A cartoon published in the New Yorker lays out a common argument: “Ask your doctor if taking a pill to solve all your problems is right for you,” a television blares at a woman sitting in her living room. The cartoon wasn’t about restless leg syndrome (RLS) specifically, but it’s not a stretch to imagine the 2011 flood of 30 second TV spots for a newly approved Horizant was a motivating factor for it, and the largely cynical response it received. Few other disorders are met with as much skepticism, but such is the life of a disorder whose initial appearance before most of America was as something called “Jimmy Legs” on an episode of Seinfeld.

BACKGROUND
Restless leg syndrome is a disorder in which there is an urge or need to move the legs to stop unpleasant sensations.1 It occurs most often in middle-aged and older adults, and stress is known to make it worse. The cause is not known in most patients. It is, however, commonly passed down in families and this may be a factor when symptoms start at a younger age. The abnormal gene has not yet been identified.

RLS can result in insomnia and in turn, daytime sleepiness, anxiety, or depression, and confusion or slowed thought processes. RLS leads to sensations in the lower legs between the knee and ankle. The National Institute of Health lists several symptoms:

- Usually occur at night when patients lie down, or sometimes during the day when sitting for long periods of time
- May be described as creeping, crawling, aching, pulling, searing, tingling, or bubbling
- May last for one hour or longer
- Sometimes also occur in the upper leg, feet, or arms
- Patients feel an irresistible urge to walk or move their legs, which typically relieves the discomfort.

A WELCOME ADDITION
On April 6, 2011, oral gabapentin enacarbil (Horizant) was approved in adult patients for the treatment of moderate to severe primary restless legs syndrome and the management of postherpetic neuralgia. Its safety and efficacy has been established in several studies, including the 12-week Patient Improvements in Vital Outcomes following Treatment (PIVOT) RLS I and II trials.2 This study followed adult patients with moderate to severe primary RLS (n>500 total evaluable) taking once-daily gabapentin enacarbil at either 600 or 1,200mg and found it “significantly improved mean International Restless Legs Scale (IRLS) total scores compared with placebo.” Moreover, there were meaningfully higher investigator-rated Clinical Global Impression-Improvement (CGI-I) responder rates in gabapentin enacarbil groups than in groups taking placebo.

The past six months have seen new research, a messy drug maker divorce, and new treatment guidelines for RLS. We take a closer look here.

BY ZAC HAUGHN, SENIOR ASSOCIATE EDITOR
There were improvements in other sleep results (assessed using various scales) that also by and large favored gabapentin enacarbil treatment. These data are supported by outcomes from a polysomnography, cross-over (two four-week treatment periods) trial (n>100 evaluable). Improvements in RLS symptoms with the drug were maintained in a 52-week extension study of clinical trials, including PIVOT RLS I and II. The longer-term efficacy of gabapentin enacarbil in patients with moderate to severe RLS was also demonstrated in the 36-week PIVOT RLS Maintenance study and a 52-week noncomparative study conducted in Japan.

But pick-up for the new therapy has been slow. In November GlaxoSmithKline relinquished the drug to partner XenoPort after what the industry considered disappointing sales and a partnership dispute. Glaxo has already taken a $164.7 million charge for its Horizant disappointment, so the company doesn’t expect any more write-offs on the drug.

The slow uptake of the drug has puzzled observers in the industry and the clinic. Positive findings for the agent have appeared throughout the literature. In September researchers found the lowest dose of gabapentin enacarbil evaluated (600mg) significantly improved RLS symptoms compared with placebo. The safety profile was consistent with previous studies.

Under the companies’ new agreement, GSK’s US marketing and development rights will end April 30. Glaxo has agreed to purchase $20 million of XenoPort stock at a 12.5 percent premium to recent market prices, and XenoPort holds the option to require GSK to buy another $20 million more until October 2013.

Glaxo says its decision to back off Horizant “is aligned with GSK’s ongoing strategy to streamline its portfolio.” The agreement also settles the companies’ legal quarrels. Glaxo has already taken a $164.7 million charge for its Horizant disappointment, so the company doesn’t expect any more write-offs on the drug.

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To study the key efficacy and safety outcomes in subjects with RLS treated with once-daily gabapentin enacarbil 600mg, 1200mg, 1800mg and 2400mg, researchers designed an integrated post hoc analysis. They used three 12-week, randomized, double-blind, placebo-controlled trials in subjects with RLS. The three studies were carried out

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<th>Strong recommendations</th>
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<td>Rotigotine transdermal patch (1–3mg) is effective for the short- and long-term treatment of primary RLS.</td>
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<td>Ropinirole is effective over the short term for improving symptoms in primary RLS when given at a mean dose of between 2.1 and 3.1mg/day.</td>
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<td>Pramipexole is labeled “effective” for short-term use at doses between 0.25 and 0.75 mg.</td>
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<td>Gabapentin enacarbil (1200mg daily) falls under the category of “effective” for the short-term treatment of primary RLS.</td>
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<td>Pregabalin (150–450mg daily) is also effective for the short-term treatment of primary RLS.</td>
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<td>Gabapentin is effective for the short-term treatment of primary RLS.</td>
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<td>There is high-quality evidence to shows that cabergoline (0.5–3 mg/day) improves RLS symptoms, but the group feels it cannot be recommended because of serious adverse risks.</td>
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<td>The augmentation risks sink levodopa. “There is high-quality evidence that shows that levodopa (up to 300 mg/day) improves RLS symptoms,” the guidelines note, “[h]owever, given the higher risk of augmentation compared with dopamine agonists, levodopa should not be given at a dosage higher than 200mg/day.” They say that in clinical practice, levodopa is now better established as a diagnostic test for RLS and as on-demand treatment in sporadic RLS. This is chief reason why the task force could only make a low recommendation for levodopa.</td>
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across the US and included 760 subjects (placebo, n = 245; gabapentin enacarbil 600 mg, n = 163; gabapentin enacarbil 1200 mg, n = 269; gabapentin enacarbil 1800 mg, n = 38; gabapentin enacarbil 2400 mg, n = 45). It was initiated at a dose of 600 mg with subsequent titration in 600 mg increments every three days up to the randomized dose.

The researchers concluded gabapentin enacarbil 600 mg significantly improved IRLS total score compared with placebo (adjusted mean [standard error] change in the International Restless Legs Scale total score from baseline to week 12 last observation carried forward: -13.6 [0.71] vs. -9.3 [0.55]; adjusted mean treatment difference: -4.3; 95% CI -6.01, -2.52; p < 0.0001). They found “a significantly higher proportion of subjects was rated as responders on the investigator-rated CGI-I scale with gabapentin enacarbil 600 mg compared with placebo (70.2% vs. 42.2%; adjusted odds ratio 3.1; 95% CI 1.96, 4.89; p < 0.0001).” Similar treatment benefits were also witnessed with both efficacy endpoints for the three higher doses. Somnolence and dizziness were the most common side effects. There was a dose-response relationship to these AEs and no new or unexpected safety issues were identified by the research team.

Hoping to examine and replicate results in Asian patients, Japanese researchers recently evaluated gabapentin enacarbil for the treatment of RLS in Japanese patients; the treatment was found to be effective and well tolerated. All three doses showed improvements in RLS compared with placebo, with 600 mg being the suitable target dose.

The study authors observed the mean change in IRLS score from baseline to the final observation was -8.96, for placebo versus -11.10, -10.28 and -11.38 for 600, 900 and 1200 mg. Williams’s multiple comparison test showed that only 1200 mg was superior to placebo (P = 0.011). “However,” they wrote, “in post hoc mixed-effects models with repeated measures, which accounted for the time-course of changes in IRLS, the placebo-adjusted changes were -2.31, -1.92 and -2.31 for 600, 900 and 1200 mg, ICGI and PCGI response rates were significantly greater for all three doses versus placebo (all Ps 0.014).” Not unexpectedly, adverse events, including somnolence, dizziness and nasopharyngitis, were common but mild to moderate in severity. “However, there was a tendency toward a dose-dependent increase in the incidence of adverse events,” they wrote.

**NEW EUROPEAN GUIDELINES**

In 2005 a task force developed a set of guidelines for RLS management in Europe. Published in November 2012, the European Federation of Neurological Societies in collaboration with the European Neurological Society and the European Sleep Research Society sought to update those findings, in light of the new evidence for treatment, and the changes in routine clinical care introduced by the approval of new drugs. Though Horizant is not currently approved in Europe, this allows the task force to think outside of the box and think critically about other options. Some of their recommendations include:

- Antiepileptic drugs. Pregabalin and gabapentin enacarbil can be considered effective for the short-term treatment of primary RLS, the guidelines note. In addition, gabapentin enacarbil was placed in the “probably effective” category for the long-term treatment of RLS. They note gabapentin continues to be considered effective in the short-term treatment of primary RLS and falls under “probably effective” for secondary RLS after haemodialysis.

- Adrenergic agents. The guidelines note that Clonidine has several tolerable side effects and can be considered “probably effective” in reducing symptoms and sleep latency in primary RLS at short-term.

- Benzodiazepines/hypnotics. Since their previous guidelines, only one new study concerned benzodiazepines and thus, the group didn’t make any updates. Their previous recommendation found “Clonazepam should be considered as probably effective for improving symptoms in primary RLS when given at 1 mg before bedtime, but also probably ineffective when given at four doses throughout the day.”

- Botox. The guidelines note there is “Class III evidence that botox onabotulinumtoxinA improves RLS symptoms during the first 4 weeks after treatment.”

The group notes in the previous guidelines dopaminergic agents were established as the first-line treatment of primary RLS. “We consider that overall, this conclusion is still valid, particularly since gabapentin enacarbil is, at the time of writing, not available in Europe.” More comparative, long-term trials are needed to evaluate “differences between drug classes, as some of the main differences in efficacy and augmentation rates can be shown when these studies are sufficiently long.”

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