MOVEMENT DISORDERS

A nondopaminergic treatment for RLS

Results from a phase III clinical trial of patients with primary restless legs syndrome (RLS) demonstrate that the nondopaminergic gabapentin prodrug XP13512 (gabapentin enacarbil) significantly improves symptoms in adults with moderate to severe cases of the disorder. "This drug [XP13512] showed comparable efficacy to that of dopamine agonists in relieving RLS symptoms," states lead investigator, Clete Kushida from the Stanford Sleep Medicine Center. "Adverse events associated with dopamine agonists, such as nausea, augmentation (paradoxical increase in symptom severity) and morning rebound, were not observed with this drug in this 12 week trial," he adds.

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RLS is a sensorimotor disorder in which affected individuals have an overwhelming desire to move their legs, usually in response to uncomfortable, and sometimes painful, sensations. Although such movement provides temporary relief, symptoms usually worsen during the day and patients frequently endure disturbed sleeping patterns. To overcome the adverse events associated with dopamine agonists—the only drugs approved by the FDA for RLS—agents from other drug classes have been sought to treat the disorder. "A prior clinical study and case reports suggested that gabapentin may be effective in improving RLS symptoms," explains Kushida. Subsequently, XP13512—a prodrug developed to improve the bioavailability of gabapentin—showed encouraging results in two phase II clinical trials for RLS.

Kushida and his colleagues randomly assigned 222 patients with RLS to receive 1,200 mg XP13152 or placebo, once a day with food. They observed treatment effects for the two primary end points at week 12: the mean change from baseline International Restless Legs Scale total score was greater with XP13512 than with placebo (–13.2 versus –8.8); and the proportion of patients investigator-rated as responders was higher with XP13512 than with placebo (76.1% versus 38.9%). XP13512 was also reported to improve sleep outcomes, as described by patients, and, in a subset of individuals, to reduce symptomatic pain associated with RLS. In general, XP13512 was well tolerated, with somnolence and dizziness being the most frequently reported adverse events.

The long-term safety of XP13512 is currently being assessed, and studies are also underway to explore the effects of this drug on sleep.

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Original article Kushida, C. A. *et al.* Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology* **72**, 439–446 (2009).