

## LOSIGAMONE: ANOTHER NOVEL DRUG FOR PARTIAL SEIZURES

**Efficacy and Safety of Losigamone in Partial Seizures: A Randomized Double-Blind Study**

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The objective of the study was to investigate the efficacy and safety of two different dosages of losigamone (LSG) in add-on treatment of partial seizures. In a multicenter, double-blind, randomized clinical trial, patients received one of three 12-week treatments: placebo, LSG 1,200 mg/day, or LSG 1,500 mg/day, in addition to up to three standard anticonvulsants after a prospective period of 12 weeks to assess baseline seizure frequency. The primary efficacy measure was the relative reduction of seizure frequency per 4 weeks in the double-blind phase as compared with baseline.

In the intention-to-treat population of 264 patients, the relative median reduction of partial seizure frequency was 3.3% for placebo, 19.7% for LSG 1,200 mg/day, and 25.3% for LSG 1,500 mg/day. The differences of both LSG groups versus placebo were significant ( $P < 0.01$ , two-tailed). In the responder analysis, 11.8% of the patients in the placebo group, 17.2% in the LSG 1,200 mg/day group, and 29.3% in the LSG 1,500 mg/day group showed a seizure reduction versus baseline of  $\geq 50\%$ . A positive association between dosage and response was observed ( $P = 0.003$ ). Adverse events during treatment were reported by 58.8% of the patients for placebo, by 62.1% for LSG 1,200 mg/day, and by 76.1% for LSG 1,500 mg/day. Most events in the LSG groups occurred during the first 4 weeks of double-blind (during or immediately after uptitration) and subsided quickly. Over the last 4 weeks of treatment, the incidence of adverse events in the LSG groups was close to the placebo level.

Based on the study's results, LSG is an effective and safe add-on drug for refractory partial epilepsy in adults.

but which appears to potentiate  $\gamma$ -aminobutyric acid (GABA)-dependent chloride influx without direct binding to GABA-associated receptors. This multicenter randomized, placebo-controlled, add-on trial of losigamone (LSG) in partial seizures demonstrated clear efficacy of two doses of LSG in comparison to placebo. The median reduction in seizure frequency as well as responder rate were significantly greater for a dose of 1,500 mg/day than for 1,200 mg/day, indicating a dose-response relation. This finding suggests that doses  $> 1,500$  mg also may be more effective and should be explored.

The trial by Baulac and colleagues was conducted in a standard add-on design, making it possible to compare LSG with other new agents through meta-analysis. The odds ratio of finding a 50% responder was 2.5, a value intermediate between those of lamotrigine (LTG) and zonisamide (ZNS). Efficacy was maintained throughout the evaluation phase. The medication was fairly well tolerated. Withdrawals related to adverse events were 4% for the placebo group and 11% and 16% for the LSG 1,200-mg and 1,500-mg groups, respectively. However, most adverse events occurred around titration, suggesting that a slower titration should improve tolerability. The most common adverse events were dizziness, headache, fatigue, and somnolence—not too different from those of most other AEDs. The authors reported several interesting analyses. Findings included greater chance of response with shorter duration of epilepsy and with an intermediate seizure frequency during baseline. Only complex partial seizures were sufficiently represented to assess efficacy by seizure type (complex partial seizures were reported by nearly 75% of patients, but simple partial and secondarily generalized seizures each occurred in  $< 20\%$  of patients). The placebo group had none; the LSG 1,200-mg group, 19.7%; and the LSG 1,500-mg/day group, 26.3% reduction in complex partial seizures in comparison with baseline.

Overall, the study suggested that LSG is an effective AED that deserves further exploration in clinical trials. However, several new AEDs were introduced in the past decade. The ensuing intense competition may discourage development of new agents, unless they have a distinctive strength, advantage, or potential use in other conditions, such as neuropathic pain, headache, and bipolar disorder. It is not clear whether further development is now planned for LSG.

## COMMENTARY

Losigamone is a novel experimental antiepileptic drug (AED) whose mechanism of action is not fully elucidated,

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