

What Can We Do to Minimize Side Effects of RLS Therapy?

Q *A recent meta-analysis¹ of the side effects and wearing-off effect of four RLS drugs found the dropout rate was highest in ropinirole and “may be the drug causing the most profound side effects.” It also found pramipexole provided the most benefit (though its trials were shorter). How do these conclusions compare with your clinical experience?*

A Our panel’s collective clinical experience was mixed. “I have found good clinical benefit with both [ropinirole and pramipexole], it just depends on what dosages your patient needs to take in order to experience the most adequate clinical response,” says Shilpa Chitnis MD, PhD. All agreed the patient determines the course of action. “The fact remains that different patients may respond quite differently to the various dopaminergic agents, so it is unlikely that any one agent will be best for most patients,” says Mark Mahowald, MD. “The side effects are actually quite infrequent, due to the very low doses usually required to treat RLS, in comparison with the doses for Parkinson’s disease.”

Physicians should interpret the findings as showing the drugs as a boon, not a bust, despite their shortcomings, according to study author William L. Baker, PharmD, BCPS. “I think that practicing neurologists should view our study as a confirmation of the benefit that the non-ergot dopamine agonists have in patients with RLS,” he says. “Our study showed that patients with moderate to severe RLS would experience relatively quick and robust improvements in their RLS symptoms, as evidenced by an increase in the clinical global impression–improvement scale and a reduction in the International Restless Legs Syndrome Study Group Scale score.”

The side effects could be expected to cease with continued drug use, but patients may complain of them following initiation of therapy, he continues. “In addition these drugs may suffer from augmentation, in that their effects decrease over time, although this effect seems less likely than with levodopa use.” Whether this reflects a decreased efficacy of the drugs or progression of the disease in the study patients is not clear from their results, Dr. Baker says.

Q *How do you manage side effects such as nausea, dizziness, wheeziness, fatigue and transient headache? Are there any predisposing factors that increase the likelihood of side effects in certain patients? The meta-analysis found that “a significant portion of patients will discontinue their use as a result of adverse events.” Is it possible to mitigate or at least delay this response?*

A Managing side effects is best done by the “start low, go slow” approach, tapering patients off when side effects become apparent, and dose timing, according to our panel. “The most problematic side effects are nausea and somnolence, but typically, you use it in the evening and thus it helps people fall asleep,” says Emmanuel Mignot, MD.

Older age and concomitant medication use—those which make patients more sleepy or more confused with hallucinations—will adversely interact with the agonists and can make side effects worse, according to Dr. Chitnis. Most of the side effects are mild to moderate in severity and resolve after approximately seven to 14 days of use, adds Dr. Baker, who says effective doctor-patient communication is another key. “The patient and the prescriber must establish an acceptable risk-

benefit threshold between side effects and RLS symptom benefits.” Taking the medications with food may help reduce GI effects; alternatively, taking the medication before bedtime may help with the dizziness and somnolence sometimes seen with their use, Dr. Baker adds.

Dr. Mahowald has not had the problems the study found. “Our center’s experience has not been that ‘a significant proportion’ of patients will discontinue the medications.” For patients with truly bothersome RLS, he says the benefit far outweighs the infrequent and generally mild side effects. “I suspect that those who do discontinue the meds have relatively mild RLS in the first place. Often switching to a different dopaminergic agent will be effective.” The bottom line, he says, is that the overwhelming majority of patients seem to respond nicely to either dopaminergics or opiates, alone or in combination, with minimal side effects, assuming the diagnosis is correct.

Q *At what point would you consider switching to a different agent? Would you consider switching to gabapentin or another AED? If so, what precautions need to be added? Also, results from trials using high-dose intravenous iron are limited² and mixed,³ but does this have a role in RLS treatment?*

A Dr. Baker says he would consider switching from a NEDA to another agent for the treatment of RLS in either of two situations. “First, if the patient is not experiencing any clinical benefits from the drug, or the drug has ceased to be beneficial for the patient after long-term use; second, if the patient is experiencing limiting side effects that result in drug therapy non-compliance.” Gabapentin seems to be a reasonable therapeutic option for RLS

patients, especially those with RLS perceived as painful, he adds, and says few other AEDs have enough data to recommend them for routine clinical use at this time. Dr. Mignot also gives gabapentin a vote of confidence, saying he would try it in a switch. However, this stands in contrast to Dr. Mahowald's view. "In our experience, gabapentin and the other AEDs are not very effective. The second class of very effective medications is opiates—with negligible issues of dependence, tolerance or abuse."

All panelists were hesitant to use IV iron, reserving it for use only in highly specified cases. "IV iron should be used only in recalcitrant cases with documented

very low serum ferritin levels," Dr. Mahowald says. "I test patients for Fe and ferritin levels but have not used IV iron," Dr. Chitnis says. I usually defer to the primary care MD who works closely with in correcting the Iron deficiency." The current evidence is nonconclusive and should be reserved for patients with true iron deficiency, a recommendation supported by recent guidelines, Dr. Baker says. **PN**

1. Baker, W et al. Effect of Nonergot Dopamine Agonists on Symptoms of Restless Legs Syndrome. *Annals of Family Medicine* 6:253-262 (2008).

2. Earley CJ et al. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. *Sleep Med.* 2005 Jul;6(4):301-5.

3. Earley CJ et al. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. *Sleep Med.* 2008 Feb 13.

William L. Baker, Pharm.D, BCPS is a Cardiovascular Outcomes Fellow at Hartford Hospital & University of Connecticut.

Shilpa Chitnis MD, PhD is Assistant Professor of Neurology at the University of Texas Southwestern Medical Center.

Mark W. Mahowald, MD is Director of the Minnesota Regional Sleep Disorders Center and Chief of the Department of Neurology, Hennepin County Medical Center.

Emmanuel Mignot, MD, PhD is HHMI investigator, Professor of Psychiatry and Behavioral Sciences at Stanford University Center For Narcolepsy.