Diagnosis and Treatment of Restless Legs Syndrome in Psychiatric Practice

September 08, 2009 | Sleep Disorders [1], Circadian Rhythm Sleep Disorders [2], Comorbidity In Psychiatry [3], Major Depressive Disorder [4], Restless Legs Syndrome [5], Somatoform Disorder [6] By Hochang Benjamin Lee, MD [7]

Restless legs syndrome (RLS) is a neurosensory disorder first described by Sir Thomas Willis in 1672. As early as the 19th century, Theodor Wittmaack observed the comorbidity of RLS with depression and anxiety. He termed this condition “anxietas tibiarum” and believed it to be a form of hysteria.

After reading this article, you will be familiar with:

• Pathogenesis of restless legs syndrome (RLS)
• Comorbidity of RLS and psychiatric disorders
• Treatment options for RLS in patients with psychiatric disorders

Who will benefit from reading this article?
Psychiatrists, geriatric psychiatrists, psychologists, primary care physicians, nurse practitioners, and other health care professionals. To determine whether this article meets the continuing education requirements of your specialty, please contact your state licensing and certification boards.

Restless legs syndrome (RLS) is a neurosensory disorder first described by Sir Thomas Willis in 1672. As early as the 19th century, Theodor Wittmaack observed the comorbidity of RLS with depression and anxiety. He termed this condition “anxietas tibiarum” and believed it to be a form of hysteria. Once thought to be rare, data now suggest that RLS is relatively common but underrecognized and undertreated. Several clinical and population-based studies have reported a high prevalence of psychiatric comorbidities—particularly depression and anxiety—in patients with RLS. Thus, for psychiatrists, understanding the clinical features and treatment of RLS has become critical in their daily practice. The symptomatic overlap between RLS and mood disorders and the potential impact of psychiatric medications on RLS symptoms make RLS a diagnostic and treatment challenge. This article provides an overview of the clinical features of and treatment strategies for RLS. It also offers a survey of the current literature on issues in the diagnosis and treatment of RLS among psychiatric patients.

Clinical features and diagnosis
The case vignette illustrates the importance of evaluating for RLS symptoms in patients with major depressive disorder (MDD) who complain of insomnia.

CASE VIGNETTE
Lisa is a 45-year-old married woman who came to see a psychiatrist initially for depressive symptoms. During the initial evaluation, she complained of difficulty in falling asleep and other depressive symptoms such as low mood, difficulty with concentration, poor appetite, and low energy along with daytime fatigue. Depression was diagnosed. An SSRI was prescribed on an as-needed basis, and the patient was advised to take a nightly dose of diphenhydramine to help her sleep. Three days later—after staying up nearly all night—Lisa called her doctor in despair and complained of worsening insomnia. On more detailed questioning about the insomnia, Lisa revealed that for the past 2 years, she has experienced leg discomfort when she gets into bed. She is so uncomfortable that she needs to walk or ride on her exercise bike past 2 or 3 am until the discomfort subsides. While not painful, this leg discomfort sometimes prevents her from relaxing and watching television because she just “has to move” her legs. Lisa describes a deep uncomfortable sensation that feels like “bugs crawling in her legs.” She also reveals that her mother used to suffer from similar nighttime leg restlessness. For the past 3 nights, Lisa’s leg discomfort has been more intense and has lasted most of the night. After secondary causes of RLS, such as iron deficiency anemia, pregnancy, uremia, and neuropathy, were ruled out, a diagnosis of RLS was made. SSRI and diphenhydramine therapy were stopped.
Low-dose dopamine agonist therapy was started, after which the symptoms subsided. However, despite resolution of the RLS symptoms, her depressive symptoms continued. Titrated bupropion was given until the depressive symptoms fully resolved.

The RLS diagnosis and epidemiology workshop at the NIH established 4 criteria for diagnosis of RLS:

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 that begin or worsen during periods of rest or inactivity, such as lying or sitting
3. The urge to move or unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations that are worse in the evening or night than during the day or only occur in the evening or night

A diagnostically supportive but not essential feature of RLS includes a history of the disorder in first-degree relatives. A polygenetic disorder with its phenotype contributed by a number of variants, RLS is a highly familial trait with heritability estimates of about 50%. Recent linkage studies in families with RLS revealed several loci but have not led to the identification of disease-causing sequence variants.

Another supportive diagnostic feature is a history of positive response to dopaminergic therapy, such as levodopa (L-dopa) or a dopamine receptor agonist. Periodic limb movements during sleep (PLMS), although not specific to RLS, occur in at least 80% of RLS patients and correlate with clinical ratings of RLS severity. While polysomnography or actigraphy evidence of PLMS is not necessary for diagnosis, PLMS supports the diagnosis of RLS and provides an objective, indirect measure of RLS severity. In more severe cases, symptoms of RLS occur during the daytime, disrupting restful activities such as sitting or trying to nap. Ascertaining the degree of interference with daytime activities may provide a measure of RLS severity.

**Differential diagnosis of RLS**

The diagnosis of RLS is made after identifying the presence of the above-mentioned 4 cardinal features and excluding other causes of symptoms that mimic RLS, such as leg cramps, positional discomfort, neuroleptic-induced akathisia, peripheral neuropathy, arthritis, anxiety, claudication of the legs, and peripheral vascular disease. Because a diagnostic biological marker for RLS is not available, the standard for diagnosis remains a clinical one based on the patient's subjective complaints and history.

Nocturnal leg cramps (“charley horse”) are often mistaken for RLS; the former is usually the result of the painful contraction of a single muscle in the leg that can be relieved through stretching. During muscle cramps, the muscle bulk is prominent and the associated sharp pain is easily distinguished from RLS sensations. Patients with peripheral neuropathy commonly report numbness, burning, and pain that are superficially felt in the skin. Although these sensory symptoms can increase at night, they are usually present throughout the day, and complete relief is not obtained by sustained movement or walking. Peripheral vascular disease or claudication is generally associated with pain during walking and relieved when sitting or lying down. Arthritis pain is centered in joints and is relieved by rest. Neither peripheral vascular disease nor arthritis is associated with the circadian pattern characteristic of RLS.

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Neuroleptic-induced akathisia is a whole-body sensation; there is no pronounced circadian pattern and no insomnia. Usually, movement provides no relief, and prior exposure to neuroleptic medication is easily established. Hypotensive akathisia is a feeling of restlessness, which may be localized in the legs when an individual with orthostatic hypotension sits still; the restless feeling should not occur when the patient is supine and it does not have a circadian pattern, unlike RLS. Positional discomfort occurs after prolonged sitting (but not lying) in the same position and is usually relieved by a simple change in position. For some people who fidget, movements of their feet are volitional—especially when they are bored or anxious. Their movements are not associated with discomfort or an urge to move as in RLS, and their volitional movements lack a circadian pattern.

**Secondary RLS**

RLS is usually idiopathic. As noted, however, RLS can be secondary to other medical conditions. A high prevalence (greater than 20%) of RLS has been reported in studies based on clinical populations with a variety of medical conditions, such as iron deficiency, pregnancy (particularly during the third
trimester), rheumatoid arthritis, and uremia secondary to end-stage renal disease. In secondary RLS, the initial treatment strategy should focus on addressing the underlying medical condition. Several neurological disorders have also been reported to be associated with RLS. RLS may be common among patients with Parkinson disease and both disorders respond to dopamine therapy. Studies have also demonstrated that subtle nerve damage (eg, peripheral neuropathy) is more common among patients with late-onset RLS. RLS is frequently comorbid with other neurological conditions, such as multiple sclerosis, Charcot-Marie-Tooth disease type 2, cryoglobulinemic neuropathy, and spinocerebellar ataxia. Lower back pain, myelopathy, and arthropathy have been reported to be associated with RLS as well.

**Treatment**

After secondary causes of RLS are ruled out, the initial treatment strategy should focus on sleep hygiene measures. Exercise and hot baths around bedtime are frequently effective in treatment of mild RLS. If medication is necessary, the American Academy of Sleep Medicine evidence-based practice parameter guidelines list dopaminergic agents as the first line of treatment. Second-line treatment options are opioids, benzodiazepines, and specific anticonvulsants (such as gabapentin and carbamazepine).

Nonergot dopamine agonists such as pramipexole, ropinirole, and rotigotine have been found effective in double-blind studies. In fact, 2 dopamine agonists, pramipexole and ropinirole, are the only medications that are approved by the FDA for treatment of moderate to severe RLS. The maker of rotigotine—another dopamine agonist delivered through a transdermal patch—filed for approval to market the drug for RLS. However, rotigotine was recently recalled in the United States and some European countries because of problems with the delivery mechanism.

Ergot-derived agonists, such as bromocriptine, pergolide, and cabergoline, have also been found to be effective in treating RLS. However, potentially serious adverse effects, such as heart valve abnormality, limit their use. Generally, treatment with dopamine agonists should start with the lowest dose possible followed by slow titration. Adverse effects—including nausea, orthostatic hypotension, dizziness, and daytime somnolence—should be monitored carefully. (L-dopa) is also effective in treating RLS. Until nonergot dopamine agonists were available, (L-dopa) was the most popular pharmacological agent, particularly for intermittent symptoms, because of its rapid onset of action. However, long-term treatment of RLS with (L-dopa) is frequently associated with augmentation and rebound. Augmentation refers to the clinical phenomenon of earlier onset, increased severity, or involvement of other parts of the body with RLS symptoms. Unlike long-term complications of (L-dopa)–induced dyskinesia in patients with Parkinson disease, augmentation usually resolves with cessation of (L-dopa) in patients with RLS. The rebound effect causes increased restlessness at night or in the morning as the dose wears off, or as tolerance to the drug builds up. While the risk may be less with dopamine agonists than with (L-dopa), augmentation has been associated with dopamine agonists.

Opiates, particularly oxycodone, are considered second-line agents for patients with moderate to severe RLS. Because of concerns about the risk of opioid dependency, sedation, and exacerbation of sleep apnea, opiates have been primarily prescribed for RLS patients who cannot tolerate dopaminergic agents. Among opiates, codeine is considered to have the least abuse or dependency potential and has been reported to be effective in treating RLS.

The efficacy of the anticonvulsant gabapentin has also been demonstrated in controlled studies, and a prodrug of gabapentin—gabapentin enacarbil—is in the FDA pipeline with an indication for RLS treatment. In controlled trials, efficacy has also been reported for other anticonvulsants, such as carbamazepine and valproic acid, but these are rarely prescribed.

**Psychiatric comorbidities of RLS**

Previous clinic-based studies reported a high prevalence of comorbidity between RLS and depression or anxiety disorders. Notably, Winkelmann and colleagues used a structured psychiatric measure, the Munich–Composite International Diagnostic Interview for DSM-IV, to assess psychopathology among 130 RLS patients. Compared with 2265 community residents, those with RLS had an increased risk of having panic disorder (odds ratio [OR], 4.7; 95% confidence interval [CI], 2.1 to 10.1), generalized anxiety disorder (OR, 3.5; 95% CI, 1.7 to 7.1), and MDD (OR, 2.6; 95% CI, 1.5 to 4.4) over a 12-month period. Several population-based studies have reported increased rates of anxiety and depression in patients with RLS. Data from the Baltimore Epidemiologic Catchment Area study showed strong associations between RLS and MDD (OR, 4.7; 95% CI, 1.6 to 14.5) and panic disorder (OR, 12.9; 95% CI, 3.6 to 46.0) among 1024 community residents over 12 months.
The underlying cause for the high prevalence of comorbidities between RLS and depression is unclear. Certainly, symptomatic overlap exists between MDD and RLS because RLS can trigger or exacerbate at least 4 of the 9 depressive symptoms listed in DSM-IV for MDD. Dysphoria, insomnia or excessive sleepiness (particularly during the day), decreased concentration, fatigue or loss of energy, and psychomotor retardation are common among RLS patients. Alternatively, an underlying shared pathophysiological mechanism between RLS and MDD might be responsible for the comorbidity.

Many studies have established the role of dopaminergic pathology in RLS. A recent systematic review supported a role for diminished dopaminergic neurotransmission in major depression based on the following evidence:

- Diminished dopamine release from presynaptic neurons or impaired signal transduction has been implicated.
- Animal models of depression have shown considerable responsiveness to dopamine neurotransmission.
- Several studies have shown reduced concentration of dopamine metabolites in cerebrospinal fluid and in brain regions that mediate mood and motivation.
- Neuroimaging studies have shown reduced dopamine transmission and compensatory up-regulation of D2 receptors.

In fact, bupropion, which has proven efficacy in the treatment of depression, acts, at least in part, by promoting dopaminergic function. Several clinical trials recently reported a potential role for dopamine agonists—the first-line agents for RLS—in managing treatment-resistant depression or bipolar depression.

Potential associations between other psychiatric disorders and RLS have been reported recently. Several studies found that RLS and PLMS are common among children or adults with attention-deficit/hyperactivity disorder (ADHD). It is still unclear whether sleep disruption from RLS rather than RLS itself is associated with ADHD-like symptoms of restlessness, overactivity, and inattention. High rates of RLS-like symptoms in patients with schizophrenia and somatoform pain disorder have been reported as well.

Effect of psychiatric medications

Because RLS and psychiatric disorders are frequently comorbid, give careful consideration when choosing a medication for RLS in a patient with a psychiatric disorder. Many psychiatric medications can affect RLS symptoms. However, other than a number of case series or anecdotal reports, few studies have examined the direct effects of psychiatric medications on RLS symptoms, although several have examined the effect of these medications on the severity of PLMS. While PLMS occur in at least 80% of RLS patients and correlate with RLS severity, it is unclear whether medication effects on PLMS can be used to infer the effect of psychiatric medicine on RLS.

Predicatably, all typical antipsychotics with dopamine receptor blocking properties exacerbate PLMS. Commonly used antiemetics, such as metoclopramide, promethazine, and prochlorperazine, also exacerbate RLS symptoms because of their dopamine receptor blocking properties. With their lower binding affinity for the dopamine D2 receptor, newer atypical antipsychotics are less likely to exacerbate PLMS. However, exacerbation of RLS-like symptoms with olanzapine and risperidone has been reported. Insufficient data are available about effects of clozapine, quetiapine, and ziprasidone on RLS or PLMS. Aripiprazole, a partial dopamine agonist, theoretically might have a favorable effect on RLS symptoms, but a systematic study is needed.

Although it has been suggested that various tricyclic antidepressants (TCAs) and SSRIs exacerbate RLS or PLMS, the specific mechanisms are unknown. In contrast, bupropion, a dopamine agonist, might alleviate RLS symptoms. The effect of trazodone and mirtazapine on RLS symptoms is unclear.

Given the effects of these medications on RLS symptoms, it is important to screen for RLS symptoms before starting antidepressant therapy. For a patient with severe RLS and mild depressive symptoms, it is reasonable to treat RLS first to see whether improvements in sleep and energy lead to resolution of depressive symptoms. When treating depression in patients with severe RLS, consider trying a non-SSRI or non-TCA (eg, bupropion) first. Keep in mind that there are no comparative studies of the efficacy and safety of bupropion and SSRIs in comorbid depression and RLS.

In the treatment of mood disorders, especially bipolar disorder, anticonvulsants (eg, valproic acid) are commonly prescribed to stabilize mood. In general, anticonvulsants that are associated with pain relief ameliorate RLS symptoms. Gabapentin and carbamazepine are second-line agents in the treatment of RLS, and valproic acid might also be helpful in reducing RLS symptoms. While
anecdotal reports of RLS induced by lithium exist, no systematic study has tested the effect of this agent on PLMS or RLS symptoms.\textsuperscript{42}

Benzodiazepines and hypnotics are often prescribed to treat insomnia related to psychiatric disorders; these medications have not been shown to exacerbate PLMS. Among them, clonazepam is preferred over short-acting benzodiazepines for the treatment of anxiety and insomnia in patients with RLS because of its longer half-life. However, studies that examined the effect of clonazepam on PLMS and RLS did not find a consistent reduction in PLMS; patients instead reported a more restful sleep.\textsuperscript{43}

Antihistamines are commonly taken for sleep problems. However, certain drugs in this class, including diphenhydramine, can exacerbate PLMS and RLS and should be avoided.

**Dopamine agonists and psychiatric symptoms**

In randomized, double-blind, placebo-controlled trials of pramipexole or ropinirole for RLS treatment, none of the participants treated with dopamine agonists experienced neuropsychiatric symptoms. Use caution when interpreting the clinical safety data because the RLS treatment studies have systematically excluded patients with psychiatric comorbidity. Therefore, clear data do not exist on the potential neuropsychiatric adverse effects of dopamine agonist treatment of RLS in patients with comorbid psychiatric disorders.

Dopamine agonist treatment of Parkinson disease has been associated with hallucinations, delusions, confusion, and mania.\textsuperscript{44,45} Lower recommended doses of dopamine agonists seem less likely to induce psychotic symptoms in RLS patients without psychiatric comorbidity. However, the potential for inducing or exacerbating behavioral symptoms in RLS patients with psychiatric disorders from dopamine agonist therapy cannot be ignored.

Compulsive gambling,\textsuperscript{46} overeating,\textsuperscript{47} and hypersexuality\textsuperscript{48} have also been associated with dopamine agonist treatment of Parkinson disease and, to a lesser degree, RLS. Therefore, those clinicians who treat RLS in patients with impulse-control disorder or affective disorders (eg, bipolar disorder) should be aware of the potential for initiating or exacerbating impulsive behavior or mood symptoms. Another problematic adverse effect of dopamine agonist treatment of Parkinson disease is daytime somnolence. Sleep attacks (ie, sudden and overwhelming sleepiness without awareness of falling asleep), particularly while driving, have been described in patients taking dopamine agonists and represent a serious public safety issue.\textsuperscript{49,50} Therefore, dopamine agonists should be prescribed and titrated with caution, especially for older patients who have RLS, to reduce the adverse effect of daytime somnolence.

**Conclusion**

RLS is a common treatable disorder, closely associated with depression and anxiety in both clinical populations and the community. Given the potential impact of various psychiatric drugs on RLS symptoms, medications need to be chosen judiciously to avoid exacerbating RLS symptoms. As more patients with psychiatric disorders receive a diagnosis of RLS and are treated with dopamine agonists, uncommon, yet problematic psychiatric adverse effects related to pharmacotherapy for RLS may develop. Future systematic studies are warranted to guide the optimum treatment of RLS in patients with psychiatric conditions, particularly depression and/or anxiety.

\[Note: The above article is an expired CME and is here for informational purposes.\]

**References:**


27. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry.* 2007;64:327-337.


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