frequently in the Halász et al. study—10.4% at 200 mg/day and 15.7% at 400 mg/day, as compared with 24% and 26%, respectively, in the Ben-Menachem et al. study. Similarly, there was a lower incidence of other less common adverse experiences in the current study. The reason for this finding is unclear, and it is not known if doses of concomitant antiepileptic drugs were lower in the study by Halász and colleagues in comparison to the previous study.

Lacosamide will be an important addition for patients with refractory partial epilepsy. However, it is not totally clear where lacosamide will be positioned for the treatment of partial epilepsy, in general. The choice of an antiepileptic drug is dependent on many factors, including safety, efficacy, tolerability, ease of use and titration, as well as usefulness in treating comorbidities. Lacosamide appeared safe in the pivotal trials, but comfort with safety requires exposure of a large number of individuals, as may occur in the first year of use. Efficacy, tolerability, and ease of use and titration have been demonstrated in the existing lacosamide trials. The availability of an intravenous formulation is another desirable feature of lacosamide shared by only a handful of antiepileptic drugs. With respect to

comorbidities, lacosamide has no indications outside of partial epilepsy, but there are data supporting its efficacy in painful diabetic neuropathy (6–8). Thus, it may be a drug that could be considered at an earlier stage for epilepsy patients who have this comorbidity. At present, lacosamide is approved only for adjunctive use, making interactions with other antiepileptic drugs an important consideration. No clinically significant pharmacokinetic interactions have been demonstrated, but the existing trial data should be examined for evidence of pharmacodynamic interactions with antiepileptic drugs (e.g., carbamazepine) that act on the sodium channel. The lacosamide adverse effects of dizziness, nausea, ataxia, and diplopia are shared with various sodium-channel-blocking medications, which were the most common concomitant antiepileptic drugs used in these trials. Analysis of adverse experiences in relationship to concomitant antiepileptic drugs may help identify such interaction. Interactions are not a factor when an agent is used as monotherapy; accordingly, a monotherapy trial of lacosamide is currently under way. If this trial demonstrates lacosamide monotherapy efficacy, it will greatly enhance its place in epilepsy therapy.

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