CASE REPORT

Medication Tolerance and Augmentation in Restless Legs Syndrome: The Need for Drug Class Rotation

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Restless legs syndrome (RLS) is a common condition characterized by an unpleasant urge to move the legs that usually occurs at night and may interfere with sleep. The medications used most commonly to treat RLS include dopaminergic drugs (levodopa, dopamine agonists), benzodiazepines, and narcotic analgesics. We report the cases of 2 patients with RLS who illustrate the problems of tolerance (declining response over time) and augmentation (a worsening of symptoms due to ongoing treatment) that can complicate the pharmacotherapy of RLS. We discuss the optimal management of RLS and propose strategies to overcome tolerance and augmentation such as a rotational approach among agents from different classes.

KEY WORDS: restless legs syndrome; levodopa; dopamine agonists; analgesics; benzodiazepines.

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Restless legs syndrome (RLS) is a common condition characterized by an unpleasant urge to move the legs that usually occurs at night and may interfere with sleep.^{1,2} The American Academy of Sleep Medicine has published clinical features required for diagnosis (Table 1).³ Restless legs syndrome is often familial and may be associated with lumbar spine disease, renal failure, and iron deficiency.^{1,2} Various treatment approaches have been proposed in review articles based on available scientific evidence and expert opinion.^{3–6} Medications used most frequently for the treatment of RLS include dopaminergic drugs (levodopa, dopamine agonists), benzodiazepines (clonazepam), narcotic analgesics and, more recently, gabapentin.^{7,8} The dopamine agonist ropinirole has recently been approved by the FDA for this indication^{3–6} and has been recommended by some authors as first line treatment, particularly for patients who require nightly therapy.⁵ Clonidine and carbamazepine have been studied but are not frequently used in clinical practice.⁵ There is evidence that supplementing iron in patients with low ferritin levels may improve symptoms.⁹ Other nonpharmacologic approaches that have been suggested (but not studied) include avoidance of caffeine, nicotine, and alcohol.⁵

Unlike many movement disorders, the drug treatment of RLS is confounded by a tendency of patients to quickly become tolerant to therapy, losing the benefits of medication within weeks or months. In addition, continued treatment with drugs that have lost benefit can actually worsen symptoms, a phenomenon referred to as “augmentation.”¹⁰ First described by

Allen and Earley¹⁰ in 1996, augmentation refers to the phenomenon in which RLS patients under dopaminergic therapy may experience an increase in symptom severity compared to baseline, with an earlier onset of symptoms at night, a shorter latency to onset of symptoms after lying down or sitting, appearance of daytime symptoms, and spread of symptoms to other parts of the body. Generally, augmentation is associated with a change in severity, timing, and body distribution but not the quality of the symptoms. For example, a patient whose symptoms are characterized by “creeping and crawling” sensations continues to experience these feelings when augmentation develops. This rapid worsening of symptoms seen in augmentation is not part of the natural history of RLS and is strictly a drug-induced effect. It is unclear if most treating physicians are aware of the problems of tolerance and augmentation or how to optimally deal with them in managing patients with RLS. We present 2 case reports to illustrate these problems and discuss the relevant literature.

REPORT OF CASES

Case 1

This 80-year-old woman was diagnosed with essential tremor at age 63 but was never treated for this condition. At age 72 she developed “crawling feelings” in both legs about 1.5 to 2 hours after falling asleep each night. These symptoms awakened her from sleep and were relieved by moving her legs, arising from bed, and walking about. The symptoms were mild at first but worsened around age 79 and she was diagnosed with RLS. She was placed on carbidopa/levodopa 25/100 0.5 tablet at bedtime with good success, but within 1 year the benefit was lost. At that time she was referred to our Movement Disorders Clinic. Her neurological examination was unremarkable and her subsequent course was characterized by initial benefit to medications, the need for steadily increasing dosages, and subsequent worsening with increasing nocturnal symptoms and appearance of daytime symptoms. Her symptoms always consisted of the same “crawling feelings” in her legs associated with the need to move the legs for relief.

Her treatment over time is illustrated in Table 2. Medications were always administered at bedtime and therapy was initiated with a single agent. Dosages were titrated upwards when she lost therapeutic benefit. In general, a medication was stopped and a new one started if tolerance developed and side effects precluded further dosage increases or when evidence of

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Table 1. Diagnostic Features of Restless Legs Syndrome³

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night

augmentation appeared. Side effects experienced by this patient included nausea and dizziness with the dopamine agonists, sedation with clonazepam, and constipation with propoxyphene. Augmentation was manifested by the onset of RLS symptoms during the day. Tolerance (usually within 4 to 12 weeks) was evident with all drug classes, but symptoms of augmentation occurred only with the dopaminergic drugs (levodopa and ropinirole). There was a several month period of time during which she was treated with a combination of medications (codeine combined first with clonazepam and then with ropinirole). Clonazepam and narcotic medication dosages were gradually tapered before these drugs were discontinued.

Case 2

This 61-year-old woman reported onset in her teens of discomfort starting in her low back and traveling down both legs, described "like an itch or tingling," with onset about 30 minutes after lying down for sleep. The discomfort caused her to repetitively move her legs and was relieved by walking about. These symptoms were mild until age 56 when they worsened and disturbed her sleep. The patient reported a positive family history of RLS with her father, brother, and 2 sons being affected. She was diagnosed by a general neurologist as having RLS and over the next 5 years, because of short-term benefits

of prescribed medications, she ended up being treated with the combination of levodopa 1400 mg/d (divided in 5 doses), ropinirole 0.25 mg t.i.d., zolpidem 10 mg q HS, gabapentin 300 mg q HS, and fluoxetine 20 mg b.i.d.

She was referred to our Movement Disorders Clinic due to severe RLS symptoms (the same itch/tingling uncomfortable sensations in her low back and legs causing her to move her legs and walk about) occurring throughout the day and night (this is apparently why she was treated with medications throughout the day). Because of her chronic low back pain, an MRI of the lumbosacral spine was performed and showed moderate spinal stenosis at the L2 to L4 levels. Her neurological examination was unremarkable and surgery for spinal stenosis was not pursued at that time. Levodopa, ropinirole, zolpidem, and gabapentin were discontinued and propoxyphene 65 mg q HS was prescribed with dramatic improvement in symptoms.

The subsequent course of medication therapy is summarized in Table 3. Like the first case, medication was administered only at bedtime. In this patient, several different medication combinations were tried over a period of several years. Dosages were increased when symptoms were inadequately controlled and the drug was not causing significant side effects. Medications were tapered and discontinued when augmentation appeared. Augmentation was evidenced by

Table 2. Summary of Medications Used to Treat Patient Described in Case 1 and Their Associated Effects

Weeks of Therapy	Levodopa (mg)	Clonazepam (mg)	Propoxyphene	Pramipexole (mg)	Ropinirole (mg)	Codeine	Tolerance*	Augmentation†
0 to 48	50							X
48 to 52		0.5‡						
52 to 56	100						X	
56 to 60	200							X
60 to 112			65				X	
112 to 116			130				X	
116 to 140			260‡				X	
140 to 148				0.25‡				
148 to 152		0.5					X	
152 to 160		1.0					X	
160 to 176		1.5					X	
176 to 204		2.0‡					X	
204 to 208					0.5‡			
208 to 224			65				X	
224 to 228			130				X	
228 to 232			130		0.25‡		X	
232 to 252			130				X	
252 to 260		0.5				30 mg	X	
260 to 264					0.25	30 mg	X	
264 to 268					0.5		X	
268 to 276					1.0			X
276 to 288			65				X	
288 to 292			130				X	
292 to current			195					

*Tolerance refers to the tendency to lose medication benefit over time.

†Augmentation refers to a worsening of symptoms due to ongoing treatment.

‡Denotes side effects.

Clonazepam, sedation; propoxyphene, constipation; ropinirole, nausea and dizziness.

Table 3. Summary of Medications Used to Treat Patient Described in Case 2 and Their Associated Effects

Weeks of Therapy	Propoxyphene (mg)	Clonazepam (mg)	Pergolide (mg)	Pramipexole (mg)	Hydrocodone (mg)	Tolerance* (mg)	Augmentation† (mg)
0 to 32	65						
32 to 40	130	0.5				X	
40 to 44	195	1.0				X	
44 to 48	260	1.5				X	
48 to 52	325	3.0				X	
52 to 64	325					X	
64 to 116	390‡					X	
116 to 168			0.05				
168 to 172			0.10			X	
172 to 236			0.25			X	
236 to 248	65		0.25			X	
248 to 260	130		0.25			X	
260 to 272	195		0.25			X	
288 to 304	195	0.25	0.25			X	X
304 to 308	195	0.5				X	
308 to 332	195	0.5		0.25		X	
332 to 336		1.0		0.5	15	X	X
336 to 340					20		
340 to 348	130			0.5		X	
348 to current	195			1.0			

*Tolerance refers to loss of medication benefit over time.

†Augmentation refers to a worsening of symptoms due to ongoing treatment.

‡Denotes side effects (confusion and constipation with higher dosages of propoxyphene).

onset of symptoms during the day and an increased severity of symptoms above pretreatment levels. Tolerance developed (usually within 4 to 12 weeks) with all drug types but features of augmentation were seen only with the dopaminergic medications. The patient underwent lumbar laminectomy and spinal fusion surgery for spinal stenosis approximately 3 years after first presenting to us. She was treated with hydrocodone therapy postoperatively. Surgery did not appear to improve RLS symptoms.

DISCUSSION

As illustrated by our cases, tolerance often develops within a few weeks with several different drug classes used to treat RLS, including dopaminergics (levodopa, dopamine agonists), benzodiazepines (clonazepam), and narcotic analgesics (propoxyphene, codeine, hydrocodone). Tolerance was manifested by loss of beneficial effects with a need for steadily increasing dosages or the addition of other medications. The problem of tolerance is magnified in RLS in that ongoing therapy is associated not only with loss of efficacy but with augmentation, a worsening of symptoms beyond the severity at the time treatment was initiated.

While tolerance can be seen with any of the medications used to treat RLS, augmentation is associated with dopaminergic therapy in particular.¹¹ Augmentation has been distinguished from rebound, a phenomenon characterized by a reappearance and worsening of symptoms as the effects of a medication wear off between doses.^{10,12} Augmentation occurs especially during long-term levodopa therapy,^{10,12} but may also occur with dopamine agonists.^{13–16} No studies have directly compared levodopa and dopamine agonists for their propensity to induce augmentation and it is unknown if patients who develop augmentation with one dopaminergic drug are just as likely to develop it with a different one. It has been estimated that over 80% of patients receiving levodopa for RLS develop augmentation.^{13,14} Increasing medication dosages and

reducing the dosing intervals have been used in response to augmentation,^{12,14} but in our experience once evidence of augmentation appears it is best to switch from a dopaminergic drug to a different drug class. It is currently unknown how long the dopaminergic drug holiday should last before the medication can be effectively reintroduced. Reintroduction of dopaminergic medications was associated with symptoms of augmentation in both of our patients after 1 month holidays. In general, we now aim for a dopaminergic drug-free period of at least 3 months. It is unclear if the latency from starting therapy to onset of augmentation shortens each time a dopaminergic drug is reintroduced but this appears to have been the case in both of our patients. In our first patient, augmentation appeared 7 months after initial levodopa therapy but after only 2 months upon reintroduction of the drug. Our second patient developed augmentation a few years after initiation of dopamine agonist therapy and then about 4 months after reintroduction of this type of drug. It is unknown if augmentation is dose related but both of our patients experienced the phenomena with what would be considered relatively low dosages of medications (50 to 200 mg of levodopa, 1 mg of ropinirole, 0.25 mg of pergolide, 0.5 mg of pramipexole). In our experience, symptoms of augmentation resolve quickly, usually within about 1 week, once the dopaminergic drug is discontinued. A recent pharmacokinetic and polysomnographic study found that symptoms and signs of augmentation were related to low plasma levodopa levels in patients treated with this drug,¹⁷ but the detailed pathogenesis of this problem is unknown. The development of augmentation during treatment of RLS with medications other than dopaminergics has not received attention in the literature and it is unclear whether or not this might occur.

The recognition of tolerance and augmentation is critical in the optimal pharmacotherapy of RLS. Treating physicians may have insufficient information about these potential problems. It is important to note that recent published trials of ropinirole therapy of RLS, for example, excluded subjects with

prior augmentation, did not monitor for this problem during the study, and may have been too brief to observe augmentation.^{18–21} In a preliminary report, Garcia-Borreguero et al.¹⁶ described the results of 2 open-label studies of ropinirole for RLS (each of which lasted 52 weeks). They noted that augmentation developed in only 4% of patients.

Often, one cannot simply prescribe a single medication for RLS and expect long-term success. Patients with this condition often require careful clinical monitoring and frequent medication adjustments. Dopaminergic drugs may not be the best first-line treatment because of associated augmentation. We generally employ a rotation approach between dopaminergics, clonazepam, and low potency narcotic analgesics. We have not found other medications to be predictably effective. There is no evidence on which to base combination therapy, although we try this in some cases. For any new medication, even if previously used, we introduce it at low dosage and titrate the dosage to control symptoms, avoid side effects, and in response to tolerance. As soon as augmentation is evident, we switch from a dopaminergic drug to a different medication class. It is unknown whether routine drug class rotation, modifications in drug dosing schedules, or drug-free periods prior to the onset of augmentation might avoid this phenomenon.

REFERENCES

1. **Clough C.** Restless legs syndrome. *Br Med J.* 1987;294:262–3.
2. **Rama AN, Kushida CA.** Restless legs syndrome and periodic limb movement disorder. *Med Clinics N Am.* 2004;88:653–67.
3. **Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH.** An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep.* 2004;27:560–83.
4. **Earley CJ.** Restless legs syndrome. *N Engl J Med.* 2003;348:2103–9.
5. **Silber MH, Ehrenberg BL, Allen RP, et al.** An algorithm for the management of restless legs syndrome. *Mayo Clin Proc.* 2004;79:916–22.
6. **Trenkwalder C, Paulus W, Walters AS.** The restless legs syndrome. *Lancet Neurol.* 2005;4:465–75.
7. **Happe S, Klösch G, Saletu B, Zeitlhofer J.** Treatment of idiopathic restless legs syndrome (RLS) with gabapentine. *Neurology.* 2001;57:1717–9.
8. **Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Marsramon X, Hernandez G.** Treatment of restless legs syndrome with gabapentine: a double-blind, cross-over study. *Neurology.* 2002;59:1573–9.
9. **O'Keefe ST, Gavin K, Lavan JN.** Iron status and restless legs syndrome in the elderly. *Age Ageing.* 1994;23:200–3.
10. **Allen RP, Earley CJ.** Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep.* 1996;19:205–13.
11. **Guilleminault C, Cetel M, Philip P.** Dopaminergic treatment of restless legs syndrome and rebound phenomenon. *Neurology.* 1993;43:445.
12. **Collado-Seidel V, Kazenwadel J, Wetter TC, et al.** A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. *Neurology.* 1999;52:285–90.
13. **Stiasny K, Wetter TC, Trenkwalder C, Oertel WH.** Restless legs syndrome and its treatment by dopamine agonists. *Parkinsonism Relat Disord.* 2001;7:21–5.
14. **Comella CL.** Restless legs syndrome: treatment with dopaminergic drugs. *Neurology.* 2002;58:S87–S92.
15. **Winkelman JW, Johnston L.** Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). *Sleep Med.* 2004;5:9–14.
16. **Garcia-Borreguero D, Lee D, Ball E.** Ropinirole is well tolerated and effective for the long-term treatment of RLS. *Neurology.* 2005;64:A42.
17. **Vetrugno R, Contin M, Baruzzi A, et al.** Polysomnographic and pharmacokinetic findings in levodopa-induced augmentation of restless leg syndrome. *Mov Disord.* 2006;21:254–8.
18. **Trenkwalder C, Garcia-Borreguero D, Montagna P, et al.** Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry.* 2004;75:92–7.
19. **Walters AS, Ondo WG, Dreykluft T, et al.** Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord.* 2004;19:1414–23.
20. **Bogan RK, Fry JM, Schmidt MH, et al.** Ropinirole in the treatment of patients with restless legs syndrome: a U.S.-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc.* 2006;81:17–27.
21. **Bliwise DL, Freeman A, Ingram CD, et al.** Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. *Sleep Med.* 2005;6:141–7.