

Challenges in the Treatment of Restless Legs Syndrome: A Case Report

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Abstract

Treatment resistant restless legs syndrome (RLS) in the setting of psychiatric comorbidities can be difficult to manage. Our patient is a 69-year-old Caucasian gentleman with bipolar disorder type I, unspecified anxiety disorder, obstructive sleep apnea (OSA), and treatment-refractory RLS. At initial presentation, the patient's prescribed medication regimen included fluoxetine 40 mg daily, gabapentin 800 mg in the morning and 3200 mg at bedtime, pramipexole 0.375 mg daily, lamotrigine 200 mg daily, trazodone 200 mg at bedtime, and temazepam 15 to 30 mg as needed for insomnia and RLS. Over the course of nearly 4 years, treatment interventions for this patient's RLS included: cognitive behavioral therapy for insomnia, discontinuation of exacerbating medications, switching dopamine agonists, use of pregabalin and iron supplement. This report demonstrates a challenging case of RLS in the setting of psychiatric comorbidities, development of augmentation, and polypharmacy.

Keywords

restless legs, mood disorder, case report, medications, psychiatry

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Introduction

Restless legs syndrome (RLS) affects 5% to 15% of the general population and is a sleep-related movement disorder.¹ It is characterized by uncomfortable sensations in the legs accompanied by an urge to move that occurs predominantly during inactivity in the evening/night and is relieved by movement.¹ Periodic limb movements in sleep (PLMS) are noted on polysomnography in over 80% of patients with RLS compared to 6% in the general population but the diagnosis is based on clinical features.²

The underlying pathophysiology of RLS is thought to relate to dysfunction of iron and dopamine metabolism in the central nervous system.³ The treatment primarily includes dopamine agonists (DAs) (commonly, pramipexole, and ropinirole) and alpha-2-delta calcium channel ligands (gabapentin and pregabalin).⁴ The severity of RLS symptoms is variable in an individual patient and over time some patients develop intractable symptoms. Interestingly, long-term treatment with DAs is associated with augmentation, characterized by greater severity and frequency of

symptoms compared to baseline, often occurring earlier in the day and/or with spread to the arms.⁵

RLS is commonly comorbid with psychiatric conditions. Prior studies have indicated a higher lifetime prevalence of psychiatric disorders in subjects with RLS (37%) versus those without RLS (15%).⁶ Pharmacotherapies for psychiatric disorders such as antipsychotics and antidepressants inhibit dopamine neurotransmission and can lead to new-onset or worsening of RLS.⁷ The case we present here highlights many of the challenges experienced in the treatment of patients with RLS. It demonstrates the interplay between RLS, mood disorders, and medication-related aberrant behaviors as well as cost barriers to effective treatment.

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Case Presentation

Informed consent was obtained from the patient described for use as a case report.

Mr. A, a 69-year-old Caucasian gentleman with bipolar disorder type I, unspecified anxiety disorder, obstructive sleep apnea (OSA) on continuous positive airway pressure (CPAP) therapy, and treatment-refractory restless legs syndrome (RLS) was referred for a psychiatric consultation for comprehensive management of bipolar I disorder. He had a history of inpatient psychiatric hospitalizations, with the most recent one for mania triggered by sleep disturbance secondary to worsening RLS. He noted a past history of misusing lorazepam to alleviate his RLS symptoms. The first polysomnogram conducted over 10 years ago showed an apnea-hypopnea index (AHI) of 22 events per hour and a periodic limb movement index (PLMI) of 41 per hour, with a periodic limb movement arousal index (PLMAI) of 1 per hour. The patient's other medical history was significant for obesity with BMI >40, gastroesophageal reflux disease, benign essential hypertension, irritable bowel disease, low back pain, moderate obstructive sleep apnea on CPAP. He has a 30-pack-year smoking history before he quit. Pertinent to the physical examination was significant for crowded oropharynx, Friedman class IV, elevated tongue base, low dripping soft palate. External inspection of ears and nose when normal. Nasal mucosa, sputum, and turbinates are normal. Lips, teeth, and gums were normal. No abnormal lymphadenopathy in neck or supraclavicular region. Focused lower extremity neurological examination showed normal strength and sensory examination without evidence of neuropathy. Romberg test was negative. Pertinent family history was significant for RLS in mother, father and paternal uncle.

At initial presentation, the patient's prescribed medication regimen included fluoxetine 40 mg daily, gabapentin 800 mg in the morning, and 3200 mg at bedtime, pramipexole 0.375 mg daily, lamotrigine 200 mg daily, trazodone 200 mg at bedtime, and temazepam 15 to 30 mg as needed for insomnia and RLS. His baseline ferritin level was 174 ng/mL. He did admit to using temazepam at higher than prescribed doses to treat his severe RLS symptoms. Due to his diagnosis of bipolar disorder type I with a recent history of mania, trazodone was tapered and discontinued. Thereafter, temazepam was also gradually discontinued to reduce the risk of misuse. Although the use of a longer half-life benzodiazepine, such as clonazepam, could have been considered for RLS, we opted not to pursue that route due to patient's history of temazepam misuse and later, concurrent codeine use would have increased risk for central nervous system and respiratory depression. The bedtime dose of gabapentin was reduced to 1600 mg and all of his other medications were left unchanged. Although fluoxetine can also worsen RLS, it was continued at this

time because the focus of the psychiatry consultation was management of the bipolar I disorder and not the RLS. Further, patient had noted his mood previously to be stable on fluoxetine 40 mg daily and lamotrigine 200 mg daily. Figure 1 outlines the timeline of medication changes following initial presentation.

A month later, he presented with concerns for worsening mood and irritability; fluoxetine was stopped and he underwent a short trial of quetiapine to manage mood lability. This was followed by a trial of olanzapine when the former was noted to be ineffective in attempt to treat what appear to be a mixed episode of bipolar I disorder due to symptoms of irritability, worsening mood and sleep disturbances. Although atypical antipsychotics can worsen RLS, quetiapine and olanzapine were chosen for trial instead of divalproex to minimize risk for developing severe cutaneous reactions such as Stevens-Johnson Syndrome as patient was already taking lamotrigine.

At the next follow-up visit, he reported further worsening of symptoms of RLS while misusing quetiapine, olanzapine and gabapentin to self-medicate for sleep disturbance brought on by severe RLS symptoms. Subsequently, the olanzapine was also discontinued due to lack of benefit. His ferritin level at the time was 228 ng/mL. Because the anti-epileptics have less risk for causing RLS, but can also be used to treat bipolar disorder, the patient was then started on divalproex 1500 mg at bedtime to stabilize his mood while he was also maintained on lamotrigine, albeit at a lower dose of 150 mg daily at bedtime, to minimize his risk of developing Stevens-Johnson syndrome. He was diagnosed with augmentation of RLS on pramipexole after 12 months of progressively increasing the dose on his own, with continued worsening of symptoms with earlier onset and nighttime breakthrough. It was then recommended that he switch to rotigotine patch to reduce the risk of augmentation due to its long half-life with fewer peaks and troughs in the plasma level. Unfortunately, the patient could not afford the rotigotine patch; he was advised not to increase the dose of pramipexole beyond 0.375 mg nightly and codeine at 30 mg at bedtime was added to his regimen. Due to the risk for respiratory depression with opioids, and given the patient's suboptimal adherence to CPAP for moderate OSA and history of hypnotic abuse, codeine was chosen because of its lower potency relative to other opioids and better evidence for treatment in refractory RLS compared to several other medications in this category.⁸

A few months later, pramipexole 0.375 mg at bedtime was transitioned to ropinirole at 0.5 mg before bedtime with a plan for further adjustment as needed to help improve control of RLS symptoms. He remained on gabapentin at a dose of 800 mg in the morning and 1600 mg at bedtime. Ferritin level at the time was 188 ng/mL.

Due to persistent severe RLS symptoms, the patient was referred to a sleep clinic at a tertiary medical center.

Date	RLS Medications							Psychiatry Medications													
	Gabapentin	Pramipexole	Codéine	Ropinirole	Carbidopa /levodopa	Pregabalin	Ferrous sulfate	Temazepam	Trazodone	Fluoxetine	Lamotrigine	Quetiapine	Olanzapine	Divalproex							
Nov-16	800 mg in AM and 1600 mg in PM	0.375 mg daily	30 mg daily at bedtime	6 mg at bedtime	1 tab BID	300 mg BID	325 mg daily	DC	DC		100 mg BID										
Dec-16																DC					
Jan-17																			DC	DC	
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Figure 1. Timeline of medication changes.

Polysomnography was conducted and revealed a PLMI of 2.7 per hour and PLMAI of 0.9 per hour. At the time that he was evaluated at the sleep clinic, RLS symptoms were fairly well controlled on gabapentin 800 mg in morning and 1600 mg at bedtime, ropinirole, which had been titrated up to 6 mg daily, and codeine 30 mg at bedtime. He was also taking combination of divalproex and lamotrigine for bipolar I disorder. No medication changes were suggested. Mr. A was diagnosed with insomnia, sleep state misperception type. Cognitive behavioral therapy for insomnia (CBT-I) was recommended and he completed a total of 6 sessions.

Several months later, he noted a recurrence of RLS symptoms. He was commenced on carbidopa-levodopa with a plan to taper ropinirole. Although carbidopa-levodopa is commonly associated with augmentation, the plan was to discontinue the ropinirole to help decrease augmentation of symptoms and use the carbidopa-levodopa as needed in conjunction with gabapentin. However, the patient took the carbidopa-levodopa twice daily on a scheduled basis. Due to a history of augmentation of RLS on a low dose of ropinirole, pharmacogenomics (PGx) testing was completed. Relevant to his RLS treatment, the patient was a rapid metabolizer for CYP1A2, which could indicate a reduced response to ropinirole, and an intermediate metabolizer for CYP2D6, which could indicate a reduced response to codeine. Subsequently, codeine was tapered and discontinued. In order to better manage his residual mood symptoms, the dose of lamotrigine was increased from 200 mg per day to a total of 300 mg per day while the dose of divalproex was reduced from 1500 mg at bedtime to 1000 mg at bedtime.

About 6 months later, gabapentin was discontinued due to an adverse drug reaction of peripheral edema and the patient noted worsening RLS symptoms in this context. Supplementation with ferrous sulfate was commenced at 325 mg daily, along with pregabalin 150 mg at bedtime, which was later increased to twice daily. Although typically dosed twice a day for RLS, a lower dose of ferrous sulfate was chosen as patient's ferritin levels had not been less than 75 ng/mL, which is the typical threshold for treating RLS with iron supplementation.⁹ A change in formulary coverage rendered the pregabalin too expensive for the patient and it was discontinued. The doses of ropinirole and carbidopa-levodopa were gradually titrated upwards for worsening RLS symptoms at various points during the next several months with continued RLS symptoms throughout. Once pregabalin became generic in 2020, the patient was able to restart this medication and taper off the carbidopa-levodopa.

His most recent regimen included pregabalin 300 mg daily at bedtime, ropinirole 8 mg 3 times a day, and ferrous sulfate 325 mg daily, on which his RLS symptoms remained stable for several months at the date of the last follow-up. For bipolar disorder type I, he was maintained on

divalproex 1000 mg at bedtime along with lamotrigine 100 mg in the morning and 200 mg at bedtime.

Discussion

Early on, the patient was taking several antidepressants including fluoxetine and trazodone that could worsen RLS and/or exacerbate mania in bipolar disorder type I.⁷ Other medications known to aggravate RLS include sedating antihistamines, antipsychotics, and dopamine-blocking anti-emetics.¹⁰ Caffeine can also worsen RLS symptoms and insomnia.⁷ Discontinuation of exacerbating medications should always be considered in the treatment plan of RLS, as was done in this case. Furthermore, mood stabilizers such as divalproex and lamotrigine from the antiepileptic category were favored in our patient as they have shown some efficacy in treating RLS and would not worsen symptoms.¹¹

Non-pharmacologic strategies for RLS should also be explored. Our patient did undergo cognitive behavioral therapy for insomnia. Other non-pharmacologic options with evidence to improve RLS include regular exercise and completing mental alerting activities during times of boredom.⁹ Although not clearly documented, our patient did report attempting these strategies. One non-pharmacologic treatment method that was not explored for this patient was pneumatic compression devices, which have been shown in small trials to reduce the symptoms of RLS.¹²

Augmentation with dopaminergic therapy occurs when RLS symptom severity increases with increasing doses of medication; this generally develops slowly over time at higher doses of the medication.¹⁰ It can be difficult to distinguish augmentation from other causes of worsening RLS symptoms, such as tolerance to the medication, rebound symptoms from end-of-dose effects, iron deficiency, sleep deprivation, and medication-related adverse effects.¹⁰ Four screening questions have been developed to help identify augmentation from dopaminergic medications, including: Do symptoms appear earlier than when the drug was first started, Are higher doses of the drug needed or taken earlier in the day to control symptoms, Has the intensity of symptoms worsened since starting the drug, and, Have symptoms spread to other body parts since starting the drug.¹³ Our patient demonstrated 3 of the 4 of these symptoms. After removing exacerbating medications and treating underlying conditions, it was ruled augmentation to be the causative factor in our patient's progressive symptoms. Treatment strategies for when augmentation develops have limited supporting evidence and include replacing depleted iron stores, switching to rotigotine, switching to an alpha-2-delta calcium channel ligand such as gabapentin, or using low potency opioids.¹⁰ All of these options were explored in our patient, ultimately finding that a combination of an oral iron supplement, dopamine agonist, and alpha-2-delta calcium

channel ligand was effective in controlling RLS symptoms. Although the maximum FDA recommended dose for ropinirole for the treatment of RLS is 4 mg per day, in some cases higher doses are required for symptom control; the maximum dose for Parkinson's Disease is 24 mg per day.

Our case also demonstrates the role of medication cost as a barrier to adequate RLS treatment. Despite noting good results with pregabalin, the patient was unable to continue this medication and was never able to try the rotigotine patch. The retail price of rotigotine patch ranges from \$700 to \$850 for a 1-month supply whereas ropinirole is available at a fraction of that cost, at \$9 to \$25 for a 1-month supply.¹⁴ A generic formulation of pregabalin has recently become available, so cost may be less of an issue with this medication in the future.

A personalized medicine approach with PGx testing was used for this patient. The results were used to identify potentially ineffective therapy with codeine and led to discontinuation of this medication; there was already a low threshold to stop the medication due to the patient's history of substance misuse. A prospective application of PGx may have been even more helpful in that the use of codeine use could potentially have been avoided altogether. The practicality of PGx-guided therapy in RLS is limited as only codeine and tramadol currently have clinical guideline annotations available for dosing based on PGx.¹⁵

Finally, and importantly, this case also illustrates the need for long-term care in patients with RLS that is patient-centric and encompasses the tenets of good clinical care-consistency of the treatment team, regular follow-up, validation of symptoms, and associated suffering, utilization of the latest evidence on diagnostic and treatment approaches with individualized application, and efforts to contain costs and minimize financial burden on patients.

Conclusion

This report demonstrates a challenging case of RLS in the setting of psychiatric co-morbidities, development of augmentation, and polypharmacy. Multiple treatment strategies may need to be considered simultaneously in these patients that may include pharmacogenomics testing, medication adherence strategies, optimizing medication management, cognitive behavioral therapy for insomnia, and treating underlying conditions. Availability of longitudinal specialty care, psychiatry and pharmacy services offered in conjunction with primary care in a community care setting facilitated safe and effective treatment to optimize the patient's outcome.

Authors' Note

The case report was presented as a poster at American Psychiatric Association (APA) 2019 Annual Meeting in San Francisco, CA, USA, May 18-22, 2019.

Declaration of Conflicting Interests


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