# Restless Legs Syndrome, Periodic Limb Movements in Sleep, and Depression

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**Study Objectives:** To review the literature on restless legs syndrome (RLS), periodic limb movements in sleep, and depression.
**Design:** Literature review.
**Setting, Participants, and Interventions:** N/A.
**Measurements and Results:** We conducted a comprehensive review of the literature searching for publications that included data on depression or antidepressants and RLS or periodic limb movements in sleep. Sixty-two relevant literature references were found and reviewed. Four population-based studies and 9 clinical studies reported significantly higher rates of depression symptoms in individuals with RLS than in controls. Conversely, the prevalence of RLS in patients presenting with depression was reported as elevated in 2 studies. Conflicting data were found regarding the effect of antidepressants on the sensory symptoms of RLS.

In contrast, several studies have found that selective serotonin reuptake inhibitor antidepressant use is associated with increased periodic limb movements in sleep.
**Conclusions:** Depression symptoms are common in adults with RLS. However, the relationship appears complex, with overlap between RLS- and depression-related symptoms confounding the issue. Given what is known at this time, we propose a specific treatment approach to patients with RLS and depression symptoms.
**Keywords:** Restless legs syndrome, periodic limb movements in sleep, periodic limb movement disorder, sleep disorder, depression, fatigue, antidepressants
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## INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) IS A SENSORIMOTOR DISORDER AFFECTING SLEEP AND WAS FIRST DESCRIBED BY SIR THOMAS WILLIS MORE THAN 300 years ago.[1,2] The prevalence of RLS is estimated at 5% to 15% of adults, with a relatively linear increase with age and a roughly 50% excess in women.[3] RLS is a clinical diagnosis and is based on the following 4 essential criteria from the patient's history:[3-6] (1) an urge to move the legs, usually accompanied by uncomfortable and unpleasant leg sensations, (2) symptoms are worse when lying or sitting, (3) symptoms are at least partially relieved by movement, and (4) symptoms are worse in the evening or at night. Other associated features commonly found in adults with RLS include sleep disturbance, daytime fatigue, a positive family history of RLS, decreased quality-of-life ratings, and attention deficits. The physical examination is typically normal. "Secondary RLS" may occur in iron deficiency, pregnancy, uremia, and spinal cord and peripheral nerve injuries and may be the result of some medications.

Periodic limb movements in sleep (PLMS) are characterized by brief (0.5- to 5.0-second) lower-extremity movements during sleep, which typically occur at 20- to 40-second intervals, most commonly during the first 3 hours of sleep.[7,8] The affected individual is usually not aware of the movements or of the transient partial arousals. Eighty percent to 90% of individuals with RLS have PLMS.[9] On the other hand, PLMS are not specific to RLS but also can be seen in a variety of sleep disorders and in individuals without sleep complaints. Periodic limb movement disorder (PLMD) is diagnosed when there are (1) PLMS exceeding norms for age, (2) clinical sleep disturbance, and (3) the absence of another primary sleep disorder or reason for the PLMS.[8] Available evidence suggests that PLMS are due to an underactivity of dopaminergic function in certain central nervous system pathways and are a marker of instability in the sleep system.

Treatment for RLS and PLMD has evolved rapidly in the past 10 years, with multiple effective medications now available.[3,5,6,10-12]

Major depression is one of the most common disorders seen in both primary care and psychiatric practice. The point prevalence of major depression is 5% to 9% for women and 2% to 3% for men, with a lifetime risk of 10% to 25% and 5% to 12%, respectively.[13] Depression not only worsens outcomes for those with comorbid myocardial infarction and diabetes, but is associated with an increased incidence of osteoporosis, coronary artery disease, cerebrovascular disease, and diabetes.[14] *The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) requires 5 of the following symptoms be present for at least 2 weeks to make a diagnosis of major depression: depressed mood, diminished interest or pleasure, change in weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide.[13]

It is common for individuals with RLS to complain of fatigue, disturbed sleep, diminished concentration, and psychomotor agitation, symptoms that could either be interpreted as symptoms of depression or as directly due to the sleep disorder.[3,4] Given the high prevalence of both depression and RLS in the general population, it would not be surprising that some individuals have both disorders by chance alone. However, emerging data indicate that the occurrence of depression symptoms with RLS is far greater

**Table 1a**—Depression Symptoms in Individuals with Restless Legs Syndrome in Population-Based Studies

| Reference | Population | Sample size | RLS diagnosis | Depression measure | Depression symptoms in RLS |
|---|---|---|---|---|---|
| Sevim et al,[21] 2004 | Turkish adults | 3234 | Questionnaire; IRLSSG criteria | Hamilton Depression Scale | Elevated |
| Sukegawa et al,[19] 2003 | Elderly Japanese | 2023 | Questionnaire; IRLSSG criteria | Geriatric Depression Scale | Elevated only in men aged 65-75 years |
| Ulfberg et al,[20] 2001 | Swedish men | 2608 | Questionnaire; IRLSSG criteria | Single question re: mood | Elevated |
| Rothdach et al,[18] 2000 | Elderly Germans | 369 | Interview; IRLSSG criteria | Center for Epidemiologic Studies Depression Scale | Elevated only in men |

RLS refers to restless legs syndrome; IRLSSG, International Restless Legs Syndrome Study Group[103]

**Table 1b**—Depression Symptoms in Individuals with Restless Legs Syndrome in Clinic-Based Studies

| Reference | Population | Sample size | RLS diagnosis | Depression measure | Depression symptoms in RLS |
|---|---|---|---|---|---|
| Winkelmann et al,[23] 2005 | Movement disorder clinic | 130 | IRLSSG criteria | Munich-Composite International Diagnostic Interview | Elevated; 18% 12-month rate of a major depressive episode; 37% lifetime prevalence of major depression |
| Vandeputte et al,[24] 2003 | Sleep clinic | 154 | ICSD-R criteria | BDI | Elevated; 53% BDI score > 10 |
| Saletu et al,[25] 2002 | Patients, not further specified | 33 RLS 26 PLMD | IRLSSG and ICSD-R criteria | SDS | Elevated depression scores |
| Bassetti et al,[26] 2001 | Sleep clinic | 55 | IRLSSG criteria | Medical history of depression | 33% with depression symptoms |
| Lee et al,[27] 2001 | Pregnant women | 7 | Single question | POMS; CES-D | Elevated POMS scores but not CES-D scores |
| Banno et al,[28] 2000 | Sleep clinic | 218 | IRLSSG criteria | Medical diagnosis of depression | Elevated; ~45% with a mood disorder diagnosis |
| Mosko et al,[29] 1989 | Sleep clinic | 31 | ICSD criteria | DSM-III criteria | 71% met major depression criteria |
| Gigli et al,30 2004 | Renal dialysis | 129 | IRLSSG criteria | Medical history of depression | Elevated; 16% had a medical history of depression |
| Tanaka et al,[31] 1999 | Renal dialysis | 12 | Criteria not specified | SDS | Elevated depression scores |

RLS refers to restless legs syndrome; IRLSSG, International Restless Legs Study Group; ICSD, International Classification of Sleep Disorders[104]; ICSD-R, International Classification of Sleep Disorders–revised; DSM, Diagnostic and Statistical Manual of Mental Disorders; SDS, Self-rating Depression Scale; BDI, Beck Depression Inventory; POMS, Profile of Mood States; CES-D, Center for Epidemiologic Studies Depression Scale;

than simple coincidence, consistent with the elevated rates of depression in other sleep disorders such as obstructive sleep apnea[15] and narcolepsy.[16] Furthermore, it has been recognized that many antidepressant medications can induce or worsen PLMS,[17] which are common in individuals with RLS. Given these considerations, we did a comprehensive literature search to further characterize the association between RLS, PLMS, and depression.

## METHODS

Computerized literature searches were first conducted in February 2002 and then updated in February 2005. Each search was performed through PubMed (National Library of Medicine) using the search terms: restless legs, periodic leg movement, periodic limb movement, nocturnal myoclonus, depression, and antidepressants. Search terms were applied both to the keyword field and as a text search. The search included literature from 1965 through January 2005. In addition, we evaluated selected references cited in articles for pertinence and applicability, and we searched for relevant abstracts from the Association of Professional Sleep Societies annual meeting, 1985 through 2004. English-language publications that included data on depression or antidepressants

and RLS or PLMS were obtained and reviewed by 1 or both authors.

## RESULTS

A total of 254 different citations were derived from the searches and reviewed for relevance. Sixty-two publications were selected for detailed consideration. Data from letters to the editor and abstracts were included only if these sources were later submitted as peer-reviewed articles.

Thirteen studies were found addressing the frequency of depression symptoms in adults with RLS. All suggest that depression symptoms are more common among adults with RLS than those without RLS (Table 1). Four studies were population based, whereas 9 others reported on patients presenting to medical clinics.

The 4 population-based studies included data on a total of 8234 individuals. The MEMO study consisted of 369 face-to-face interviews of randomly chosen elderly Germans by 2 RLS-trained physicians using standardized RLS screening questions.[18] This study found significantly elevated depression scores in men but not women (on the Center of Epidemiologic Studies Depression

Scale) compared with age-matched controls without RLS (odds ratio [OR] 13.06; 95% confidence interval [CI] 2.32-73.26). The diagnosis of RLS by trained physicians in this study is important, as there are many mimics of RLS that can create false-positive diagnoses, 1 of which could be depression itself. However, other potential confounders (eg, other medical disorders or pain) were not controlled for in the logistic regression. Similarly, a Japanese population-based study of 2023 elderly individuals who responded to questionnaires regarding depression, sleep, and RLS found that men between the ages of 65 and 75 years were 3.6 times (95% CI 1.2-10.6) more likely to have elevations in depression scores (by the Geriatric Depression Scale) if they had probable RLS.[19] Simple and multiple logistic regression analysis was done. Women with RLS, and those over the age of 75 years, did not demonstrate an elevated risk of depression scores with RLS. In another population-based study (which also controlled for confounding variables) utilizing questionnaires returned by more than 2608 Swedish men, Ulfberg et al found that those with RLS more frequently reported "depressed mood" than did those without RLS (OR 2.6, 95% CI 1.8-3.8).[20] Other symptoms of depression—including decreased concentration, irritability, fatigue, and decreased libido—were also statistically more common in those with RLS. In a group of 103 Turkish adults with RLS derived from a community sample of 3234, Hamilton Depression Scale scores were found to be significantly higher than in controls ($P <$ .001), even when the 3 sleep questions in this Scale were omitted, with a positive correlation between severity of RLS and depression symptoms ($r = 0.201$, $P = .04$).[21] The interviews were face to face, but comparison was with 103 age- and sex-matched controls rather than the surveyed population as a whole. Depression scores were not found to vary with sex, cigarette smoking, income status, or existence of any comorbid disease. Although depression symptoms were not specifically addressed, 1 other population-based study examined the association of RLS (diagnosed by a single question) and self-described "poor mental health" in 1803 adults in Kentucky. Those reporting symptoms consistent with RLS were 3.1 times (95% CI 2.0-4.6) more likely to report poor mental health on all of the previous 30 days than were those who did not have such symptoms.[22]

Nine studies examined individuals diagnosed with RLS in a clinical setting, who were then compared to noncomplaining populations, to historical controls, or in 2 studies to other hemodialysis patients. Winkelmann et al administered DSM-IV–based depression and anxiety questionnaires (M-CIDI/DIA-X) to 130 RLS patients and found higher 12-month rates of a major depressive episode, compared with the control population (17.7% vs 8.7%; OR 2.55; 95% CI 1.5-4.4).[23] Lifetime prevalence rates of major depression also exceeded controls (36.9% vs 15.2%; OR 3.30, 95% CI 2.1-5.0), with the majority (77%) reporting the onset of depression after the onset of RLS. Vandeputte and de Weerd reported elevated Beck Depression Inventory scores in 53% of 154 consecutive sleep clinic patients with RLS or PLMD.[24] This was in spite of patients with "clinically overt depression" being excluded from the study. Comparing 33 adults with RLS to controls, Saletu et al[25] found higher depression scores on the Zung Self-Rating Depression Scale in the RLS group (mean scores 39.9 and 29.6 respectively, $P <$ .001). Patients requiring psychoactive medication were excluded from the study. Of 55 RLS patients seen in a Swiss sleep clinic, 33% described "depression symptoms" at some point during their life, and several reported exacerbation of

RLS coinciding with the worsening of the depressive disorder.[26] Lee et al found significantly higher depression scores in pregnant women with RLS during the third trimester compared with pregnant women without RLS, on the Profile of Moods States.[27] In contrast, they did not find differences on the Center of Epidemiologic Studies Depression Scale. Banno et al looked at International Classification of Diseases-9-CM codes in the 5-year period prior to RLS diagnosis for 218 patients without concurrent sleep apnea in a Canadian province where a comprehensive health database is maintained.[28] The control group was matched for age, sex, and postal code, but controls were not individuals who had come to a sleep clinic for medical care. A prior clinical diagnosis of depression, neurotic disorder, or affective psychosis was much more common in the RLS patients (43.7% of men and 46.1% of women) than in the population-based controls (10.4% of men and 22.8% of women). The OR for having 1 of these psychiatric disorders in the RLS patients compared with controls was 5.3 for men and 2.9 for women. At the time of RLS diagnosis, 13.6% of men and 27.0% of women were on antidepressants. Mosko et al lumped together 31 adults with RLS or PLMD (mean age 49.8), finding 71.0% to meet minimum Diagnostic and Statistical Manual of Mental Disorders, Third Edition criteria for major depression.[29] One was on a tricyclic antidepressant, and 4 were on benzodiazepines at the time of study.

In a group of 601 renal dialysis patients, Gigli et al found a medical history of depression more often in those with RLS than in dialysis patients without RLS (16% vs 9%, $P <$ .022).[30] Using logistic regression analysis, Tanaka et al found RLS symptoms "during hemodialysis" (n = 12) and "in daily life" (n = 10) to be associated with elevated Zung Self-Rating Depression Scale scores, compared with hemodialysis patients without RLS (OR 39.3 and 29.1 for the 2 RLS groups).[31]

Of these 9 clinical studies, 8 included men and women. Two reported no significant sex difference for the depression symptoms, 1 reported an increase for men, and 5 did not present analysis by sex.

Two older studies reported an association of RLS with "depression and anxiety" but did not contain sufficient control data to include at the evidence level of the other studies.[32,33] Although we did not specifically search for studies of anxiety and RLS, 2 of the population-based studies[18,21] and 1 of the patient-based studies[25] investigated anxiety symptoms and found elevated rates in individuals with RLS. In a group of patients presenting to a psychiatric clinic for anxiety, 20% were found to have RLS.[34]

We found 2 studies that measured depression-symptom response to the treatment of RLS with dopaminergic medication. One study found that treatment of RLS with a single nighttime dose of pramipexole (mean dose 0.28 mg) improved depression symptoms on the Zung Self-Rating Depression Scale ($P =$ .006).[35] However, another study by the same group did not find improvement in the Self-Rating Depression Scale scores with L-dopa (100 mg regular-release plus 100 mg sustained-release L-dopa/benserazide given in combination at night).[36] The L-dopa improved RLS, PLMS, and subjective sleep quality but not objective sleep efficiency.

Three studies were found that looked at PLMD (without RLS) and depression. Saletu et al found higher depression scores on the Zung in 26 adults with PLMD compared with controls (mean scores 35.1 and 26.1 respectively, $P <$ .001).[25] All were off of psychoactive medication at the time of assessment. Aikens et al[37]

examined individuals presenting for sleep study and reported that 58% (16/28) of PLMD patients had an elevated depression scale on the Minnesota Multiphasic Personality Inventory. This was significantly higher than patients with psychophysiological insomnia and sleep apnea, even after controlling for age, body mass index, and sleep latencies on the Multiple Sleep Latency Test. In addition, they reported that 32% of the patients with PLMD had a prior history of depression treatment. However, this study did not report the use (or not) of antidepressant medication at the time of polysomnography. This confounds interpretation of the results, since antidepressant medication can induce or worsen PLMS (see below). Mendelson[38] found 29.8% of patients with PLMD (defined as more than 5 leg movements per hour of sleep associated with arousals) to have a history of depression treatment, compared with 18.8% of those without periodic limb movements on overnight sleep study. In this study, 3 of 27 patients (11%) were on antidepressants at the time of polysomnography (all tricyclics). Patients with RLS were excluded from the analysis.

Only 3 studies were found that specifically investigated the prevalence of RLS or PLMS in a depressed population. Of 198 patients interviewed at a psychiatric clinic who were seeking help for symptoms of unipolar depression, 26% were found to have RLS by International RLS Study Group criteria.[34] While there was no comparison to a concurrent control group, study criteria included entry before starting antidepressant therapy, and RLS was differentiated from akathisia. A population-based study of 1506 adults, 55 to 84 years of age, found those with a medical diagnosis of depression to have a higher risk of RLS symptoms (OR 1.64, CI 1.07-2.56).[39] One sleep laboratory study did not report more PLMS in patients with untreated major depression than in age-matched controls.[40] In a population-based study, Ohayon and Roth performed a telephone survey of 18,980 individuals in 5 European countries using the Sleep-Eval system to assess symptoms of RLS, PLMD, and psychiatric disorders.[41] Although the authors did not differentiate between various mental disorders in the data presented, those with mental disorders had a 50% higher risk of RLS and a 3.5-fold risk of PLMD (by history) than those without mental disorders.

Limited and conflicting data were found regarding the effect of antidepressants on RLS sensory symptoms. The above Sleep-Eval study found that use of selective serotonin reuptake inhibitors (SSRIs) was a risk factor for RLS (OR 3.11, 95% CI 1.66-5.79).[41] In another study, Leutgeb and Martus[34] found no significant increase in RLS with paroxetine and amitriptyline but did find a difference for sertraline and mirtazapine, comparing RLS symptoms prospectively before and at least 6 months after antidepressant treatment. Six case reports indicated induction or exacerbation of RLS coincident with the use of fluoxetine (N = 1),[42] paroxetine (N = 1),[43] low-dose venlafaxine ( = 2/6),[44] mianserin (N = 9),[45,46] and lithium (N = 2).[47]

Several studies have found increased PLMS with the use SSRIs. Yang et al studied 274 consecutive patients referred for sleep studies who were taking SSRIs or the serotonergic-noradrenergic antidepressant venlafaxine.[48,49] Roughly one fourth of patients on those agents had PLM indexes greater than 20, and, on logistic regression, these antidepressants substantially increased the probability of a PLM index greater than 20 per hour (OR 5.15, 95% CI 2.09-12.68 and OR 5.24, 95% CI 1.70-16.21, respectively) compared to both a matched control population not taking antidepressants, and one taking bupropion. In a smaller study (N = 9),

Dorsey et al[17] reported that 44% of depressed patients on fluoxetine had PLMS-arousal indexes of more than 5 per hour (mean 10.0), compared with 0% of untreated depressed controls. Their patients had a mean age of 23.4 years and had been referred with sleep maintenance insomnia, fatigue, or both. These studies suffer in that they are retrospective and consist of individuals referred to a sleep clinic and, thus, generally have a sleep complaint. In a controlled study in which polysomnography was performed both before and after initiation of low-dose venlafaxine, 75% of normal volunteers (N = 8) had PLMS induced, from a mean PLMS index of 0 per hour to 45 per hour, accompanied by significant increases in wake time.[44] It should be noted that dosing was 150 mg per day or less, at which doses venlafaxine is predominantly a serotonergic reuptake inhibitor and has little of the noradrenergic reuptake inhibition found at higher doses. Armitage et al reported fluoxetine to induce moderate to severe PLMS in 2 of 7 patients with major depression.[50] Armitage et al[52] also reported fluoxetine to induce PLMS in 6 children treated for major depression.[51]

No peer-reviewed publications were found specifically addressing tricyclic antidepressants and PLMS. Guilleminault et al found 3 of 21 narcoleptics to develop "symptomatic lower extremity jerking" when put on clomipramine. A few other references were found associating "myoclonus" with various antidepressants, including lithium and monoamine oxidase inhibitors.[53-57] In general, data from these studies are confounded by (1) lack of polysomnography, (2) overlap with antidepressant-induced serotonin syndrome (in which awake myoclonus is common),[58] or (3) inclusion of apnea-associated PLMS.

In contrast to SSRI antidepressants and venlafaxine, limited data indicate that the atypical antidepressants bupropion, trazodone, and nefazodone do not induce or exacerbate PLMS. Nofzinger et al[59] studied 5 patients with PLMD and major depression. On bupropion, their mean PLMS index fell from 14.9 per hour (medication-free) to 9.1 per hour (on 400 mg per day of bupropion). Yang et al[49] found patients on bupropion (N = 34) to have PLMS indexes and PLMS-arousal indexes that were no different from those of control patients. Bupropion increases dopamine and norepinephrine without increasing serotonin.[60] Similarly, trazodone was found to reduce the mean PLMS index from 21.2 to 12.6 at a dosage of 100 mg, in a small case series (N = 11).[61] Shen et al[62] reported no significant change in PLMS index in 9 patients put on nefazodone, who each had a baseline and 2 follow-up polysomnograms.

## DISCUSSION

The most important finding of this review is that symptoms of depression are common in individuals with RLS. The association between RLS and depression symptoms is likely a complex one. Because the epidemiologic studies supporting this association are cross-sectional and thus correlational, possible explanations for the observed association between these two include: RLS causes depression, depression causes RLS, or a third factor causes both RLS and depression. Another possibility is that symptoms of one disorder are misdiagnosed as the other disorder, thus producing a spurious association between the two disorders. Each of these will be addressed in turn.

RLS could cause depression through its adverse influences on sleep, daytime alertness, or energy. Numerous recent epidemiologic studies have demonstrated that insomnia,[63-65] hypersom-

nia,[63] and fatigue[66] are all independent risk factors for incident major depression. Although the underlying causes of insomnia, hypersomnia, and fatigue in such studies are not identified, and probably diverse, each of these symptoms can be observed in those with RLS. In this way, the sleep disruption or fatigue caused by RLS would be the mediating factor in producing depression. Pain and social isolation are also predictors of depression,[67,68] and these symptoms are frequently observed in people with RLS.[20,28] Finally, RLS could be considered as a nonspecific stressor that may induce depressive symptoms.[69]

The means by which depression could cause RLS are unclear. However, symptoms of depression such as sleep deprivation,[70] poor nutrition,[3,71,72] or lack of exercise[73] may predispose an individual to the development of RLS. Alternately, those with depression may amplify subclinical or mild RLS, making occasional RLS symptoms appear to meet threshold criteria. Finally, the treatment of depression may be implicated, since SSRI antidepressants may worsen RLS and PLMS (as reviewed above).[60,74,75]

It is also possible that a third factor is associated with both RLS and depression, falsely suggesting a causal association between the two. This factor could range from an abnormality in dopaminergic transmission in both RLS[12] and depression[76,77] to a genetic association between the two disorders. Dopaminergic hypofunction potentially underlies the symptoms of both RLS and depressive illness. The remarkable efficacy of dopamine agonists in the treatment of RLS provides inferential support for the role of dopaminergic abnormalities in RLS, though imaging data in support of this are inconsistent.[78] The role of dopamine in depressive illness is less well established. Dopamine systems are certainly involved in motivation and reward systems. Furthermore, roughly 45% of Parkinson disease patients (who have loss of dopamine cells in the substantia nigra) have depression.[79] In addition, evidence of dopamine hypofunction in depression comes from postmortem studies of unmedicated, depressed suicide victims.[80] Finally, a number of dopamine-receptor agonists have been shown to be effective in the treatment of depression.[81-83]

On the other hand, the epidemiologic association could be an artifact of the overlap of symptoms of the 2 disorders. Four of the 9 DSM-IV criteria for major depression[13] can also be caused by RLS: "insomnia or hypersomnia," "fatigue/loss of energy," "diminished concentration," and "psychomotor retardation or agitation" (Table 2). Only 5 of 9 criteria are required to make a diagnosis of major depression. In this way, an individual with RLS may have nearly enough of these symptoms to exceed the threshold for an abnormal score on a depression questionnaire, even in the absence of a genuine major depressive episode. On the other hand, individuals with major depression could be misdiagnosed in the epidemiologic studies as having RLS, since elderly individuals with depression often somatize,[84] which may lead to a positive response bias on questions relating to restlessness and discomfort in the legs. Similarly, side effects of depression treatment, such as akathisia, could be misinterpreted as RLS, though more probably RLS is misdiagnosed as akathisia. These issues bring up the weaknesses of epidemiologic studies in which questionnaires are administered (for either RLS or for depression), rather than making diagnoses by face-to-face interviews. Clearly, epidemiologic studies with face-to-face interviews by interviewers who are knowledgeable about both disorders are indicated. In this way, additional understanding of the temporal association between the development of the 2 disorders (when present) may also be available.

| Table 2—Major Depression Symptoms* |
|---|
| Depressed mood |
| Diminished interests |
| Feeling worthless |
| Thoughts of death |
| Weight change |
| Insomnia or hypersomnia |
| Fatigue/loss of energy |
| Diminished concentration |
| Psychomotor retardation or agitation |

*5 of 9 required for diagnosis

Given the apparent comorbidity of RLS and depression, interrelated diagnostic and treatment issues are important to consider. First, we carefully assess patients with RLS for the presence of a comorbid mood disorder. Of particular value in the assessment is focusing on specific features not directly related to RLS symptoms, such as depressed mood, loss of interest, guilty preoccupation, and suicidal ideation. It is helpful to supplement the clinical interview by using self-report rating scales for mood disorders, e.g., Beck Depression Inventory, Profile of Mood States, and Hopkins Symptom Checklist.

In the absence of evidence-based guidelines for treatment of comorbid RLS and depression, we have developed a practical therapeutic approach to these patients. We have found that the most important initial treatment issue to consider is the severity of the underlying depression. In cases of dysthymia or minor depression, or when the mood disorder appears to be a consequence of the sleep disorder, we treat the sleep disorder first. In this way, there is the possibility that treatment of RLS may attenuate or eliminate the mood disorder, whereas it is unlikely (as described above) that depression treatment will eliminate the RLS. Treatment for RLS is well described in recent reviews,[3,5,6,10-12] and includes correction of any underlying causes for RLS (e.g., iron deficiency) and, if absent, use of dopaminergic agents. In direct support of this approach is one study that found treatment of RLS with a single nighttime dose of pramipexole (mean dose 0.28 mg) improved depression symptoms.[35] However, another study by the same group did not find improvement in depression measures with L-dopa.[36] Of note are recent studies of pramipexole as a primary treatment for depression that have shown it to have antidepressant properties.[81,85,86] However, the antidepressant effect was reported at doses of 1.0 and 5.0 mg per day, which is higher than doses commonly used in RLS.[86] In addition to optimal treatment for RLS, cognitive therapy for depression is encouraged. Also, regular physical exercise is recommended since exercise may help both PLMS[73] and depression.[87]

When antidepressant medication is needed in patients with RLS, either due to the severity of the depression or in the context of effectively treated RLS, bupropion is our first choice because of its adrenergic mechanism of action. Bupropion increases norepinephrine and dopamine without increasing serotonin activity[60] and has been found to decrease PLMS.[59] We recommend taking it during the day to minimize any stimulant effect at bedtime. A number of studies have demonstrated that its antidepressant effect is comparable to serotonergic antidepressants but with less somnolence and sexual dysfunction.[88] In patients whose depression is unresponsive to bupropion, an alternate adrenergic antidepres-

sant such as desipramine (or reboxetine) may be of value. If these agents are not effective and the depression is substantial, a serotonergic antidepressant should be employed, utilizing as low a dose as is effective and with a close eye on RLS symptoms. If RLS symptoms worsen, an increase in the dose of the dopaminergic agent or addition of a supplemental agent (e.g. benzodiazepine, anticonvulsant, opioid) may be necessary.

In patients with substantial RLS who are already taking antidepressant medication, we first try to optimize RLS and PLMS therapy, as described above. Then we will consider cautiously reducing, changing, or eliminating antidepressant medication, particularly if fatigue, sleepiness, poor motivation, decreased memory, or sexual dysfunction is present.[74,75,89,90] Since most of our patients in this group present on SSRIs, it is common for us to try switching to bupropion or desipramine or lowering the dose of the SSRIs and supplementing with low doses of these antidepressants.[91] Serotonergic medications must be tapered slowly to avoid withdrawal symptoms. Like the SSRIs, bupropion has anxiolytic action for those with comorbid anxiety or posttraumatic stress disorder.[60,92-94] However, the anxiolytic effect may be delayed in onset[60] and not as robust as with SSRI, requiring the addition of a benzodiazepine for some of our patients.

Optimal treatment of sleep disturbance in mood disorders has been shown to assist with maintenance of remission and prevention of relapse.[95] Similarly, sleep deprivation is thought to exacerbate RLS.[70] Thus, treatment of sleep disturbance is an important component of both RLS and depression symptom control. In addition, the RLS morbidity of "emotional distress" (irritability and moodiness) has been found to be associated with the sleep disturbance.[96] For these reasons, use of supplemental hypnotics are commonly used in patients with RLS and depression to treat persistent insomnia that may result from (1) activating aspects of antidepressants and/or dopaminergic agents, (2) conditioned insomnia as a result of chronic RLS-related sleeplessness, (3) refractory RLS, or (4) depression.[97,98] We commonly use trazodone for this purpose, as it has been shown to consolidate sleep in patients with depression on antidepressants,[99,100] and does not appear to worsen PLMS.[61] While trazodone at hypnotic doses (50-100 mg at bedtime) does not typically work for depression, it is one of the most commonly used medications for insomnia.[99-102] In males, the rare risk of priapism (roughly 1 in 7,000) should be discussed and instructions on management reviewed. Alternate agents for sleep consolidation in those with comorbid RLS and depression include gabapentin (300-1200 mg before going to bed) or a short-to intermediate-acting benzodiazepine-receptor agonist (e.g., temazepam, zolpidem, zaleplon, lorazepam).

In summary, the comorbidity of RLS and symptoms of depression appears to be common. It is unclear whether RLS patients with depression have a different response to RLS treatment or a worse course of either their mood or sleep disorders. Future research in this area should address such prognostic issues. Thoughtful treatment approaches are necessary for RLS patients with depressive comorbidity. We propose that vigorous treatment of RLS symptoms and careful choice of antidepressant agents can lead to effective long-term management of both RLS and depression.

## ACKNOWLEDGEMENTS

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