Mental Health Disorders Associated with RLS

2

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In the middle of the nineteenth century, Wittmaack reported on the co-occurrence of restless legs and psychiatric symptoms including depression and anxiety, coining the term *anxietas tibiarum* to describe this clinical co-occurrence [1]. Because the pathophysiology of restless leg syndrome (RLS) was not understood at the time and RLS was commonly comorbid with depression and anxiety, he considered that it may be a form of hysteria or neurasthenia [2]. Since its early descriptions, RLS has often been limited to reports in neurology, though the co-occurrence of mood symptoms was not entirely overlooked [3]. Early psychiatrists rarely appreciated the significance of RLS in mental health treatment prior to the twenty-first century. It is notable that the Swedish neurologist Karl Ekbom is credited with having described the psychiatric condition delusional parasitosis in 1937 [4] and subsequently RLS in 1945 [5].

Epidemiological studies among patients with RLS have revealed high rates of psychiatric comorbidity. The odds of a patient with RLS having clinically significant depression or anxiety are two to five times that of the general population [6]. Despite the fact that descriptions of RLS have identified co-occurring depression, anxiety, and somatic distress date back to the nineteenth century, only in 2013 was RLS defined as an independent psychiatric diagnosis in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [7]. Previously, RLS had been subsumed under Dyssomnia Not Otherwise Specified. Several reasons underlie the need to conceptualize RLS a unique clinical diagnosis. Most pressing among these is the prevalence and suffering associated with syndromal

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RLS in the population [8, 9]. Specifically, RLS symptoms are often encountered in patients with mental illness and in patients taking psychotropic medications. Implicit in recognizing RLS as an independent diagnosis is that RLS demands clinical attention including screening, clinical and laboratory evaluation, physical examination, and treatment. One anticipates that adding RLS to DSM-5 will encourage enhanced awareness of this condition, particularly among psychiatric populations but also in primary care settings.

In this chapter, we explore the ways in which RLS and mental health interface. We begin by reviewing psychiatric conditions in which RLS is often comorbid. After reviewing the epidemiological data for these conditions, we consider the potential for bidirectional effects between RLS and these conditions it frequently accompanies. Next, we discuss the relationship between RLS and psychopharmacology. Several classes of psychotropic medications are known to influence RLS or induce RLS-like symptoms such as akathisia. Finally, because the agents used to treat RLS have psychotropic effects, we review of the mental health considerations related to RLS pharmacology.

Epidemiology of RLS and Mental Health

Depression and Anxiety in RLS Patients

Depression and anxiety, along with their common feature sleep disruption, are common among RLS patients. Overall, patients with RLS are more impaired functionally, experience higher levels of somatic distress, and have impaired sleep. In fact, patients with RLS may have lower quality of life than patients with other medical conditions such as hypertension, congestive heart failure, history of myocardial infarction in the past year, patients with angina, or even diabetes [10]. Patients with RLS also tend to have numerous somatic symptoms, which appears to be mediated, at least in part, by greater burden of stress and anxiety [11].

RLS and mood disorders share several epidemiological features. RLS and major depressive disorder (MDD) have similar prevalence rates in the community: 2–7% of the general population has RLS symptoms of varying severity [12, 13], and the annual prevalence of depression has been reported to be similar (e.g., 6.7% in the National Epidemiological Survey on Alcoholism and Related Conditions [14]). The mean age of onset for both conditions is in the 30s with a wide distribution [15], and each demonstrates a female preponderance of 2:1 [16, 17]. Additionally, genetic predisposition accounts for a large portion of developing each of these conditions [18, 19].

RLS is a Sleep–Wake Disorder that exhibits disrupted sleep—as demonstrated on nocturnal electroencephalography [20]—and excessive daytime sleepiness with decreased quality of life [21, 22]. On this basis alone one would expect higher rates of depression and anxiety among patients with RLS than among those without [6].

However, the chronic distress caused by internal restlessness may be interpreted as anxiety and over time serve as a stressor that precipitates irritability or dysphoria.

Several cross-sectional, community-based epidemiological studies have found higher rates of self-reported depression and anxiety symptoms as well as self-reported psychotropic use among patients with RLS than among those without RLS [23–33]; however, these population-based studies tend to rely on depression and anxiety screens rather than validated diagnostic evaluations. Nevertheless, these data are internationally consistent and include findings from the UK, Germany, Italy, Portugal, and Spain [23]; the US [24, 25]; Sweden [26–28]; Norway and Denmark [29]; Korea [30]; Japan [32]; Turkey [31]; and France [33].

Using a structured psychiatric interview called the Munich-Composite International Diagnostic Interview for DSM-IV, Winkelmann et al. evaluated a clinical population of 130 patients with RLS for psychiatric disorders, and these data were compared with a population of 2265 residents who participated in a community-based study [34]. Using formal diagnostic criteria for psychiatric disorders (unlike the international cross-sectional surveys above), they found a significantly elevated 12-month prevalence of panic disorder (PD) (OR 4.7; 95% CI = 2.1–10.1), generalized anxiety disorder (GAD) (OR = 3.5; 95% CI = 1.7–7.1), and major depression (OR = 2.6; 95% CI = 1.5–4.4) in RLS patients when compared with a nationally representative sample of community respondents [34]. Given that this study employed a clinical sample, study patients may be expected to have a greater RLS symptom burden than community samples by way of referral bias.

Using the validated Center for Epidemiologic Studies Depression Scale (CES-D) to screen for clinical depression and the International RLS Study Group (IRLSSG) criteria for RLS, Rothdach and colleagues surveyed 369 geriatric community patients in Germany [35]. Using face-to-face interviews, these researchers found higher average rates of depression among study participants with RLS than among those without RLS (CES-D scores of 11.6 vs. 7.8; $p = 0.01$). Stratifying for gender revealed that this association was limited to male subjects. A door-to-door study in Turkey identified 103 subjects positive for RLS per IRLSSG criteria out of 3234 community subjects screened [36]. Those with RLS had significantly higher Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale scores than those without RLS.

Two population-based epidemiological studies using validated diagnostic criteria for RLS and screening instruments for psychiatric diagnosis have demonstrated significantly higher rates of depression and anxiety among patients with RLS relative to those without [37, 38]. In the first of these, Lee and associates examined data from the Baltimore site of the Epidemiologic Catchment Area (ECA) program, a multi-site initiative supported by the National Institute of Mental Health [37]. In this epidemiological study, 1024 participants completed the seven-item RLS Questionnaire and Diagnostic Interview Schedule. After adjusting for demographics, overall health, and antidepressant use, Lee et al. found that patients with RLS had a greater 12-month prevalence of depression (OR = 4.7; 95% CI = 1.2–18.3), PD (OR = 12.9; 95% CI = 3.6–46), and obsessive-compulsive disorder (OCD) (OR = 5.6; 95% CI = 1.4–21.9) than patients without RLS [37]. These data

were replicated in a community sample of 6509 Korean adults [38]. In this replication study, face-to-face interviews included a Korean translation of the IRLSSG criteria and the Korean version of Composite International Diagnostic Interview. Relative to matched participants without RLS, those with RLS had higher lifetime rates of major depression (OR = 2.57; 95% CI = 1.33–4.96), PD (OR = 18.9; 95% CI = 4.72–75.9), and posttraumatic stress disorder (PTSD) (OR = 3.76; 95% CI = 1.32–10.7). Additionally, RLS participants endorsed a lower quality of life based on EuroQol scores than those without RLS [38].

Three recent prospective studies have evaluated whether RLS predicts clinically significant depression or vice versa [39, 40]. In the first of these, 56,399 women were screened for depression and RLS at baseline (based on self-report of physician-based diagnosis), and they were followed for six years [39]. Self-report of physician-diagnosed RLS at baseline increased the risk of developing clinically significant depression as defined as regular use of an antidepressant and physician-diagnosed depression (RR 1.5; 95% CI = 1.1–2.1) as well as higher scores on the CES-D and the 15-item Geriatric Depression Scale. The second report includes two population-based prospective studies [40]: the first cohort comprised 1312 subjects who were followed for a mean of 2 years; the second cohort 4308 subjects who were followed a mean of 5 years. Clinically significant depressive symptoms (CSDS) at baseline, as defined by a CES-D score of 16 or greater or positive screen on the Munich-Composite International Diagnostic Screener, were a risk factor for developing new-onset RLS in both cohorts (ORs 1.94 and 2.37, respectively) after appropriate adjustments. Conversely, RLS per IRLSSG criteria at baseline increased the risk of incident CSDS on follow-up in the second of these cohorts.

Taken together, data from community and clinic-based epidemiological studies suggest that patients with RLS should be screened for major depression and anxiety disorders given the higher rates of these conditions found among this patient population. Moreover, in view of recent prospective studies, it may be prudent to screen patients with RLS regularly for incident depression as well.

RLS in Mental Health Cohorts

The question of whether RLS is higher among patients with mental illness has been much less evaluated in epidemiological studies, and data are inconsistent. For instance, in a geriatric outpatient mental health clinic in Spain, researchers documented an 11% prevalence of definite RLS with an additional 10% prevalence of possible RLS among a cohort of non-demented patients for RLS using the Revised IRLSSG criteria [41]. Even higher rates of RLS and RLS symptoms were found in a cohort of 182 hospitalized patients with schizophrenia receiving antipsychotics [42]. Using the IRLSSG criteria, 21.4% of these patients were diagnosed with RLS, and 47.8% met at least one criterion. The prevalence of RLS was over twice as common among patients treated for schizophrenia as compared with an age- and sex-matched cohort without schizophrenia (21.4% vs. 9.3%; $p = 0.009$). A third study, though, found only one case of RLS out of 100 patients

taking neuroleptics [43]. The findings from this third study are difficult to interpret given that this rate of 1% is *lower* than in the general population and is consternating because dopamine antagonism is expected to cause or exacerbate movement disorders.

The preponderance of the evidence would suggest that patients with mental illness are at an elevated risk of developing RLS than the general population regardless of whether this is because they share neurobiological features or psychotropic-induced (see below) [40]. Perhaps the high prevalence of RLS in the first two studies above could be attributed, in part, to the older population included in these studies. Several psychotropic agents may also contribute to RLS symptom burden as well. Additionally, as described below, the RLS and mental illness may share overlapping neuropathology accounting for a portion of the elevated incidence of RLS among psychiatric cohorts.

Explaining the Comorbidity Between RLS and Mental Illness

Depression and Anxiety

Several of the diagnostic criteria of major depression are common in RLS including insomnia, psychomotor slowing, daytime fatigue, and impaired concentration, and this may contribute to the clinical overlap between these two syndromes. However, as seen in epidemiological studies, patients with RLS have a higher incidence of syndromal major depression as well [37, 38]. In fact, the close association between RLS and major depression suggest that this relationship is more than epiphenomenal. The majority of patients with RLS experience sleep disruption due to the crepuscular predilection of symptoms in RLS [7], and reduced sleep not only contributes to depressive symptoms but may also precipitate major depressive episodes [44]. Beyond its effects on sleep, RLS causes unsettled sensations that may serve as an independent stressor thereby contributing to depression [45].

Dopamine is likely involved in the neurobiological convergence of RLS and MDD. The most consistently characterized neurotransmitter abnormality in RLS is decreased dopaminergic activity in the striatum and substantia nigra [46, 47]. Depression, on the other hand, is associated with alterations in dopamine activity, though this abnormality is most prominent in the prefrontal cortex [48].

The clinical co-occurrence of RLS and anxiety disorders deserves particular consideration for several reasons [38]. One would expect patients with RLS, which experience an internal restless sensation, would be more likely to develop state anxiety. Thus, the association between RLS and GAD requires little imagination; however, RLS has been associated with OCD, PD, and PTSD—each of which has a distinct neurobiological signature. Functional neuroimaging has revealed that dysfunction in the cortico–striatral–thalamo–cortical circuit, which involves dopamine, glutamate, and γ-aminobutyric acid (GABA), is integral to OCD [49].

This may, in part, explain the reason for elevated incidence of OCD among patients with RLS, which also involves reduced dopamine activity in the striatum. PD and PTSD, on the other hand, are much more closely aligned with fear responses. It remains unclear how the "fear network," which includes the amygdala, insula, and anterior cingulate cortex, may overlap with neurological findings in RLS. Nevertheless, positron emission tomography and single-photon emission computed tomography studies of compulsive and anxiety disorders including PD and PTSD have revealed decreased striatal D2 receptor binding, which may account for the higher incidence of these disorders with RLS [50].

RLS and Neurocognitive Impairment

Studies suggest that RLS may be associated with mild impairment in cognition; however, the results of the few studies remain inconsistent limiting the scope of conclusions that can be drawn. Several authors have proposed that RLS may be associated with neurocognitive impairment in large part due to fragmented sleep [33, 51–53]. In the earliest of these studies, Pearson et al. compared 16 RLS subjects off RLS treatment for at least two weeks with 15 age and gender-matched controls [51]. Patients with RLS were found to have significant deficits on tasks of prefrontal cortical function relative to controls—deficits roughly consistent with those seen after a night of sleep deprivation. Similarly, cognitive testing of 23 unmedicated RLS subjects compared with 23 age, sex, and education-matched controls revealed subtle deficits in short-term attention and verbal fluency, but no differences were found in working memory, memory, learning, cognitive flexibility, and abstract reasoning [52]. To test whether sleep-restricted controls without RLS would demonstrate deficits comparable to RLS subjects, Gamaldo and colleagues subjected 13 healthy controls to a 14-day partial sleep-restriction protocol prior to comparing their neurocognitive function against 16 RLS subjects [53]. Unexpectedly, RLS subjects performed *better* than sleep-restricted controls on letter and category fluency, two tests that are particularly sensitive to sleep impairment. In discussing their results, the authors propose that patients with RLS may adapt partially to chronic sleep loss.

At most, population-based studies demonstrate only mild impairment in select neurocognitive domains among those with RLS. A French study evaluated a community sample of 318 subjects for RLS using the IRLSSG criteria and found a prevalence of 24% [33]. Subjects with RLS performed slightly worse on the Stroop interference task and verbal fluency than subjects without RLS—a finding that remained statistically significant even after accounting for the greater rates of hypnotic and antidepressant use as well as higher depression and anxiety scores. A subsequent study of patients included a community research database identified subjects with RLS for at least one year and subjects without RLS, and despite a neurocognitive battery consisting of 36 independent tests, only those related to forward digit span were statistically impaired among patients with RLS [54]. A similar study conducted on the RLS in the Baltimore site of the Epidemiological

Catchment Area (RiBECA) study identified 91 subjects based on RLS status (37 without RLS; 23 untreated RLS subjects; 31 treated RLS subjects) revealed only minimal impairment in clock draw and clock copy despite conducting a neurocognitive battery of 19 unique tests [55].

In summary, it appears that patients with RLS may exhibit very mild clinical deficits relative to healthy controls, but the degree to which these findings are clinically significant or simply related to chronic sleep restriction remains unclear. Evaluations of Mini-Mental State Examination have failed to demonstrate a statistically significant difference between elders with and without RLS [33, 35, 54], and even when excluding patients with dementia only very slight differences have been identified among patients with RLS [54, 55].

RLS and Attention-Deficit/Hyperactivity Disorder

Growing evidence supports an association between attention-deficit/hyperactivity disorder (ADHD) and RLS [56]. RLS and PLMS appear to be common in children and adults with ADHD [57, 58]. For instance, a 2005 review estimated that RLS or RLS symptoms are found in 44% of subjects with ADHD whereas ADHD or ADHD symptoms are found in 26% of those with RLS. These data should be interpreted cautiously given the very significant risk of sampling or referral bias in the studies included in this review, which almost certainly inflate the true cross-prevalence of these conditions.

Similar to the discussion in the **Cognition** section above, ADHD-like symptoms such as inattention or restlessness may be due to disrupted sleep. Conversely, the motoric features of restlessness or hyperactivity found in ADHD may also be misinterpreted as akathisia, particularly in children who have greater difficulty articulating their experience verbally. ADHD *symptoms* appear to be more common in adults with RLS relative to adults with insomnia without RLS or no sleep disorder [59]; however, whether these symptoms represent a formal diagnosis of ADHD remains unclear. Dopamine agonists may be effective for RLS or PLMD in children with ADHD, but a small study was unable to demonstrate that L-dopa improves ADHD symptoms [60].

RLS and Personality

Two features of personality closely aligned with depression and anxiety are high neuroticism and introversion [61], and it has been proposed that personality traits may account for a portion of the comorbidity between RLS. In the RiBECA study, 42 RLS subjects and 982 subjects without RLS completed a personality assessment based on the 240-item NEO Personality Inventory [62]. RLS subjects had higher neuroticism even after adjusting for depression or PD. Steinig and colleagues performed a small-scale replication study and obtained similar results [63]. They enrolled 30 de novo RLS patients and 30 age- and gender-matched healthy controls,

and participants completed the 60-item NEO Five-Factor Inventory. RLS participants had higher rates of neuroticism. RLS patients have higher levels of neuroticism than the general population, which may create a vulnerability to stress and increase the propensity of these patients to develop clinical depression or anxiety. This second study also found RLS patients to score lower on openness to experience. This is notable because openness to experience has been associated with incident coronary artery disease in the community and RLS has been associated with coronary artery and cerebrovascular disease [64]. These personality traits specific to RLS may explain some of the well-established association between RLS and mood disorder or RLS and cardiovascular disease.

Psychotropics and RLS

Serotonergic Antidepressants and RLS

Several lines of evidence have found an association between RLS and antidepressants [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and serotonin 1A agonists (e.g., buspirone)]. Some population-based studies have found increased rates of antidepressant use among subjects with RLS [23, 33] while others have not [37, 38]. Nevertheless, a French pharmacovigilance study of mandatorily reported adverse drug reactions revealed that antidepressants and neuroleptics were more commonly imputed as the cause of RLS than other agents reported in association with RLS [65].

Despite the central role of serotonin in the pharmacological management of depression, dopamine activity is also altered in major depression [66]. The effect of serotonin and dopamine activity on one another appears to be specific to brain region and receptor-subtype. As pertains to RLS, activation of serotonin 1A receptors may stimulate dopamine release in the prefrontal cortex and nucleus accumbens but may inhibit dopamine release in the striatum [66]. This distinction provides a potential mechanistic rationale for why serotonergic antidepressants improve symptoms of anergia and anhedonia while also inducing movement disturbances such as RLS, akathisia, or even periodic limb movements in sleep (PLMS) [67–70].

However, no prospective, controlled studies have documented a link between pro-serotonergic antidepressants and the worsening of RLS symptoms. Numerous case reports and case series of SSRI-induced RLS symptoms have been published [71–77], which may be a result of their propensity to dampen dopamine activity [78]. A recent case report of RLS associated with the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine was also reported [79]. A combination of venlafaxine and quetiapine has been reported to induce RLS [80], and monotherapy venlafaxine has been reported to worsen PLMS [69]. No reports of TCA-induced RLS have been published though one report documented worsening of PLMS with TCA [68], and TCAs such as desipramine [81] and imipramine [82] are known to affect dopamine activity in the nucleus accumbens and striatrum. The relative

frequency of these reports are consistent with the premise that serotonin selectivity as seen in SSRIs and more with venlafaxine than either duloxetine or TCAs increases the risk of RLS symptoms more than a more balanced serotonin-to-norepinephrine profile. As such, one may wonder whether the greater norepinephrine selectivity of secondary amine TCAs or levomilnacipran may offer a clinical advantage in treating depression among patients with RLS [83].

Despite these sparse case reports, retrospective studies have reported that patients experienced *improvement* in RLS symptoms when starting treatment with SSRIs [84] or were unable to identify an association between SSRI use and RLS symptoms [85]. In the first of these reports, 113 consecutive patients receiving SSRIs attending a hospital-based clinic were screened for RLS symptoms, and 43 of 66 returned responses (65% of respondents) endorsed symptoms of RLS [84]. Twenty-five respondents (58%) reported improvements in RLS symptoms after starting SSRI, five (12%) experienced abolition of RLS symptoms, and another five (12%) experienced worsening of symptoms. The remainder experienced no change in RLS symptoms. Two of 23 patients without RLS prior to SSRI developed RLS symptoms upon starting SSRI. A subsequent study that evaluated 200 consecutive patients presenting for sleep initiation insomnia at a sleep disorders clinic did not find a statistical association between antidepressant use and RLS, though only half of the patients were on either an SSRI or an SNRI with the remainder on TCAs, trazodone, bupropion, or other common antidepressants [85]. These studies are limited by being retrospective, unblinded, and self-report. Importantly, neither study used a validated screening tool for RLS diagnosis.

No data were found on an association between buspirone and RLS symptoms; however, a report of two cases suggested that tandospirone (a serotonin 1A agonist available in East Asia) improved RLS symptoms [86]. As described above, serotonin 1A receptors may specifically augment dopamine activity though this effect appears to be specific to the frontal lobes. With this site specificity in mind, one would expect serotonin 1A agonism rather to contribute to RLS symptoms.

The question of whether pro-serotonergic agents influence RLS remains unsettled, particularly in view of contradictory evidence. Either way, the clinical notion that these agents are uniformly associated with worsening of RLS symptoms is not supported by current data. The balance of the evidence suggests that pro-serotonergic agents are liable to induce secondary RLS and perhaps even improve primary RLS. Prospective randomized trials will be needed to clarify the nature of this association.

Other Antidepressants

The effect of mirtazapine, a heterocyclic antidepressant with antagonism at serotonin 2A, 2C, and 3 receptors, on RLS symptoms remains unclear as well. Mirtazapine's use is considered often when treating depressed patients with insomnia due to its sedating antihistaminic properties. Despite its being used to improve sleep, case reports suggest that it may actually worsen RLS symptoms [87–91]. To study the association between mirtazapine and RLS, Kim et al. conducted a

retrospective chart review of 181 patients on mirtazapine to identify clinical features associated with developing RLS per IRLSSG criteria [91]. Eight percent of patients on mirtazapine developed RLS, and most RLS cases occurred within days of starting mirtazapine. Use of tramadol and neuroleptics was more common among mirtazapine patients who developed RLS than among those who did not.

In contrast, bupropion generally *improves* RLS symptoms [92–96]. In addition to several case reports of bupropion improving RLS symptoms, a randomized, double-blind, placebo-controlled trial of bupropion that enrolled 60 patients with moderate to severe RLS revealed clinical benefit [92]. After three weeks, patients receiving 150 mg bupropion sustained release daily had statistically improved RLS symptoms (IRLSSG improvements of 10.8 vs. 6.0, $p = 0.016$). At six weeks, subjects receiving bupropion continued to have lower IRLSSG scores relative to the placebo group, but this was no longer statistically significant (IRLSSG improvements of 10.4 vs. 7.6, $p = 0.108$). Given that it shares dopamine-enhancing activity with standard treatments for RLS [97], bupropion may be considered to treat depression with comorbid RLS provided it is not contraindicated. Limited evidence suggests that trazodone may also have a favorable profile regarding RLS [98]. No data were found suggesting that related compounds vilazodone or nefazodone are associated with RLS symptoms.

Sedative-Hypnotics

Insomnia is common among psychiatric illness—either included in the diagnostic criteria of mood and anxiety disorders or as an associated clinical feature. Although behavioral management should always be included in insomnia treatment, sedative-hypnotic agents such as benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists (BRAs; more commonly known as the Z-drugs) are commonly used. These agents are likely to be either neutral or therapeutic for RLS and PLMS. Clonazepam has long been used to treat RLS clinically, particularly because it improves sleep [99], and is generally preferred to other benzodiazepines due to its longer half-life. In some instances, benzodiazepines may improve sleep without specifically improving PLMS [99]. Additionally, a report of eight patients treated with open-label zolpidem revealed significant improvement in RLS symptoms all patients within a week [100]. Antihistamines are also commonly taken by patients for sleep problems. Whereas diphenhydramine may exacerbate PLMS and RLS [101], hydroxyzine may not be as RLS-averse [102].

Neuroleptic Agents

Typical and atypical neuroleptics, traditionally known as antipsychotics, are commonly used to treat a range of psychiatric illness including schizophrenia, bipolar disorder, and treatment-resistant depression. Neuroleptic-induced movement disorders are common with the use of these agents. In fact, historically, they were

Table 2.1 Differentiating RLS from the more common psychotropic-induced akathisia[a]

	RLS (DSM-5 criteria)	Psychotropic-induced Akathisia
Location	Legs principally or exclusively involved (A)	Generalized, including upper extremities as well
Dysesthesias	Very common (A)	Rare
Relation to movement	Worse during inactivity or rest (A1)	Typically continuous
Response to movement	Partially or totally relieved by rest (A2)	Unaffected by movement
Diurnal variation	Worse in evening or night (A3)	Limited circadian variation
Psychotropic exposure	Independent of psychotropic exposure	Neuroleptics most common though also described with various antidepressants

From Benes et al. [152], with permission

[a]Akathisia is derived from the Greek *a* ("without") and *kathizein* ("seated"), and akathisia is a core feature of RLS. In fact, in movement-disorder terms, RLS has been described as a "movement-responsive quiescegenic nocturnal focal akathisia usually with dysesthesias."

titrated to the "neuroleptic dose," or the dose that led to mild parkinsonism (the term neuroleptic is derived from the Greek roots *neuron*, "sinew," and *lepsis*, "to seize"). Their propensity to induce movement disorders is due to dopamine antagonism in the nigrostriatal pathway. The neuroleptic-induced movement disorder most closely associated with RLS is akathisia, which is characterized by an internal, generalized restlessness or urge to move. Akathisia may be difficult to differentiate from RLS proper (Table 2.1). Clinicians should also bear in mind that several anti-emetics are also typical neuroleptics (e.g., metoclopramide, promethazine, and prochlorperazine). In general, second-generation or atypical neuroleptics less commonly cause movement disorders, which is thought to be because their additional serotonin 2A attenuates dopamine antagonism in the striatum.

Numerous cases of neuroleptics causing RLS symptoms have been reported including those for haloperidol [103], risperidone [104], and olanzapine [105–107]. Even the two neuroleptics with least D2 receptor antagonism and, consequently, the least risk of causing akathisia or other movement disorders—quetiapine [77, 80, 108–111] and clozapine [112]—have been reported to induce RLS symptoms. Although ropinirole was effective in managing a case of quetiapine-induced RLS, this practice cannot be uniformly recommended [109] given the potential for dopamine agonists to precipitate psychiatric destabilization (e.g., psychosis among patients with psychotic illness or mood elevation and impulsivity among patients with bipolar disorder). Studies suggest that certain dopamine receptor and monoamine oxidase alleles may increase a person's vulnerability to neuroleptic-induced RLS [113–116] though the clinical utility of genotyping in the clinic remains limited.

The absence of randomized clinical trials supporting an association between neuroleptics and RLS notwithstanding, the fact that neuroleptics cause akathisia and other movement disorders makes their propensity to cause RLS not only plausible

but quite likely. In general, one may expect atypical neuroleptics to be more benign than typicals with regard to RLS, and quetiapine and clozapine may be the safest options in RLS based on their preferential use in Parkinson's disease and other alpha synucleinopathies. Aripiprazole, given its unique pharmacodynamics as a partial agonist/antagonist of D2 receptors, may offer a more favorable profile regarding RLS. Most reports suggest that aripiprazole does not cause RLS and may improve these symptoms [117–120], but a case report of aripiprazole-related RLS has been reported [121]. Clinicians, however, should note that roughly a third of patients on aripiprazole will experience akathisia. In many clinical situations, no adequate alternative to neuroleptics exists, and it may safest to treat RLS with an adjunctive $\alpha_2\delta$ ligand such as gabapentin [122] or gabapentin enacarbil.

Mood Stabilizers

Bipolar disorder and, at times, major depression are managed with mood stabilizers, which include lithium and several anticonvulsants (e.g., valproic acid, carbamazepine, lamotrigine, or oxcarbazepine). Anticonvulsants that improve neuropathic pain may improve RLS symptoms, and in particular carbamazepine and gabapentin (which is not a traditional mood stabilizer) have long been considered second-line agents for RLS on the basis of randomized clinical trials supporting their efficacy in RLS [123, 124]. Valproic acid [125] and lamotrigine [126] may also improve RLS symptoms. Lithium, however, may worsen RLS symptoms in select patients based on a few case reports [127–129]. Therefore, anticonvulsants may be preferred over lithium in the management of mood disorders with comorbid RLS. Clinicians should be extremely cautious in discontinuing lithium in patients who are euthymic even if RLS symptoms emerge. Lithium remains the gold-standard mood stabilizer and is highly effective. Discontinuation of lithium risks destabilizing bipolar disorder and should not be undertaken lightly.

Psychiatric Considerations of RLS Treatment

The two medication classes approved for RLS—dopamine agonists and $\alpha_2\delta$ ligands—have psychoactive properties that must be considered as well. Although uncommon, dopaminergics are well-documented to cause impulse-control syndromes in a minority of patients. Examples of impulse-control syndromes include pathological gambling [130–132], hypersexuality [130], hoarding [133] and other compulsive [134] behavior, punding [135], and nocturnal eating syndrome [136]. Patients should be monitored closely for these destructive behavioral consequences of treatment, and in virtually all cases the offending agent should be discontinued as rapidly as feasible. Although rare, abrupt discontinuation of dopamine agonists can precipitate a potentially lethal syndrome known as parkinsonism-hyperpyrexia syndrome, which is thought to be akin to neuroleptic malignant syndrome [137].

Agonists of $\alpha_2\delta$ may cause sedation and are often accompanied by anxiolysis. Although not approved for psychiatric use in the US pregabalin is efficacious for the management of general anxiety disorder [138, 139] and approved internationally for this purpose. Also, the potential for misuse of pregabalin and other agents should not be overlooked [140].

Treatment Implications

Balancing the management of psychiatric disorders with RLS and the potential for psychotropics to induce or worsen RLS presents many clinical challenges. Patients with RLS should be screened for major depression and anxiety disorders. Patients on dopamine agonists should be monitored closely for impulse-control syndromes and patients on $\alpha_2\delta$ ligands for medication misuse. On the other hand, patients with psychiatric illness should be actively screened for RLS given the high comorbidity. In either case, the comorbidity of RLS and mental illness may influence pharmacological selection.

In patients with RLS and comorbid depression, dopamine agonists are first-line as recommended by the International RLS Task Force [141]. If RLS is prominent and depression is mild, dopamine agonists may be preferable for RLS, which may improve depression as well [142–144]. The use of dopaminergics on depressive symptoms melds biological plausibility (dopamine activity is disrupted in depression) with the knowledge that enhancing sleep also improves mood (mitigating RLS symptoms is likely to improve sleep quality) [145]. If major depression is moderate to severe, bupropion may be considered before pro-serotonergic agents provided it is not contraindicated due to seizures or eating disorders that involve purging. If pro-serotonergic agents are considered, agents with a more balanced serotonin-to-norepinephrine reuptake profile may be less likely to worsen RLS. It should also be kept in mind that mild to moderate major depression may be adequately treated with cognitive behavioral therapy, interpersonal therapy, or psychodynamic psychotherapy per the American Psychiatric Association's treatment guidelines for MDD. For severe major depression, electroconvulsive therapy also remains a viable clinical option.

For patients with RLS and comorbid GAD, $\alpha_2\delta$ ligands are preferred over dopamine agonists for the management of RLS symptoms [141]. As noted above, several randomized, controlled trials have demonstrated efficacy of pregabalin for GAD. Although it is approved in several countries throughout Europe for GAD [139], its use for GAD in the US remains off-label. Benzodiazepines may also be considered for the management of GAD in patients with comorbid RLS. Similarly, the pharmacological management of PD may involve benzodiazepines, but attempts at starting a pro-serotonergic agent could still be considered given their efficacy in preventing future panic attacks. The first-line pharmacological treatment of OCD and PTSD include pro-serotonergic agents, which may make clinical management with comorbid RLS particularly difficult. Psychotherapy should be given strong

consideration for OCD or PTSD when comorbid with RLS because data on comparative efficacy of medications versus CBT in these disorders remain equivocal.

Anticonvulsants should be considered for managing bipolar disorder in the context of RLS as they may actually improve RLS symptoms as well. In general, valproic acid may be a reasonable first-line agent with consideration of carbamazepine as well. The use of lamotrigine for bipolar disorder is generally limited to managing bipolar II disorder given its dearth of anti-manic activity. Lithium may worsen RLS symptoms; though, again, clinicians should be well-advised not to discontinue this without compelling reason in patients who are affectively stable. Treating RLS in bipolar disorder is critical particularly because insomnia may precipitate mood episodes in bipolar disorder. It seems reasonable to consider $\alpha_2\delta$ ligands over dopaminergic agents. The fact that two patients with bipolar disorder tolerated ropinirole without manic switch [109] does not outweigh the potential for this disastrous clinical outcome [146].

For patients with comorbid RLS and schizophrenia, $\alpha_2\delta$ ligands are preferred to dopamine agonists due to the concern that dopamine agonism could pharmacologically work against antipsychotics. The data in support of pramipexole [147] or ropinirole [148] as adjuncts to neuroleptics in schizophrenia is far too meager to support their use in this population. No adequate alternative to neuroleptic agents exists for psychotic disorders. Therefore, patients with schizophrenia and RLS should be treated with antipsychotics with very few exceptions. Atypical neuroleptics are less likely to affect RLS symptoms than typicals, and quetiapine and clozapine may pose the least risk of neuroleptic-induced RLS symptoms based on their comparatively limited D2 receptor binding at therapeutic doses. Nevertheless, the emergence of RLS during neuroleptic use should be treated symptomatically unless these symptoms are severe or threaten patient non-adherence. Additionally, benzodiazepines such as clonazepam are commonly used as adjuncts in schizophrenia and could be considered as second line for RLS symptoms in this population.

Psychiatrists who diagnosis RLS should be well-aware of RLS mimics and consider a broad differential for symptoms consistent with RLS, particularly because such symptoms may be a harbinger of serious medical illness [149, 150]. For instance, misdiagnosis of peripheral neuropathy could risk overlooking type 2 diabetes mellitus. Claudication or pseudoclaudication should alert the clinician to heart disease or spinal cord compression, respectively. Uremia may present with RLS symptoms as may iron deficiency anemia, which could be the presenting symptom of colon cancer. In the same way that psychiatrists diagnose major depression after medical conditions such as hypothyroidism have been ruled out, RLS remains a clinical diagnosis of exclusion. Moreover, clinicians should not rely on the core clinical features of RLS (i.e., DSM-5 Criterion A or the IRLSSG essential criteria 1–4) to rule out conditions other than "true" RLS given the potential for false positives [149].

A differential diagnosis of RLS should be broad, and mental health professionals considering a diagnosis should familiarize themselves with other conditions that may present with RLS symptoms. A differential diagnosis for RLS should include

metabolic (iron deficiency anemia, uremia, dehydration), obstetric (pregnancy), behavioral (positional discomfort or volitional movements ["foot tapping" or "leg rocking"]), sleep–wake-disorder-related (sleep starts, periodic movements in sleep disorder), musculoskeletal/nociceptive (muscle cramping, pain, myalgia, positional discomfort, arthritis, myxedema), vascular (claudication/peripheral vascular disease, peripheral venous insufficiency, hypotensive akathisia, congestive heart failure/peripheral edema), neurological (sciatica, peripheral neuropathy/radiculopathy/myelopathy, pseudoclaudication, painful [or painless] legs-moving toes, reflex sympathetic dystrophy), or medication-induced (akathisia) conditions [151, 152].

Conclusions

RLS is a common disorder that may share a bidirectional association with depression and anxiety. It was elevated to a unique diagnosis in DSM-5 because it is operationally valid, significantly impairs quality of life, and may be effectively treated with a several pharmacologic agents. Patients with RLS or with mental illness should be screened for the other in an ongoing fashion. The treatment of mental illness in RLS patients demands careful consideration of treatment planning including the decision to pursue medication versus therapy and, if using psychotropics, which psychotropic to use. Often, medications will need to be used and RLS symptoms managed in parallel with ongoing psychotropics. Prospective, randomized, controlled studies are needed to define the role of psychotropics in patients with RLS as well as the effects of RLS pharmacology on mental illness.

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