

# ADOPTING AN ORPHAN DRUG: RUFINAMIDE FOR LENNOX–GASTAUT SYNDROME

**Rufinamide for Generalized Seizures Associated with Lennox–Gastaut Syndrome.** Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. *Neurology* 2008;70(21):1950–1958. **BACKGROUND:** Lennox–Gastaut syndrome is a catastrophic pediatric epilepsy syndrome characterized by multiple types of treatment-resistant seizures and high rates of seizure-related injury. Current available treatments are inadequate, leaving patients with few treatment options and opportunities. **METHODS:** We conducted a double-blind, randomized, placebo-controlled trial of the antiepileptic drug rufinamide in patients with Lennox–Gastaut syndrome. Eligible patients between 4 and 30 years of age had multiple types of seizures (including tonic–atonic and atypical absence seizures) with a minimum of 90 seizures in the month before baseline and a recent history of a slow spike-and-wave pattern on EEG. **RESULTS:** After a 28-day baseline period, 139 eligible patients were randomized; 138 patients received either rufinamide ( $n = 74$ ) or placebo ( $n = 64$ ) in addition to their other antiepileptic drugs. The median percentage reduction in total seizure frequency was greater in the rufinamide therapy group than in the placebo group (32.7% vs 11.7%,  $p = 0.0015$ ). There was a difference ( $p < 0.0001$ ) in tonic–atonic (“drop attack”) seizure frequency with rufinamide (42.5% median percentage reduction) vs placebo (1.4% increase). The rufinamide group had a greater improvement in seizure severity ( $p = 0.0041$ ) and a higher 50% responder rate compared with placebo for total seizures ( $p = 0.0045$ ) and tonic–atonic seizures ( $p = 0.002$ ). The common adverse events (reported by 10% of patients receiving rufinamide) were somnolence (24.3% with rufinamide vs 12.5% with placebo) and vomiting (21.6% vs 6.3%). **CONCLUSIONS:** Rufinamide was an effective and well-tolerated treatment for seizures associated with Lennox–Gastaut syndrome.

## COMMENTARY

The Lennox–Gastaut syndrome (LGS) is a severe childhood-onset epilepsy syndrome that is composed of

a triad of multiple seizure types (atonic, tonic, atypical absence, myoclonic, and generalized tonic-clonic), cognitive dysfunction, and slow spike-and-wave activity (slower than 2.5 Hz) on EEG. LGS can be symptomatic secondary to a brain insult, such as perinatal anoxia or cerebral dysgenesis, or cryptogenic in a previously normal child. LGS accounts for 1 to 4 percent of childhood epilepsy but constitutes a larger proportion (10%) of all refractory epilepsy, as most patients never achieve seizure freedom (1).

Glauser et al. report a randomized, controlled trial of rufinamide for refractory LGS in subjects aged 4 to 37 years. Rufinamide is a structurally novel triazole-derivative antiepileptic drug (AED). The proposed mechanism of action is the limitation of sodium-dependent action potential firing (2). Rufinamide has a broad efficacy spectrum in animal models of epilepsy. Two large double-blind, placebo-controlled trials demonstrated rufinamide to be efficacious and well tolerated as adjunctive therapy for partial seizures in adults, although it is not yet FDA-approved for this indication (2). In 647 subjects with refractory partial seizures, rufinamide add-on therapy was superior to placebo at 400-, 800-, and 1,600-mg doses (treatment difference vs placebo were 11%, 16%, and 17%, respectively) (2). In a second trial of 313 patients with refractory partial epilepsy, the mean seizure frequency in the rufinamide group (target dose 3,200 mg) showed a 20.4% decrease in the median seizure frequency compared with a 1.6% median increase in the placebo group. The  $\geq 50\%$  responder rate was 28.2% for rufinamide versus 18.6% for placebo (2).

Glauser and colleagues report that rufinamide was significantly superior to placebo for both primary study endpoints: percent change in seizure frequency and parent/guardian ratings of seizure severity. Tonic-atonic seizures, which often are disabling because of associated falls and injuries, were significantly reduced. Similarly, absence and atypical absence seizures were decreased, although the frequency of these often subtle but innumerable daily seizures may be underestimated without video-EEG monitoring. Adverse effects included sedation (24%) and vomiting (21%); six patients (8%) in the rufinamide group discontinued because of adverse effects. Cognitive or psychiatric adverse events were less common in the rufinamide group (17.6%) than in the placebo group (23.4%). Based on these results, rufinamide is efficacious and well tolerated for all seizures, including tonic-atonic seizures, for LGS.

Integrating the results of this study into clinical practice will be less straightforward. There are no class I or II studies for the treatment of early LGS. Broad-spectrum AEDs are preferred, as they may have activity against multiple seizure types and are less likely to exacerbate generalized seizures. Valproate is usually the treatment of choice for initial therapy of LGS, despite the absence of controlled trials assessing efficacy (3,4). Several newer AEDs have demonstrated efficacy for refractory LGS in class I

studies. A Cochane review (5) and the American Academy of Neurology/American Epilepsy Society guidelines (6) support the efficacy of felbamate, lamotrigine, and topiramate as adjunctive therapy for LGS (predominantly for atonic or astatic seizures) in adults and children. Felbamate use is constrained by potential hepatotoxicity and aplastic anemia. Clobazam (not approved for use in the United States) and other benzodiazepines are commonly used when initial valproate therapy fails (3,4). Narrow-spectrum AEDs, such as carbamazepine and tiagabine, may exacerbate certain seizure types (e.g., atypical absence and myoclonic) or even precipitate nonconvulsive status epilepticus (SE). Anecdotal reports and uncontrolled studies provide preliminary support for efficacy of other broad-spectrum AEDs, such as levetiracetam and zonisamide (1). When AEDs fail, vagus nerve stimulation and corpus callosotomy improve seizure control, particularly for atonic seizures (1).

What is rufinamide's place among these various treatment options? There are no head-to-head comparative trials of commonly used AEDs for LGS. Although the magnitude of seizure reduction in this rufinamide trial by Glauser et al. is similar to or better than that reported in trials of felbamate, topiramate, and lamotrigine, no direct comparisons can be made because of differences in methodology, baseline seizure frequency, concomitant AEDs, titration schedules, and outcome measures. This cohort may have been more refractory than other randomized LGS trials, with very high baseline monthly seizure counts. Forty percent of rufinamide patients were taking lamotrigine and 27% were taking topiramate—AEDs that were not available at the time of prior LGS randomized trials.

Likewise, adverse effect rates cannot be directly compared. Rufinamide was initiated at 10 mg/kg/day, divided twice daily, and increased by 10 mg/kg/day every 2 days to a maximal dose of 45 mg/kg/day (or 3,200 mg/day for adults  $>70$  kg), divided twice daily. The rate of dose escalation was rapid; most patients reached the target dose by 7 days and nearly 90% by 14 days. A slower dose escalation may be better tolerated, particularly for patients already taking multiple AEDs. This report does not give details of adverse effect rates stratified by the number or type of baseline concomitant AEDs. This information will be essential to optimize clinical use. Similarly, the relationship between adverse effects and rufinamide serum levels was not reported; in the future, serum levels may help to individualize dosing regimens.

The main advantages of rufinamide are a good cognitive and psychiatric adverse effect profile, few drug interactions (although valproate may increase rufinamide levels), and the ability to rapidly escalate dosing in as few as 7 days. Because AED polytherapy is typical in LGS, avoidance of drug interactions and AED adverse effects are the paramount concerns. Patients with LGS often have seizure clusters and exacerbations of seizure frequency; thus, the ability to rapidly achieve improvements in seizure frequency with rufinamide also is a major advantage.

Safety concerns and clinical experience govern how quickly a new AED is adopted into common practice. Other newer AEDs, such as topiramate and lamotrigine, were FDA-approved for treatment of partial seizures in adults and children as well as for LGS, and there was extensive familiarity with their clinical use, safety, and tolerability before they were widely used for LGS. In contrast, fewer than 2,000 patients with epilepsy have been treated with rufinamide in double-blind or extension phases of clinical trials, with time periods ranging from less than 1 month to more than 4 years (2). This exposure is far too low to detect rare side effects, such as hypersensitivity reactions, hematologic adverse effects, and hepatotoxicity. Because of the limited FDA indication for rufinamide, it may take a significant amount of time to reach a safety comfort level—approximately 100,000 patient exposures are necessary for the detection of rare idiosyncratic adverse events.

SE is common in LGS and was seen in 4% (3/74) of patients in the rufinamide group versus 0% in the placebo group. The type of SE (convulsive or nonconvulsive) was not reported. Other sodium channel blockers, such as carbamazepine, may increase the frequency of some seizure types and even precipitate SE. Overall, SE occurred in 0.9% of patients in rufinamide clinical trials run to date. Whether the higher SE rate in this trial is a rufinamide effect or merely due to chance will become clear with wider use.

High seizure severity and overall poor prognosis justify rapid adoption of rufinamide for refractory LGS. Rufinamide use is most appropriate when LGS patients have failed valproate, topiramate, and lamotrigine and probably before felbamate, other newer AEDs, vagus nerve stimulation, or corpus callosotomy is considered. Whether rufinamide should be used earlier

in LGS will depend on clinical experience and future comparative clinical trials—is it more efficacious or better tolerated than available drugs, and is safety acceptable? For now, rufinamide is a welcome addition to the treatment armamentarium for this devastating epilepsy syndrome.

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## References

1. Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, Genton P, Guerrini R, Kluger G, Pellock JM, Perucca E, Wheless JW. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol* 2009;8:82–93.
2. Arroyo S. Rufinamide. *Neurotherapeutics* 2007;4:155–162.
3. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. *Epileptic Disord* 2007;9:353–412.
4. Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion, 2005. *J Child Neurol* 2005;20(suppl 1):S1–56.
5. Hancock E, Cross H. Treatment of Lennox-Gastaut syndrome. *Cochrane Database Syst Rev* 2003;CD003277.
6. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, Wilner A, Faught RE Jr, Sachdeo RC, Beydoun A, Glauser TA, Therapeutics, Technology Assessment Subcommittee of the American Academy of N, Quality Standards Subcommittee of the American Academy of N and American Epilepsy S. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004;62:1261–1273.