Special Considerations in Treating Depression when the patient has Restless Legs Syndrome (RLS)
RESTLESS LEGS SYNDROME (RLS) is a common and treatable physical disorder estimated to affect 5% to 10% of adults in some countries. In the United States alone, where more than 12 million people are believed to have RLS, it has been called "the most common disorder you’ve never heard of." RLS is associated with disturbed sleep and significantly diminished quality of life, but the development of new and more effective treatments has brought hope to many who have suffered silently for years. The four essential features of RLS are listed in Table 1. Most people who have RLS also have periodic limb movements in sleep (PLMS) — jerking of the arms or legs that is often associated with sleep disruption.

Symptoms of depression are very common in adults with RLS. Approximately 40% of people with RLS complain of symptoms that would be indicative of depression if assessed without knowledge or consideration of the sleep disorder. Table 2 lists the nine symptoms of major depression; any five of these must be present.

**TABLE 1. ESSENTIAL DIAGNOSTIC CRITERIA FOR RLS**

These four essential features must be present for a diagnosis of restless legs syndrome:

1. There is an urge to move the legs, which is usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs.
2. The symptoms begin or worsen during periods of rest or inactivity, such as while lying down or sitting.
3. The sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. Symptoms are worse in the evening or night than during the day, or only occur in the evening or nighttime hours.
in order to confirm a diagnosis. Of interest is that four or more of these symptoms can arise simply and directly from a sleep disorder such as RLS.

In some cases, effective treatment of RLS will result in a significant improvement in depression. In other situations, treatment with antidepressant medications will be needed. When a patient has RLS and depression, treatment can involve a delicate balancing act, as some of the most effective and widely used antidepressants can worsen certain aspects of RLS.

Many published reports have documented the induction or aggravation of PLMS by antidepressant medications in the serotonergic or "Prozac" class.10-15 Table 3 lists the generic and brand names of some medications in this class. Serotonergic agents have the effect of raising levels of the brain transmitter serotonin. High doses of tricyclic antidepressants have also been found to exacerbate PLMS.14,16,17 In contrast, it remains unclear how often either tricyclic or serotonergic agents negatively impact upon, exacerbate, or uncover RLS sensations. However,

**TABLE 2. SYMPTOMS OF MAJOR DEPRESSION**

Five or more symptoms must be present for a diagnosis of major depression (those listed in italics are particularly sensitive to disturbed sleep):

- Depressed mood
- Diminished interests
- Feelings of worthlessness
- Thoughts of death
- Weight gain or loss
- **Insomnia or excessive sleepiness**
- Fatigue or loss of energy
- Diminished concentration
- Mental/physical sluggishness or agitation
many individuals with RLS complain of sleepiness, fatigue, poor motivation, and decreased memory associated with both classes of antidepressants, even when they report improved mood and reduced irritability. This partial response — control of depression without full remission of symptoms — is too often accepted as a satisfactory result. The term "serotonin fatigue" has sometimes been used to characterize this state.\textsuperscript{18-20}

Exacerbation of PLMS and the associated disruption of sleep could contribute to this problem in individuals with RLS. The mechanism by which serotonergic and tricyclic antidepressants might induce or aggravate PLMS is unclear. It may involve the mild dopamine antagonist effect brought about by the antidepressant,\textsuperscript{17,19} or a relative imbalance between the serotonin and dopamine/norepinephrine systems. In contrast, the antidepressants bupropion (Wellbutrin) and trazodone (Desyrel) appear to

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\caption{Names of some common antidepressation medications}
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\textbf{Serotonergic class} \\
• Celexa (citalopram)  \\
• Effexor (venlafaxine)  \\
• Lexapro (escitalopram)  \\
• Luvox (fluvoxamine)  \\
• Paxil (paroxetine)  \\
• Prozac, Sarafem (fluoxetine)  \\
• Serzone (nefazodone)  \\
• Zoloft (sertraline)  \\
\textbf{Tricyclic class} \\
• Elavil (amitriptyline)  \\
• Surmontil (trimipramine)  \\
• Tofranil (imipramine)  \\
\textbf{Unique antidepressants} \\
• Wellbutrin (bupropion)  \\
• Desyrel (trazodone)
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reduce PLMS.\textsuperscript{10,21,22} Bupropion is reported to increase levels of dopamine and norepinephrine without increasing serotonin,\textsuperscript{20} and a small study of patients with PLMS and depression has reported decreased frequency of PLMS associated with bupropion use.\textsuperscript{22} If the sleep disruption from PLMS is reduced, a reduction in daytime symptoms is a reasonable expectation.

Because symptoms of depression and RLS are so often present together, a practical approach is useful in treating these problems. The first step is to assess the severity of depression-related symptoms and to consider whether poor sleep might be a major factor. Treating the sleep disorder, before treating depression, can be successful, especially when depression-related symptoms are mild. Patients with moderate to severe depression are more likely to need antidepressant medication, and their treatment is more complicated.

If the patient is not on antidepressant medication and is not suicidal, a sound initial strategy may involve optimization of therapy for RLS and PLMS.\textsuperscript{23} Simple self-directed strategies that can prove helpful include maintaining regular sleep hours, avoiding caffeine after lunch, and abstaining from alcohol in the evening. While the effect of exercise regimens upon RLS has not been studied, physical exercise can be beneficial for both PLMS\textsuperscript{24} and depression.\textsuperscript{25} Medically-directed therapies include oral iron supplementation, which has proven beneficial for RLS and PLMS if the patient’s ferritin level is below 50 mcg/L.\textsuperscript{1,23,26}
Dopamine agonists are generally the preferred initial treatment for clinically significant RLS, and often lead to virtually complete remission of RLS symptoms, which in itself can sometimes reduce or eliminate the depression. In addition, dopamine agonists may have a mild antidepressant effect. Trazodone, gabapentin (Neurontin), or a traditional sleeping pill can be a helpful adjunct for consolidation of sleep in patients with RLS. Although trazodone is typically less effective in treating depression than serotonergic agents and bupropion, it is very commonly used to treat insomnia. Cognitive techniques that include "positive structured thinking" can be of significant benefit.

When antidepressant medication is needed, bupropion in an extended-release formula is the recommended first choice. Because bupropion can cause insomnia, it should be taken in the morning. Its antidepressant effect is comparable to that of serotonergic agents, as has been demonstrated in several studies. In addition, lower rates of somnolence and sexual dysfunction are reported with bupropion than with serotonergic agents.

For RLS patients already taking serotonergic antidepressants, optimization of RLS therapy and reduction of PLMS should be the initial approach, with a goal of establishing 6 to 8 hours of solid sleep per night. Based on individual response, consideration can next be given to reduce, eliminate, or change the antidepressant medication.
If the RLS appears to have begun when the antidepressant was introduced, reducing the antidepressant dosage may be a necessary first step. Treatment of residual RLS, if any, should follow. Most commonly, the change in antidepressant treatment will involve a switch from a serotonergic agent to bupropion. Serotonergic medications must be tapered slowly to avoid withdrawal symptoms. If the serotonergic agent cannot be eliminated, it should be used at the lowest effective dose. In patients who have major depression with an anxiety component, some studies have found bupropion to be an effective anxiolytic.\textsuperscript{33,34} However, the anxiolytic effect may be delayed in onset\textsuperscript{18} and not as robust as that seen with serotonergics, requiring the addition of a benzodiazepine or buspirone for some individuals.

In summary, the co-occurrence of RLS and depression-related symptoms is common and presents a challenging management problem. Further research is needed to delineate the relationship between these conditions and to optimize treatment regimens.
REFERENCES


The Restless Legs Syndrome Foundation is dedicated to improving the lives of the men, women, and children who live with this often devastating disease. The organization’s goals are to increase awareness of restless legs syndrome (RLS), to improve treatments, and, through research, to find a cure.

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