

Mood Disorders in Restless Legs Syndrome (Willis-Ekbom Disease)

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ABSTRACT

Objective: Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a sensorimotor disorder that can result in considerable sleep disruption. This narrative review provides an overview of RLS diagnosis and reports epidemiologic evidence for an association between RLS and mood disorders. Possible links between RLS, sleep disturbances, and mood disorders are considered, and theoretical pathophysiologic pathways are discussed. Finally, pharmacologic therapies for RLS are summarized.

Data Sources: A PubMed search was performed using the search term *restless legs syndrome* in combination with *affective/anxiety, antidepressants, anxiety/anxiety disorder, attention deficit hyperactivity disorder, depression/depressive disorder, mood/mood disorder, neuropsychiatric, panic/panic disorder, psychiatric disorder, and psychosis*. English-language articles published between January 1993 and May 2013 were retrieved. Additional studies were identified from the reference lists of relevant publications.

Study Selection: 173 publications were retrieved. Articles related to the association between idiopathic RLS and depression, anxiety, and mood disorders were reviewed. In total, 32 epidemiologic studies were identified. These studies were reviewed in detail and ranked according to quality.

Data Extraction: Data were extracted on the basis of relevance to the topic. Epidemiologic studies were assessed using 3 parameters: methodology, data quality, and generalizability of the results. Each factor was scored from 1 (high quality) to 4 (low quality), giving a total score of between 3 and 12 for each study.

Results and Conclusions: RLS and mood disorders are frequently comorbid. Recognition and appropriate treatment of comorbid RLS are particularly important in patients with psychiatric disorders, as RLS is a common medical reason for insomnia, and antidepressant use may exacerbate sensory symptoms.

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Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common, chronic sensorimotor disorder with a prevalence of between 3%–29% of the general population in Western industrialized countries.^{1–4} Around 2.7% of individuals experience at least moderately distressing symptoms likely to warrant treatment, of whom 55.5% experience disturbance of daytime functioning.¹ In a US survey of RLS prevalence and burden, 1.5% of respondents were identified as RLS sufferers (symptoms ≥ 2 times per week with moderate-to-severe distress), with a mean work productivity loss of 1 day per week.⁵ The disorder is characterized by an overwhelming urge to move the legs (or other body parts), often accompanied by paresthesias or dysesthesias. Symptoms worsen in the evening and at night around the peak of core body temperature and can result in significant sleep disruption.⁶ RLS is thought to be a central nervous system disorder related to dopaminergic dysfunction and impaired iron homeostasis in the brain.⁷ Proteomic analysis of the cerebrospinal fluid of patients with RLS reveals a protein profile that is consistent with clinical findings of disruptive sleep, cardiovascular dysfunction, and painful symptoms.⁸ Around 60% of patients with idiopathic/primary RLS have a first-degree relative who also suffers from the disorder,^{6,9} and genome-wide association studies have identified genetic risk factors.^{10–12} Secondary RLS is associated with iron deficiency, pregnancy, and end-stage renal disease; all 3 conditions are characterized by reduced central iron availability.¹³

RLS has a significant impact on patient well-being and has been associated with reduced general health, poor mental health status, and depressed mood.^{14–18} Although the association between RLS and cognitive impairment needs further evaluation, recent evidence suggests that the disorder may also affect cognitive function^{19–21}; impaired executive functioning, as indicated by impaired performance in the Wisconsin Card Sorting Test, has been observed in 10 adults with frequent RLS symptoms (≥ 2 per week).²¹ Common comorbidities of RLS include insomnia, anxiety, and depression.²² A bidirectional relationship between clinically relevant depressive symptoms and RLS has been suggested.²³ As RLS has a significant impact on sleep and is associated with mood disorders, it may present in psychiatric practice. A large US cross-sectional study (N = 1,024) reported a strong association between RLS and a diagnosis of major depressive disorder (12-month prevalence: 9.5% [odds ratio (OR) = 4.7 (95% CI, 1.2–18.3)]).²⁴ Among 99 elderly patients attending a Spanish psychiatric clinic, the prevalence of confirmed RLS was 11%.²⁵ An additional 10% of patients had “possible RLS”; the diagnosis could not be confirmed due to doubts regarding the accuracy and reliability of the information provided by the patient. None of the patients in the study had previously been diagnosed with RLS. In many cases, patients commented either that they had never reported their symptoms to a clinician or that their symptoms had never been investigated. These results suggest that, although relatively common among psychiatric patients, RLS is frequently underdiagnosed. The potential presence of RLS should be considered in all patients presenting with major sleep onset insomnia and mood disorders.

- Epidemiologic studies report a higher risk of depression and/or anxiety or a higher severity of anxiety and depression in patients with restless legs syndrome (RLS).
- Although the etiology of RLS remains unclear, other factors, such as pharmacologic agents affecting dopamine neurotransmission, may influence development of the disease, thus underscoring the importance of recognizing RLS in patients with psychiatric disorders.

Periodic leg movements during sleep (PLMS) are rhythmic movements of the toes, ankles, and/or legs and are observed in 85%–95% of patients with RLS.²⁶ The presence of PLMS is important because these movements can lead to partial or complete arousals from sleep, which may lead to other comorbid complications. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other types of antidepressants can increase the occurrence of PLMS. Treatment with antidepressants, such as amitriptyline, mirtazapine, and multiple SSRIs (fluoxetine, paroxetine, sertraline), has been shown to evoke or increase the frequency of PLMS compared to placebo.^{27–31} The effect of these agents on PLMS has been observed in healthy subjects as well as in subjects with depression. In patients with depression, Yang et al³⁰ reported that patients given venlafaxine or SSRIs had a more than 5 times greater risk of PLMS compared to control subjects. In healthy subjects, antidepressants, such as amitriptyline and mirtazapine, also induce or increase PLMS.^{27,28}

This narrative review first discusses the diagnosis of RLS and then examines the epidemiologic evidence for an association between RLS and mood disorders. The relationships between RLS, sleep disturbances, and mood disorders and the theoretical pathophysiologic pathways linking RLS and mood disorders are discussed. Finally, potential associations between RLS and antidepressant use and current pharmacologic therapies for RLS are summarized.

METHOD

Relevant publications were identified via a comprehensive PubMed search using the term *restless legs syndrome* in combination with *affective/anxiety, antidepressants, anxiety/anxiety disorder, attention deficit hyperactivity disorder, depression/depressive disorder, mood/mood disorder, neuropsychiatric, panic/panic disorder, psychiatric disorder, and psychosis*. English-language articles published between January 1993 and May 2013 were retrieved. Additional studies were identified by careful review of the reference lists of identified publications. Although a true systematic approach to study selection was not implemented, data were extracted on the basis of their relevance to the potential link between mood disorders and idiopathic RLS.

A total of 173 publications were retrieved, of which 32 studies (25 studies in adults and 7 in children) reported epidemiologic evidence for the relationship between

idiopathic RLS and depression, anxiety, and mood disorders. These studies were reviewed in detail and ranked according to their quality. Study quality was assessed by the authors using 3 parameters: the study methodology, the quality of data, and the generalizability of the results. Each parameter was scored from 1 (high quality) to 4 (low quality), resulting in a total score of between 3 and 12. Therefore, the highest-quality studies received the lowest scores (ie, those studies that used a face-to-face interview and the help of valid, replicable instruments to collect data from the general population). Each of the authors provided their ratings independently, and an average total score for each study was calculated. These ratings are presented to provide context and as a means for comparison of the currently available evidence resulting from the above searches.

DIAGNOSIS OF RLS

As RLS is diagnosed clinically, physicians must rely on patient history rather than specific physical findings. Diagnosis can be difficult and time-consuming if a patient's urge to move is not elicited. Many patients with RLS are initially referred to specialist care with a diagnosis of insomnia and/or depression. In the RLS Epidemiology, Symptoms and Treatment (REST) primary care study, only 13.6% of RLS sufferers (patients with at least twice-weekly symptoms likely to warrant treatment) had a previous diagnosis of the disorder; conditions commonly diagnosed by the primary care physician included back pain (34.8%), depressed mood/depression (26.9%), hypertension (26.1%), insomnia/sleeping disorder (26.0%), and anxiety (23.2%).³² A retrospective database review, which examined diagnoses received by patients in the 5 years prior to a sleep laboratory evaluation, found that a prior diagnosis of a mood disorder was significantly more common among both male (43.7% vs 10.4%) and female (46.1% vs 22.8%) patients with RLS than among matched controls.³³

The observed associations between RLS and depression and anxiety disorders may make differential diagnosis challenging. Many patients with RLS, as well as those with depression and anxiety, complain of sleep disturbance.³² Sleep disruption due to RLS symptoms may result in 4 of the symptoms of depression: insomnia, loss of energy, diminished concentration, and psychomotor retardation/agitation.²⁴ In many cases, it can be difficult to determine whether these symptoms occur as the result of depression or are related to RLS. Differential diagnosis may be difficult in cognitively impaired patients with affective disorders, who may have difficulty explaining their array of sensory complaints and distinguishing them from psychiatric complaints.²⁵ Recognition of RLS is particularly important in patients receiving treatment for mood disorders and anxiety, as some of the medications commonly used to treat insomnia and depression may result in exacerbation of RLS symptoms.

There are no physical markers for RLS; therefore, the disorder is a clinical diagnosis based on the essential criteria defined by the International Restless Legs Syndrome Study

Group (IRLSSG).^{6,34} These criteria can be easily remembered using the acronym URGE: **U**=urge to move the legs often accompanied by unpleasant/uncomfortable sensations; patients may describe their symptoms using terms such as *creeping, crawling, burning, electric-current, or bugs underneath the skin*; **R**=rest or being still worsens the urge to move; **G**=gyration or movement provides partial or total relief from symptoms (at least temporarily); **E**=evening or nighttime worsening/symptoms only occur in the evening or at night. A fifth criterion was added in 2011,³⁵ changing the acronym to “URGED”: **D**=denial of other explanations of urge—occurrence of features 1–4 are not solely accounted for as symptoms primary to another medical or behavioral condition. Several other conditions can cause motor restlessness and/or leg pain and discomfort and may mimic the essential diagnostic criteria of RLS.³⁶ For example, akathisia is characterized by a feeling of motor restlessness; in contrast to RLS, this restlessness is not circadian, generally affects the entire body, may not be relieved by movement, and is not accompanied by unpleasant sensations.³⁶ Dysesthesias occur in patients with claudication in addition to those with RLS; however, the symptoms of claudication are not associated with an urge to move, generally increase in intensity with walking, and are relieved by rest.³⁶ Peripheral neuropathy is characterized by painful sensations in the extremities, but, unlike RLS symptoms, these sensations are not accompanied by an urge to move, do not improve with movement, and do not show a prominent circadian pattern.³⁶ In the majority of cases, these mimic disorders can be ruled out by physical examination and patient history; however, clinicians may find themselves occasionally perplexed as to which sensory disorder best explains a patient’s particular complaint.

Supportive features for an RLS diagnosis include a history of the disorder in first-degree relatives, a good response to dopaminergic therapy, and the presence of PLMS.⁶ It is important to recognize that *RLS* and *PLMS* are not synonymous. Although not unique to RLS, PLMS are highly suggestive of the disorder and are observed in up to 95% of patients with RLS.²⁶ Polysomnography is required to diagnose PLMS. PLMS are defined as repetitive leg movements that occur in 5- to 90-second intervals and are 0.5 to 10 seconds in duration.^{37,38} PLMS can be quantified either by recording the activity of the anterior tibialis muscles with surface electrodes during polysomnography (electromyography) or by using accelerometers attached to the big toe, ankle, or foot to capture leg movements (actigraphy). This latter procedure can be done in the patient’s home.²⁶ Ascertaining the presence and frequency of PLMS in patients with RLS is valuable, as these stereotypical movements can result in arousals from sleep, with consequent autonomic activation and excessive daytime sleepiness.^{37,39} The suggested immobilization test (SIT) was also developed to quantify subjective leg discomfort and objective leg movement and has a high sensitivity and specificity for diagnosing RLS.⁴⁰ The SIT is performed during a 1-hour period prior to bedtime.⁴¹ Leg movements are quantified via surface electromyography from anterior tibialis muscles, and leg discomfort is measured via a visual

analog scale. A SIT index of >40 leg movements per hour can be used to identify patients with RLS in approximately 80% of cases.⁴²

EPIDEMIOLOGIC EVIDENCE FOR AN ASSOCIATION BETWEEN RLS AND MOOD DISORDERS IN ADULTS

The association between RLS and mood disorders has been investigated in several epidemiologic studies (Table 1, Figure 1). Most used the IRLSSG criteria to identify patients with RLS and assessed depression and/or anxiety according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)/International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM)* criteria or via a validated scale. The highest-quality studies applied the IRLSSG diagnostic criteria, performed elevated measures of RLS and psychiatric disorders, excluded disorders that might complicate diagnosis, and had well-defined populations of patients and controls.

In each study, RLS was associated with a higher risk of depression and/or anxiety or a higher severity of anxiety/depression scores (Table 1). In a cross-sectional study performed in the United States using the RLS diagnostic interview, lifetime prevalence of any psychiatric disorder was found to be higher among individuals with RLS (36.8% [n = 14]) than among those without RLS symptoms (14.6% [n = 129]).²⁴ The most common psychiatric diagnosis was *DSM-IV* major depressive disorder, with a lifetime prevalence of 19% (adjusted OR = 2.7 [95% CI, 1.1–6.7]; *P* = .031) and a 12-month prevalence of 9.5% (OR = 4.7 [95% CI, 1.2–18.3]; *P* = .026) among patients with RLS, in comparison to lifetime and 12-month prevalences of 8.4% and 2.2%, respectively, among controls. Individuals with RLS also had a higher lifetime prevalence of panic disorder than controls (16.7% vs 4.1%), and lifetime (adjusted OR = 5.3 [95% CI, 2.0–14.0]; *P* = .001) and 12-month (adjusted OR = 12.9 [95% CI, 3.6–46.0]; *P* = .001) odds ratios showed a strong association between panic disorder and RLS. Similar results were observed in a Korean study.⁴³ Lifetime prevalence of any *DSM-IV* psychiatric disorder was higher in individuals with RLS than in controls (40.3% vs 27.7%; adjusted OR = 2.26 [95% CI, 1.39–3.67]); major depressive disorder was the most common psychiatric diagnosis. RLS was also strongly associated with lifetime (RLS vs controls: 13.9% vs 6.7%; adjusted OR = 2.25 [95% CI, 1.14–4.46]) and 12-month (11.1% vs 5.3%; adjusted OR = 2.27 [95% CI, 1.07–4.82]) prevalence of *DSM-IV* anxiety disorders, particularly panic disorder (lifetime: 4.2% vs 0.1%; adjusted OR = 18.9 [95% CI, 4.72–75.9]; 12-month: 2.8% vs 0.1%; adjusted OR = 17.0 [95% CI, 3.02–96.1]). Collectively, the results of these studies indicate that RLS and depression, and potentially other mood disorders, have significant comorbidity.

The correlation between RLS and mood disorders may be related to the frequency and severity of RLS symptoms (Table 1). The results from the Wisconsin Sleep Cohort Study indicated an increased risk of anxiety and depression among individuals with RLS.⁵⁰ These associations were

Table 1. Studies Reporting Data for Restless Legs Syndrome (RLS) and Depression and Anxiety Disorders in Adults

Study	Patients	Assessment of RLS	Assessment of Depression, Mood, and Anxiety	Results	Study Rating ^a
Cross-sectional studies					
Cho et al, 2009 ⁴³	6,509 respondents assessed via face-to-face interviews	IRLSSG criteria	Korean version of the CIDI (used to make psychiatric diagnoses according to the DSM-IV criteria), CES-D, EQ-5D	Individuals with RLS: 1% (72/6,509) Adjusted ORs (95% CIs) for individuals with RLS compared to those without the disorder: MDD—lifetime: 2.57 (1.33–4.96); 12-month: 2.99 (1.26–7.06) Anxiety disorders—lifetime: 2.25 (1.14–4.46); 12-month: 2.27 (1.07–4.82) Panic disorder—lifetime: 18.9 (4.72–75.9); 12-month: 17.0 (3.02–96.1) Individuals with RLS were more likely to report taking medication for emotional or mental health problems during the past year (12.5% vs 3.0%; adjusted OR = 3.54 [95% CI, 1.72–7.31]; $P < .01$)	3.0
Lee et al, 2008 ²⁴	1,024 individuals completing RLS Questionnaire and Diagnostic Interview Schedule	7-item RLS questionnaire based on the IRLSSG criteria	Diagnostic interview based on DSM-IV	Individuals with RLS: 42 (4.2%) RLS was associated with a diagnosis of MDD (adjusted OR = 4.7 [95% CI, 1.2–18.3]; $P = .026$), panic disorder (12.9 [3.6–46.0]; $P = .001$), and comorbidity of MDD and panic disorder (9.7 [1.4–69.0]; $P = .002$) in the previous 12 months. Use of SSRIs or TCAs was not an independent predictor of RLS (adjusted OR = 0.5 [95% CI, 0.2–1.2])	3.0
Kim et al, 2010 ⁴⁴	714 individuals (301 men, 413 women) assessed via face-to-face interviews	NIH criteria IRLS	Mini-International Neuropsychiatric Interview version 5.0, GDS, CES-D Diagnoses of major psychiatric disorders made according to DSM-IV criteria	Individuals with RLS: 59 (8.3%) Diagnosis of MDD, RLS vs non-RLS: 15.3% vs 4.1% (OR = 3.76 [95% CI, 1.66–8.52]; $P < .01$). Depression scores were significantly higher in individuals with RLS than those without RLS ($P < .01$ for GDS scores; $P < .05$ for CES-D scores)	4.0
Kim et al, 2012 ⁴⁵	Face-to-face household survey with 1,990 respondents	IRLSSG criteria (IRLSSG criteria for use in cognitively impaired older people were used for respondents with an MMSE score of 12 or communication difficulties)	Diagnostic section for depressive disorders of the CIDI (Korean version), GDS (Korean version)	Individuals with RLS: 202 (10.2%) Lifetime prevalence of depression—RLS vs no RLS: 14.1% vs 6.3%; adjusted OR = 2.57 (95% CI, 1.95–3.38); $P < .001$ RLS was associated with depression as assessed by CIDI (adjusted OR = 2.01 [95% CI, 1.45–2.79]; $P < .001$) and GDS (1.62 [1.34–1.94]; $P < .001$). There were no significant differences between individuals with and without RLS in terms of antidepressant use (1.7% vs 1.5%)	4.0
Nomura et al, 2008 ⁴⁶	2,824 individuals (1,223 men, 1,601 women) responding to a questionnaire	IRLSSG consensus questionnaire, IRLS. Individuals who fulfilled at least 2 of the IRLSSG criteria were interviewed by a sleep disorder expert neurologist in order to confirm the RLS diagnosis	CES-D, depression defined a score of < 12 points	Individuals with RLS: 50/2,811 patients (1.8%) (13 patients with possible RLS did not complete the telephone interview) Individuals with RLS had higher mean CES-D scores than those without the disorder (11.7 ± 6.3 points vs 8.6 ± 4.9; $P = .001$). RLS was significantly associated with depression (OR = 2.32 [95% CI, 2.03–2.61]; $P = .003$)	4.5
Sevim et al, 2004 ⁴⁷	Adults aged over 17 y (N = 3,234) assessed via face-to-face interviews	IRLSSG criteria, IRLS	Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale	Individuals with RLS: 103 (3.18%) Mean anxiety and depression scores were significantly higher among RLS patients than controls ($P < .001$ for both). Severity of RLS was correlated with the severity of anxiety ($r = 0.21$, $P = .03$) and depression symptoms ($r = 0.201$, $P = .04$)	5.0

(continued)

Table 1 (continued). Studies Reporting Data for Restless Legs Syndrome (RLS) and Depression and Anxiety Disorders in Adults

Study	Patients	Assessment of RLS	Assessment of Depression, Mood, and Anxiety	Results	Study Rating ^a
Ulfberg et al, 2001 ¹⁸	2,608 men responding to a questionnaire	IRLSSG criteria	Single question: "Are you affected by depressed mood without any recognizable reason?"	Individuals with RLS: 231 (5.8%) RLS was associated with a higher prevalence of depressed mood (OR = 2.6 [95% CI, 1.8–3.8])	5.0
Broman et al, 2008 ⁴⁸	1,335 adults (586 men, 749 women) aged 20–59 y completing a mailed questionnaire	IRLSSG	Hospital Anxiety and Depression Scale	Infrequent RLS (symptoms less than twice a week): 173/1,335 (13%); frequent RLS (symptoms at least twice a week): 78/1,335 (6%) Frequent RLS was associated with anxiety (OR = 2.86 [95% CI, 1.65–4.98]; $P < .0001$) and depression (OR = 2.17 [95% CI, 1.07–4.37]; $P < .05$). Infrequent RLS was not associated with either disorder	5.5
Horniyak et al, 2005 ⁴⁹	Questionnaire completed by 100 consecutive patients with idiopathic RLS attending a sleep disorders unit	IRLS	BDI	Mean IRLS score: 23.6 ± 6.7 (indicating moderate-to-severe RLS) Mean BDI score: 9.3 ± 5.6. Patients scored highest on the BDI reduced sleep, loss of energy, and work difficulties items	5.5
Rothdach et al, 2000 ¹⁶	369 participants (173 women, 196 men) from a cohort of elderly individuals	IRLSSG criteria	CES-D	Individuals with RLS: 36 (9.8%) RLS was associated with a higher incidence of depression ($P = .012$) and lower self-reported mental health scores ($P = .029$)	5.5
Ulfberg et al, 2007 ¹⁷	1,000 adults aged 18–90 y assessed via telephone interviews	IRLSSG criteria IRLS	Single question: "During the past 4 weeks, how often have you felt depressed most of the day, or experienced diminished interest or pleasure in activities you usually enjoy (never, sometimes, usually, always)?" Respondents were also asked whether they were being treated with a drug for depression	Individuals with RLS: 50 (5%) Individuals with RLS were more likely to report depressed mood ($P = .01$) than those without RLS. No associations were observed between RLS and antidepressant use	6.0
Winkelmann et al, 2006 ⁵⁰	2,821 adults assessed via mailed questionnaires	Respondents were considered to have RLS symptoms if they reported leg symptoms (repeated urge to move their legs and strange and uncomfortable feelings) that occurred at least monthly, were relieved by movement, and produced sleep disruption	Zung SDS score > 50 and/or use of an antidepressant; State-Trait Anxiety Inventory Score in the top quartile and/or use of an anxiolytic medication	Frequent RLS symptoms (1–6 d/wk): 163 (6%) respondents; daily RLS symptoms: 137 (5%) respondents Individuals with daily RLS symptoms (OR = 2.17 [95% CI, 1.20–3.95]) or frequent RLS symptoms (OR = 1.8 [95% CI, 1.0–3.24]) were more likely to have depression than those without RLS. Individuals with daily RLS symptoms (OR = 3.41 [95% CI, 1.89–6.71]) or frequent RLS symptoms (OR = 2.42 [95% CI, 1.35–4.36]) were also more likely to have an anxiety disorder	6.0
Froese et al, 2008 ⁵¹	Door-to-door survey completed by 430 adults	IRLSSG criteria	PHQ-9 Use of antidepressants	Individuals with RLS symptoms: 76/430 (17.7%) RLS symptoms were associated with an increase in PHQ-9 score (OR = 1.82 [95% CI, 0.53–3.12]; $P = .006$). Use of antidepressants was not a significant predictor of RLS ($P > .18$)	6.6
Phillips et al, 2000 ¹⁵	1,803 people completing a telephone interview	Single question developed to reflect IRLSSG criteria: "Do you have unpleasant feelings in your legs—for example creepy-crawly or tingly feelings—when you lie down at night that make you feel restless and keep you from getting a good night's sleep?"	Single question: Number of days of the past 30 with mental health status considered to be "not good." Poor mental health status was defined as poor mental health on each of the past 30 days	Individuals with RLS: 170 (9.4%) Prevalence of self-reported poor mental health status was higher in individuals with RLS (40%) than in individuals without RLS (12%) (OR = 3.0 [95% CI, 2.0–4.6])	7.0

(continued)

Table 1 (continued). Studies Reporting Data for Restless Legs Syndrome (RLS) and Depression and Anxiety Disorders in Adults

Study	Patients	Assessment of RLS	Assessment of Depression, Mood, and Anxiety	Results	Study Rating ^a
Wesstrom et al, 2008 ⁵²	Mailed questionnaire completed by 3,516 women aged 18–64 y	IRLSSG criteria	Yes/no question regarding depression	Women with RLS: 551/3,516 (15.7%) RLS sufferers more commonly suffered from depression (adjusted OR = 2.09 [95% CI, 1.53–2.85])	7.0
Agüera-Ortiz et al, 2011 ²⁵	Cross-sectional study of 99 nondemented psychiatric outpatients	“Definite” RLS: Patient fulfilled the IRLSSG criteria and at least 1 supportive criterion. “Possible” RLS: Patient fulfilled the IRLSSG criteria, but the examiner had doubts regarding the reliability of the information provided (eg, due to a psychiatric condition)	DSM-IV criteria, clinical psychiatric interview, and neurologic examination	“Definite” RLS: 11 patients (11.11%); “possible” RLS: 10 patients (10.10%); no RLS: 78 patients (78.8%) Psychiatric diagnoses among patients with definite RLS vs possible RLS vs no RLS—MDD: 63.6% vs 0% vs 35.9%; bipolar disorder: 18.2% vs 0% vs 19.2%; psychosis: 0% vs 10.0% vs 11.5%; minor depression: 9.1% vs 40.0% vs 9.0%; anxiety/neurosis: 0% vs 0% vs 20.5%; adjustment disorder: 9.1% vs 50.0% vs 3.8% “Definite” RLS was associated with MDD, and “possible” RLS was associated with adjustment disorder and minor depression. No clear differences/patterns in terms of psychiatric drug use were observed between the 3 groups of patients	8.0
Phillips et al, 2006 ³³	1,506 adults (731 men, 775 women) assessed via telephone interviews	Two questions based on IRLSSG criteria. Individuals who reported unpleasant feelings in their legs on at least a few nights a week, which were worse at night, were considered to be “at risk for RLS”	Respondents were asked whether they had ever been told by a doctor that they had an anxiety disorder or depression	Individuals at risk for RLS: 9.7% Depression and anxiety were both associated with RLS symptoms ($P < .05$ for each)	8.0
Sukegawa et al, 2003 ³⁴	2,023 elderly people (1,008 men, 1,015 women) completing a questionnaire	IRLSSG criteria. Individuals fulfilling 2 or more criteria were considered to have “probable RLS”	GDS	Individuals with depression: 634 (31%) Among men aged 65–74 y, the incidence of RLS was higher among those with depression (8.4%) than those who were not depressed (1.8%) (adjusted OR = 3.6 [95% CI, 1.2–10.6]; $P < .05$). No association between RLS and depression was observed among men aged ≥ 85 y or among women in either age group	9.0
Celle et al, 2010 ³⁵	318 elderly individuals (219 women, 99 men)	IRLS	MMSE, Brief Self-Evaluation Questionnaire for Depressive, Asthenic, and Anxious Dimensions (QD2A), French version of the Goldberg scale.	Individuals with RLS: (24.2%) Participants with RLS reported greater hypnotic ($P < .001$) and antidepressant medication intake ($P < .001$) and had higher anxiety ($P < .001$) and depression ($P < .001$) scores	9.5
Case-control studies					
Wagner et al, 2004 ³⁶	Prospective study of sequential adult patients with RLS (n = 62) or insomnia (n = 32) attending a hospital and controls (n = 77)	IRLSSG criteria, IRLS	DSM-IV ADHD criteria, Brown Attention Deficit Disorder Scale for adults, structured psychological interview	ADHD symptoms: adults with RLS, 26%; adults with insomnia, 6%; controls, 5% ($P < .01$) Mean Brown Attention Deficit Disorder Scale score: patients with RLS, 37 ± 28 ; patients with insomnia, 24 ± 18 ; controls, 21 ± 18	5.5
Banno et al, 2000 ³³	Retrospective review of diagnoses made 5 y prior to sleep laboratory evaluation of 218 patients with RLS and 872 matched controls from the general population	International Classification of Sleep Disorders criteria for RLS	Prior diagnosis by physician based on ICD-9-CM	Diagnosis of mood disorder (depression or affective psychosis): men, 43.7% of RLS patients vs 10.4% of controls ($P < .05$); women, 46.1% of RLS patients vs 22.8% of controls ($P < .05$)	6.0

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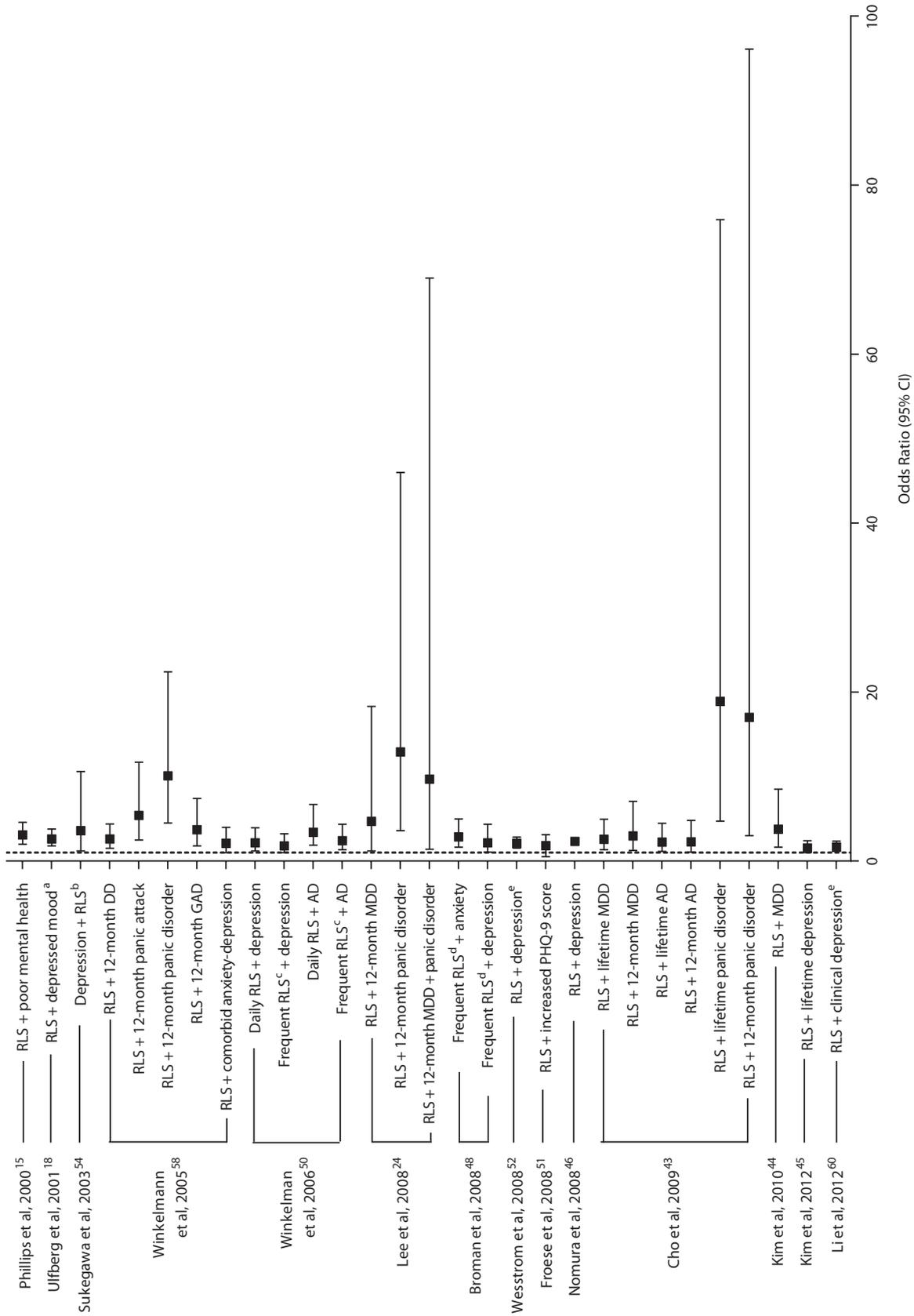
Table 1 (continued). Studies Reporting Data for Restless Legs Syndrome (RLS) and Depression and Anxiety Disorders in Adults

Study	Patients	Assessment of RLS	Assessment of Depression, Mood, and Anxiety	Results	Study Rating ^a
Saletu et al, 2002 ⁵⁷	Clinical and neurophysiologic study of 33 patients with RLS, 26 patients with PLMD, and age- and sex-matched controls	IRLSSG criteria	Zung SDS and SAS	Mean SDS scores (RLS patients vs controls): 39.9 ± 8.5 vs 29.6 ± 4.6 ($P < .001$) Mean SAS scores (RLS patients vs controls): 36.8 ± 8.4 vs 26.9 ± 3.8 ($P < .001$) EEG mapping demonstrated findings characteristic of major depression in RLS patients and of generalized anxiety disorder in PLMD patients	7.0
Winkelmann et al, 2005 ⁵⁸	Telephone interview of 130 patients with RLS attending a movement disorders clinic and 2,265 controls with somatic morbidity	Unspecified	Munich-CIDI for DSM-IV	Patients with RLS reported higher 12-month rates of depressive disorder (OR = 2.6 [95% CI, 1.5–4.4]), panic attacks (adjusted OR = 5.4 [95% CI, 2.5–11.7]), panic disorder (adjusted OR = 10.1 [95% CI, 4.5–22.4]), and generalized anxiety disorder (OR = 3.7 [95% CI, 1.8–7.4]). RLS was also associated with comorbid anxiety and depression (OR = 2.1 [95% CI, 1.0–4.0])	7.0
Brown et al, 2005 ⁵⁹	Retrospective chart review of 200 patients attending a sleep disorders center with a chief complaint of insomnia	Diagnosis recorded on patient chart (based on IRLSSG criteria)	Diagnoses of depression and use of antidepressants recorded on patient chart	Diagnosis of depression: 112 patients (56%) Use of antidepressant medication: 76 patients (38%) Diagnosis of RLS: 90 patients (45%) RLS was not associated with the use of antidepressants in general (χ^2 analysis, $P = .95$) or with the use of any specific class of antidepressant (SSRI: $P = .94$; TCA, $P = .24$; other, $P = .21$) ORs for RLS and antidepressant use—any antidepressant: 0.98 (95% CI, 0.55–1.74); SSRI: 0.97 (0.47, 2.01); TCA: 0.74 (0.70–4.43); "other": 0.62 (0.28–1.31)	8.0
Prospective study	Observational study of 56,399 women with no history of depression, depressive symptoms, or antidepressant use	Self-reported diagnosis of RLS by a physician	Patients were considered to be clinically depressed if they reported physician-diagnosed depression and the use of antidepressant medication. 10-item CES-D, 15-item GDS	Women with RLS at baseline: 928/56,339 (1.6%) RLS was associated with a higher age-adjusted relative risk of clinical depression (1.66 [95% CI, 1.18–2.35]) and a higher risk of developing clinically relevant depressive symptoms as assessed by CES-D and GDS scores (1.53 [1.33–1.76])	6.5

^aStudies rated from 3 (high quality) to 12 (low quality).

Abbreviations: ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression scale; CIDI = Composite International Diagnostic Interview; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; EEG = electroencephalography; GDS = Geriatric Depression Scale; ICD-9 CM = *International Classification of Diseases, Ninth Edition, Clinical Modification*; IRLS = International Restless Legs Syndrome Study Group Rating Scale; IRLSSG = International Restless Legs Syndrome Study Group; MDD = major depressive disorder; MMSE = Mini-Mental State Examination; NIH = National Institutes of Health; OR = odds ratio; PHQ-9 = Patient Health Questionnaire-9; PLMD = periodic limb movement disorder; SAS = Self-Rating Anxiety Scale; SDS = Self-Rating Depression Scale; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Figure 1. Odds Ratios for the Associations Between Restless Legs Syndrome (RLS) and Mood Disorders in Adults



^aMen aged 18–64 years. ^bMen aged 65–74 years. ^cRLS symptoms 1–6 days per week. ^dRLS symptoms at least twice per week. ^eWomen. Abbreviations: AD = anxiety disorder; DD = depressive disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9.

stronger among those with daily RLS symptoms than among those whose RLS symptoms occurred between 1 and 6 times per week. Similarly, a Swedish questionnaire study⁴⁸ reported associations between RLS and anxiety and depression in individuals whose RLS symptoms occurred at least twice a week; no such associations were observed among individuals with infrequent symptoms (occurring less than twice a week). A Turkish study⁴⁷ showed a correlation between the severity of RLS (as assessed by the International Restless Legs Syndrome Study Group Rating Scale [IRLS]) and the severity of anxiety and depression symptoms. As severity and frequency of RLS symptoms generally increase over time, further studies are needed to determine whether progression of RLS is associated with an increasing risk of developing depression and mood disorders.

Gender differences have been reported in the prevalence of depression among patients with RLS. In 2 studies,^{16,54} an increased risk of depression was observed only in male patients; female patients did not show an elevated depression risk (Table 1). In the Memory and Morbidity in Augsburg Elderly (MEMO) study, high scores on the Center for Epidemiologic Studies Depression scale (CES-D) were associated with RLS in men (OR = 13.06 [95% CI, 2.32–73.26]), but no such association was observed in women (OR = 0.90 [95% CI, 0.24–3.34]).¹⁶ In a study of elderly Japanese patients, RLS was associated with depression in men aged 65–74 years.⁵⁴ However, no associations were observed among men aged ≥ 75 years or among women in either age group. Other studies, however, have shown stronger associations between depression and RLS in women (Table 1). In a Swedish study,⁵² women with RLS ($n = 551$) were more likely to suffer from depression than individuals without the disorder ($n = 2,950$) (adjusted OR = 2.09 [95% CI, 1.53–2.85]). A very large prospective study⁶⁰ followed 56,399 women over a 6-year period. At baseline, the women were free from depressive symptoms, and 928 reported a diagnosis of RLS. The presence of RLS at baseline was associated with a higher risk of developing clinical depression (multivariate adjusted relative risk [RR]: 1.5 [95% CI, 1.1–2.1]; $P = .02$) and clinically relevant depressive symptoms as assessed by the 10-item CES-D and the 15-item Geriatric Depression Scale. The authors also performed a meta-analysis including data from 19 case-control and cross-sectional studies; the pooled odds ratio for developing clinical depression and/or depressive symptoms was 2.25 (95% CI, 1.94–2.60) (P for heterogeneity = .02) for women with RLS in comparison to women without the disorder. Thus, the results from these 2 studies indicate that the presence of RLS in women and in men may contribute to an increased risk of developing depression.

RLS, SLEEP DISTURBANCES, AND MOOD DISORDERS

Sleep disruption is thought to be a risk factor for both panic disorder and depression^{58,61}; therefore, sleep disturbances and impaired quality of life due to RLS are likely to play a role in the development of these disorders. The results of a

controlled study have suggested that, in most cases, RLS occurs as the primary condition (Table 1).⁵⁸ The majority of patients with major depression (76.7%), dysthymia (83.3%), generalized anxiety disorder (63.6%), and panic disorder (60%) reported that the onset of their RLS symptoms preceded that of the psychiatric disorder. In comparison to patients with somatic morbidities, patients with RLS were more likely to consider sleep disturbances (47.8% vs 5.4%, OR = 12.7 [95% CI, 4.0–40.7]), depressed mood (43.5% vs 3.1%, OR = 24.9 [95% CI, 7.5–82.3]), reduced interest (34.8% vs 2.8%, OR = 19.7 [95% CI, 5.2–74.2]), and suicidal thoughts (34.8% vs 2.6%, OR = 24.1 [95% CI, 6.4–90.5]) as being entirely due to their underlying medical condition.

Epidemiologic data have suggested that RLS may be more strongly associated with sleep-related physical features of depression (eg, reduced sleep, loss of energy) than with nonsomatic depressive symptoms. In a questionnaire study,⁴⁹ untreated patients with RLS generally scored higher on the Beck Depression Inventory (BDI) items related to sleep, such as reduced sleep, fatigue, and irritability, than on items related to cognitive symptoms, such as feelings of failure, guilt, and self-reproach. In addition, comparable levels of depressive symptoms unrelated to sleep impairment such as depressed mood, anhedonia, and guilt have been seen in individuals with and without RLS.²⁴ However, the association between RLS and depression and anxiety disorders cannot be fully explained on the basis of sleep disruption. In a female-only prospective study,⁶⁰ the association between RLS and depression (multivariate-adjusted RR: 1.51 [95% CI, 1.07–2.14]; $P = .02$) was only slightly weaker after adjusting for sleep duration and persistent snoring (multivariate-adjusted RR: 1.49 [95% CI, 1.06–2.10]; $P = .02$). Similarly, in a cross-sectional study⁶² of patients with chronic kidney disease, the association between RLS symptoms and depression (OR = 3.96 [95% CI, 2.12–7.1], $P < .001$) remained significant after adjusting for insomnia (OR = 2.9 [95% CI, 1.55–5.43]; $P < .001$), suggesting that this association may be independent of the sleep disorder.

THEORETICAL PATHOPHYSIOLOGIC PATHWAYS OF RLS AND MOOD DISORDERS

RLS and mood disorders, in particular depression, may have similar neurobiological pathways. The results of a neurophysiologic study add support to the association between RLS and depression.⁵⁷ Daytime electroencephalography (EEG) mapping demonstrated significant differences in electrophysiologic brain function in 33 patients with RLS in comparison to age- and sex-matched controls. The greatest differences between patients with RLS and controls were seen in EEG measures that have shown the highest correlation with the Hamilton Depression Rating Scale (HDRS) score in depressed patients: alpha and delta power, dominant frequency, and the relationship of different EEG bands across the hemispheres. These findings suggest dissociated vigilance in patients with RLS, similar to the changes described in major depression.

Although the neurobiological pathways involved in RLS have not yet been established, the effect of dopamine agonists on RLS symptom alleviation suggests that dopaminergic dysfunction may be involved.^{13,63-65} A dopaminergic deficiency has also been implicated in the pathophysiology of depression.⁶⁶⁻⁶⁸ Dopamine-containing circuits in the central nervous system are thought to be involved in the regulation of motivation, concentration, and the ability to experience pleasure, all 3 of which are impaired in patients with depression.⁶⁹ Several dopamine receptor agonists such as pramipexole and bromocriptine have been shown to be effective in reducing depressive symptoms in otherwise healthy patients.^{66,70-72} Antidepressant effects of dopamine agonists may be related to their receptor binding profiles. Positron emission tomography has shown that pramipexole binds to D₂/D₃ receptors in extrastriatal dopaminergic regions in the human brain, including the mesolimbic dopamine system, which is involved in mood and behavior.⁷³ The antidepressant effect of pramipexole may be related to its activation of the D₂ receptor subfamily, particularly D₃ receptors, which have been implicated in the pathogenesis of depression due to their pharmacology and distribution in the brain.⁷³

The potential role of dopaminergic dysfunction in the pathogenesis of depression is supported by the high prevalence of depressive symptoms among patients with Parkinson's disease, as this disorder is associated with loss of nigrostriatal dopaminergic neurons.⁶⁹ Improvements in depressive symptoms have been observed in patients with Parkinson's disease receiving dopamine agonists.⁷⁴ Two double-blind studies^{75,76} evaluated the effects of pramipexole in patients with Parkinson's disease without motor complications. In a 14-week double-blind trial comparing the antidepressant effects of pramipexole to the SSRI sertraline, both pramipexole (n = 67) and sertraline (n = 34) improved depressive symptoms as measured by the HDRS total score (-10.76 ± 5.74 for pramipexole vs -9.03 ± 7.28 for sertraline; $P = .055$).⁷⁵ In a 12-week, placebo-controlled trial, pramipexole (n = 139) reduced depressive symptoms as measured by the BDI (treatment difference vs placebo [n = 148]: -1.9 [95% CI, -3.4 to -0.5]; $P = .01$) and Geriatric Depression Scale (-0.8 [95% CI, -1.5 to -0.1]; $P = .035$).⁷⁶ Further analysis revealed that 80% of the total treatment effect could be accounted for by the direct antidepressant effect of pramipexole, with the remaining 20% mediated through alleviation of motor symptoms.⁷⁶ These results suggest that the antidepressant effects of pramipexole in Parkinson's disease are not simply the result of a treatment-mediated improvement in motor symptoms.

Dopamine dysregulation cannot fully explain the relationship between RLS and depression. Improvements in depressive symptoms have been seen in some patients with RLS receiving dopamine agonists, but not in others. In a placebo-controlled crossover trial,⁷⁷ a significant improvement in mean Zung Self-Rating Depression Scale scores was observed in 11 patients with RLS following 4 weeks of therapy with the dopamine agonist pramipexole (pretreatment: 45.6 ± 11.7 ;

posttreatment: 37.0 ± 11.6 ; $P = .006$). However, a similar study⁷⁸ in 18 patients with RLS receiving levodopa showed no difference between pretreatment and posttreatment Zung Self-Rating Depression Scale scores following 4 weeks of therapy. In a larger-scale 12-week double-blind study⁷⁹ of patients with moderate-to-severe idiopathic RLS and at least mild depressive symptoms, Montgomery-Asberg Depression Rating Scale (adjusted mean treatment difference: -3.6 [95% CI, -5.6 to -1.6]; $P < .001$), HDRS (adjusted mean treatment difference: -2.7 [95% CI, -4.4 , -1.1]; $P < .001$), and BDI-II (adjusted mean treatment difference: -2.6 [95% CI, -4.6 , -0.7]; $P = .009$) scores all improved with ropinirole (n = 171) vs placebo (n = 60). More research is needed to elucidate fully the potential role of dopamine and dopaminergic therapy in the relationship between RLS and mood disorders.

RLS AND MOOD DISORDERS IN CHILDREN

Many adults with RLS report that their symptoms began during childhood or adolescence, with around 25% reporting symptom onset between the ages of 10 and 20 years.⁸⁰ Children with RLS may exhibit mood and behavioral problems such as inattentiveness, daytime somnolence, hyperactivity, and aggression, which are often attributed to disrupted sleep.⁸¹ The IRLSSG criteria have been adjusted for the diagnosis of pediatric RLS, to account for possible difficulties children may have in describing their symptoms.⁶ Diagnosis may be complicated by the presence of comorbid mood and anxiety disorders. In a study that examined psychiatric disorders among 347 children with RLS, 64% were found to have 1 or more psychiatric comorbidities.⁸² Common comorbidities included mood disturbances (29.1%), attention-deficit/hyperactivity disorder (ADHD) (25%), anxiety disorders (11.5%), and behavioral disturbances (10.9%). Girls with RLS were more likely to experience mood disturbances (OR = 1.6) and anxiety disorders (OR = 1.26), whereas ADHD and disruptive behavior disorders were more common in boys (OR = 1.94).

Evidence for the possible association between childhood RLS and ADHD has been provided by several clinical and epidemiologic studies (Table 2). Lack of sleep can lead to inattentiveness and hyperactivity in children⁸⁹; however, adults with RLS have been reported to have higher Brown Attention Deficit Disorder Scale scores than adults with insomnia, suggesting that the association between RLS and ADHD is not purely due to sleep disruption.⁵⁶ There may be a pathophysiologic link between the 2 disorders; deficits in both dopamine and iron have been associated with ADHD,⁸⁹ and dopamine agonists may be beneficial in reducing ADHD symptoms in patients with RLS.^{56,90,91} ADHD and RLS may share some genetic components, and a positive family history is a feature of both disorders. The results of a large-scale cross-sectional study (N = 65,554) indicated that mothers of children with ADHD have an increased risk of having RLS (multivariate adjusted OR = 1.27 [95% CI, 1.15-1.41]; $P < .0001$); these results suggest that an association between the 2 disorders may exist across generations.⁹² Among the parents of children with ADHD, the presence of RLS may

Table 2. Studies Reporting Data for Restless Legs Syndrome (RLS) and Mood Disorders in Children

Study	Patients	Assessment of RLS	Assessment of Mood Disorders	Results	Study Rating ^a
Cross-sectional studies					
Chervin et al, 1997 ⁸³	Questionnaire completed by parents of 70 children attending a child psychiatry clinic and 73 children attending a general pediatric clinic	Pediatric Sleep Questionnaire	DSM-IV-derived inattention/hyperactivity scale	RLS was present in 15% (4/27) of children with ADHD, 5% (2/43) of children with non-ADHD psychiatric disorders, and 10% (7/73) of general pediatric patients	7
Pullen et al, 2011 ⁸²	Review of medical records of 374 patients with RLS	Findings consistent with the 2003 NIH workshop diagnostic criteria for probable or definite RLS	DSM-IV diagnostic criteria	Any psychiatric disorder: 239/374 patients (64%); ADHD: 94/374 patients (25%); mood disturbances: 109/374 patients (29%); anxiety disorders: 43/374 patients (12%); behavioral disturbances: 40/374 patients (11%)	7
Picchiotti and Stevens, 2008 ⁸⁴	Retrospective assessment of 50 patients with RLS attending a pediatric sleep/neurology practice	Diagnostic criteria for pediatric RLS	DSM-IV diagnostic criteria	18 children and adolescents met the study criteria Comorbidities: parasomnia (7), ADHD (13), oppositional defiant disorder (4), anxiety disorders (6), depression (5)	8
Chervin et al, 2002 ⁸⁵	Questionnaire completed by parents of 866 children attending clinic appointments	Pediatric Sleep Questionnaire (RLS item)	DSM-IV-derived inattention/hyperactivity scale, Conners' Parent Rating Scale hyperactivity index	High hyperactivity scores were found in 18% of children with RLS and 11% of children without RLS ($P < .05$)	9
Kotagal and Silber, 2004 ⁸⁶	538 children examined in a pediatric sleep disorders clinic	IRLSSG criteria for childhood RLS	Unspecified, data for "inattentiveness" were recorded	Children with RLS: 32/538 (5.9%) Among children with RLS, 25% (8/32) showed "inattentiveness," and 72% (23/32) had a family history of RLS. Mothers of children with RLS were more likely to suffer from the disorder (17/23 cases) than fathers (6/23 cases) ($P = .02$)	9
Picchiotti et al, 2007 ⁸⁷	Survey completed by parents of 10,523 children (8- to 11-year-olds) and adolescents (12- to 17-year-olds)	IRLSSG criteria for "definite" and "probable" childhood RLS	Question regarding medical history (prior diagnoses)	Definite RLS: children, 1.9%; adolescents, 2.0% Common diagnoses among individuals with definite RLS: Growing pains: children, 29.6%; adolescents, 36.8% ADD/ADHD: children, 14.8%; adolescents, 17.6% Depression: children, 3.7%; adolescents, 14.4% RLS: children, 9.9%; adolescents, 12% Anxiety disorders: children, 4.9%; adolescents, 8%	10
Case-control study					
Picchiotti et al, 1998 ⁸⁸	69 children with ADHD and 38 controls referred to a sleep laboratory	Version of the IRLSSG criteria modified for children, 5 or more PLMS per hour of sleep	DSM-III-R criteria	PLMS: 18/69 children with ADHD (26%); 2/38 controls (5%) RLS symptoms: 8/18 (26%) children with ADHD and ≥ 5 PLMS per hour of sleep; 1/2 control patients with ≥ 5 PLMS per hour of sleep	9

^aStudies rated from 3 (high quality) to 12 (low quality).

Abbreviations: ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; IRLSSG = International Restless Legs Syndrome Study Group; NIH = National Institutes of Health; PLMS = periodic limb movements during sleep; RLS = restless legs syndrome.

indicate an increased vulnerability to psychiatric disorders such as ADHD and anxiety disorders.⁹³ There is also the possibility that children with RLS may be misdiagnosed with ADHD, as their leg discomfort may lead to hyperactivity, restlessness, and difficulty concentrating.^{88,89} As is the case with RLS, the symptoms of childhood-onset ADHD may persist into adulthood. In a prospective study, a higher prevalence of ADHD symptoms was observed among adult patients with RLS (26%) than among patients with insomnia (6%) or controls (5%).⁵⁶

RLS AND ANTIDEPRESSANTS

Anecdotal evidence and case reports have suggested a possible association between RLS and the use of antidepressants.^{59,80} Given the purported involvement of dopamine deficiency in the etiology of RLS, it is logical to presume that medications that decrease or modify the availability of dopamine may lead to or exacerbate RLS symptomatology. Elevated PLMS indexes have been observed in patients receiving the SNRI venlafaxine and the SSRIs citalopram, fluoxetine, paroxetine, and sertraline.³⁰ The effects of these medications on PLMS may be the result of serotonergically mediated dopamine inhibition.³⁰ The results of a large cross-sectional study⁹⁴ indicated that the use of SSRIs (OR = 3.11 [95% CI, 1.66–5.79]; $P < .001$) is more prevalent in those with questionnaire-defined symptoms of RLS. No significant associations were observed between RLS and the use of tricyclic antidepressants (TCAs) (OR = 0.56 [95% CI, 0.22–1.45]) or “other” types of antidepressants (OR = 0.70 [95% CI, 0.17–2.98]). Patients taking hypnotics were at greater risk of periodic limb movement disorder (OR = 2.35 [95% CI, 1.68–3.27]; $P < .001$) but were not significantly more likely to have RLS (OR = 1.17 [95% CI, 0.89–1.55]). In an observational study⁹⁵ of 271 patients with depression receiving antidepressants for the first time, 9% experienced the appearance or worsening of RLS symptoms. The frequency of drug-induced RLS varied between the antidepressants. RLS was particularly common with mirtazapine (28%), occurred occasionally (frequency of 2%–10%) with the SSRIs (paroxetine, sertraline, escitalopram, fluoxetine, and citalopram) and SNRIs (venlafaxine and duloxetine), and did not occur with the norepinephrine reuptake inhibitor reboxetine.

Other studies have not shown a link between RLS and antidepressants. A retrospective chart review in patients with sleep disorders found no significant associations between RLS and use of antidepressants in general (OR = 0.98 [95% CI, 0.55–1.74]) or between RLS and the use of any specific class of antidepressant (SSRI: OR = 0.97 [95% CI, 0.47–2.01]; TCA: 0.74 [95% CI, 0.70–4.43]; “other”: OR = 0.62 [95% CI, 0.28–1.31]) (Table 2).⁵⁹ In a study of 243 patients with affective and anxiety disorders, antidepressants and neuroleptics were not shown to be a major risk factor for RLS; nonopioid analgesics did appear to increase the risk.⁹⁶ A case-control study²⁴ indicated that the use of SSRIs and TCAs was not an independent predictor of RLS (adjusted OR = 0.5 [95% CI, 0.2–1.2]; $P = \text{NS}$) (Table 1). Further studies

are needed to examine fully the relationship between RLS and antidepressants.

PHARMACOLOGIC TREATMENT FOR RLS

In milder cases, RLS symptoms may be improved by changes in lifestyle. Improvements in sleep hygiene and the avoidance of caffeine and excessive alcohol can be beneficial.⁹⁷ Patients may find that activities such as a pre-bedtime hot bath, massage, moderate exercise, and stretching can help to relieve their symptoms.⁹⁷ These measures may not be sufficient for patients with moderate-to-severe symptoms, for whom pharmacologic treatment may be indicated.⁹⁸

Dopamine agonists are the agent of choice for the signs and symptoms of RLS.^{37,99} Three non-ergot dopaminergic agonists, ropinirole (0.25–4 mg/d), pramipexole (0.125–0.75 mg/d), and rotigotine transdermal patch (1–3 mg/24 hours), are approved by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe primary RLS.¹⁰⁰ Ropinirole and pramipexole are oral medications administered 2 hours prior to symptom onset. Rotigotine is administered via a patch on the skin. Potential side effects of the dopamine agonists include nausea, vomiting, headaches, insomnia, and somnolence.^{22,99} In randomized, double-blind, placebo-controlled clinical trials, administration of ropinirole,^{101,102} pramipexole,^{103–105} and rotigotine^{106,107} has resulted in significant improvements in RLS symptoms, which are typically measured using the IRLS and the Clinical Global Impressions scale (CGI). The IRLS measures changes in RLS symptom severity (ie, no symptoms to very severe symptoms),¹⁰⁸ whereas the CGI measures changes in disease status (ie, not ill at all to extremely ill). In addition, all of these agents have reported response rates (generally determined by a > 50% increase in CGI score) ranging from 46% to 60% in treated patients.^{101–107} It should be noted, however, that response rates for placebo in clinical trials with dopamine agonists for RLS have been as high as 43%.^{101–107}

The anticonvulsant gabapentin enacarbil (600 mg/d) is also approved for moderate-to-severe primary RLS and should be considered for patients with RLS-related pain or painful comorbid conditions.¹⁰⁰ Orally administered at 5:00 PM with a light snack, gabapentin enacarbil has been shown to significantly improve IRLS and CGI scores in randomized clinical trials. Over 77% of patients randomized to gabapentin enacarbil responded to treatment; 45% of patients receiving placebo also responded.¹⁰⁹ Common adverse events included somnolence and dizziness.⁹⁸ Patients should be closely monitored for any indication of suicidal thoughts or depression. In addition to the approved RLS therapies, levodopa/carbidopa (25–100 mg) is commonly used off-label.

The main limitation of dopaminergic therapy is the long-term side effect of augmentation, defined as a treatment-emergent worsening of RLS symptoms. Among 266 patients with RLS receiving dopaminergic treatment over an average of 2.7 ± 2.4 years, 54 (20%) reported definite or highly suggestive clinical indicators of augmentation.¹¹⁰ Augmentation rates with different drugs cannot be directly compared, as the

available studies differ in terms of their duration and the methodology used to assess augmentation. However, the risk of developing augmentation does appear to be far lower with dopamine agonists than with levodopa. In 6-month studies that used established diagnostic criteria,^{6,111} incidences of augmentation were 60% with levodopa,¹¹² 9.2% with pramipexole (placebo: 6%),¹⁰⁴ 3.5% with ropinirole (placebo: <1%),¹¹³ and 1.5% with rotigotine (placebo: 0.5%).¹¹⁴ Augmentation has not been reported in clinical studies of gabapentin enacarbil, which has no dopaminergic activity.⁹⁸

The potential complication of augmentation should be considered and monitored in all patients with RLS who are receiving dopaminergic medications, particularly those who are taking doses at or above the FDA-approved limits. Ferritin levels should be assessed, as low ferritin may represent a potential biomarker of augmentation.¹¹⁵ Characteristic features of augmentation are an earlier onset of symptoms during the day, more rapid onset of symptoms when at rest, an increase in symptom intensity, a shorter period of relief following administration of medication, and the spread of symptoms to previously unaffected parts of the body.¹¹¹ Augmentation can be distinguished from tolerance and from the natural course of disease progression, as it involves an initial response to dopaminergic therapy and then a paradoxical response (increase of symptoms with increasing dosages/decrease of symptoms with lower dosages) with a worsening of symptoms beyond baseline levels.¹¹¹ Augmentation may be addressed by switching the patient to a longer-acting dopamine agonist or by reducing or stopping agonist therapy^{113,116}; symptom worsening due to disease progression or tolerance would not respond similarly to a reduction in dosage.¹¹¹ It is sometimes necessary to change to an entirely different class of medication such as alpha 2-delta compounds, benzodiazepines, or opioids.

As previously mentioned, dopaminergic treatment may have beneficial effects on comorbid mood disorders in addition to improving symptoms of RLS.⁸⁰ While treatment of the underlying RLS may improve mood in patients with mild mood disorders, those with more severe symptoms may require an antidepressant.⁸⁰ The choice of antidepressant should be carefully considered, as SSRIs and SNRIs may exacerbate RLS symptoms. Atypical antidepressants such as bupropion,^{30,117,118} trazodone,¹¹⁹ and nefazodone¹²⁰ do not appear to exacerbate PLMS and may be suitable therapies. Other drugs that may worsen or induce RLS symptoms include the atypical antipsychotics quetiapine,¹²¹⁻¹²³ risperidone,¹²⁴ and olanzapine.¹²⁵⁻¹²⁷ There are case reports of improvement of RLS symptoms in patients taking the atypical antipsychotic aripiprazole, which has partial agonist and antagonist properties.¹²⁸⁻¹³⁰ At present, there is no literature on RLS and electroconvulsive therapy for depression.

PRACTICAL POINTS FOR THE DIAGNOSIS AND TREATMENT OF RLS

Some practical points regarding the diagnosis and treatment of RLS are worth considering. First, it is important to establish whether the symptoms of RLS are of an idiopathic

nature or triggered by an underlying cause. As discussed, potential secondary causes include iron deficiency, pregnancy, and end-stage renal failure with dialysis.³⁷ Iron deficiency can be addressed with iron supplementation in both patients with anemia and those receiving dialysis.¹³¹ In women who develop RLS during pregnancy, RLS symptoms may resolve within the first postpartum weeks.³⁷ Since patients with mood disorders, including depression, may be prescribed agents that may affect central dopamine activity, it is important to recognize that these drugs are potential triggers of RLS symptoms. Exacerbating agents include dopamine antagonists (including antiemetics), centrally active antihistamines, and many antidepressants (except bupropion).³⁷

Diagnosis of RLS can be achieved following the 5 criteria described by the IRLSSG.³⁵ One of the key diagnostic factors of RLS is that the urge to move the legs due to the uncomfortable sensations has a very definite circadian rhythmicity. There are conditions that mimic and may fulfill some of the diagnostic criteria for RLS, such as akathisia and peripheral neuropathy; however, these syndromes lack the circadian rhythmicity that defines RLS.³⁶ Sleep disruption is a major complaint of patients with RLS.^{32,49} Therefore, patients reporting sleep disturbances also should be evaluated for the presence of RLS.

The symptoms of RLS are chronic and progressively worsen over time in a majority of patients; therefore, long-term pharmacologic treatment of symptoms is quite likely necessary. In more mild or moderate cases of RLS, symptoms may be alleviated by eliminating alcohol or caffeine later in the day or into the early evening, practicing good sleep hygiene, and considering brief activity before bedtime.³⁷ The decision to pharmacologically treat RLS is based on the frequency and severity of symptoms and the extent to which these symptoms negatively affect the patient's sleep, quality of life, and overall daytime and social functioning.³⁷ In many cases, a suspicion of RLS can be confirmed by a positive response to a trial course of dopaminergic therapy.⁶ Dopamine agonists are thought to be the first-line pharmacologic therapy for symptoms of RLS.⁶⁵ Treatment complications, such as augmentation, can develop with dopaminergic agonists over time. Other medications, including the alpha 2-delta compounds, benzodiazepines, sleep-promoting compounds, and opioids, can be added to the pharmacologic regimen if sleep problems persist, if the response to dopamine agonists begins to wane, if the disease progresses to more severe levels, or if augmentation develops.

CONCLUSIONS

As RLS and mood disorders are frequently comorbid, RLS may present in the psychiatry practice. RLS is a sensorimotor neurologic disorder with a significant impact on sleep and quality of life. Sleep disruption due to RLS symptoms may have a negative impact on mood and may contribute to higher rates of depression and anxiety disorders in RLS patients. In addition, RLS, depression, and mood disorders may share similar pathophysiologic networks in the central nervous

system. Dopaminergic dysfunction has been implicated in the pathophysiology of both RLS and depression. Recognition of comorbid RLS is particularly important in patients with psychiatric disorders, as many commonly used antidepressants and atypical antipsychotics may exacerbate the sensory symptoms of RLS, worsening sleep disruption and the underlying psychiatric disorder. Dopamine agonists are generally effective in improving RLS symptoms and may have a beneficial effect on comorbid mood disorders. Given the likely associations between RLS and mood disorders, clinicians should consider the potential presence of RLS in patients who are prescribed medications that may alter dopaminergic neurotransmission, who complain of sleep disturbances (especially in the first half of the night), or who have psychiatric comorbidities that may be related to RLS.

Drug names: aripiprazole (Abilify), bromocriptine (Parlodel, Cycloset, and others), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), gabapentin enacarbil (Horizant), levodopa and carbidopa (Sinemet CR, Parcopa, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex and others), quetiapine (Seroquel), risperidone (Risperdal and others), ropinirole (Requip and others), rotigotine (Neupro), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

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