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Review article

Diagnosis, comorbidities, and management of restless legs syndrome

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Abstract

Objective:
This narrative review describes the differential diagnosis of restless legs syndrome, and provides an overview of the evidence for the associations between RLS and potential comorbidities. Secondary causes of RLS and the characteristics of pediatric RLS are also discussed. Finally, management strategies for RLS are summarized.

Methods:
The review began with a comprehensive PubMed search for 'restless legs syndrome/Willis-Ekbom disease' in combination with the following: anxiety, arthritis, attention-deficit hyperactivity disorder, cardiac, cardiovascular disease, comorbidities, depression, end-stage renal disease, erectile dysfunction, fibromyalgia, insomnia, kidney disease, liver disease, migraine, mood disorder, multiple sclerosis, narcolepsy, neuropathy, obesity, pain, Parkinson's disease, polyneuropathy, pregnancy, psychiatric disorder, sleep disorder, somatoform pain disorder, and uremia. Additional papers were identified by reviewing the reference lists of retrieved publications.

Results and Conclusions:
Although clinical diagnosis of RLS can be straightforward, diagnostic challenges may arise when patients present with comorbid conditions. Comorbidities of RLS include insomnia, depressive and anxiety disorders, and pain disorders. Differential diagnosis is particularly important, as some of the medications used to treat insomnia and depression may exacerbate RLS symptoms. Appropriate diagnosis and management of RLS symptoms may benefit patient well-being and, in some cases, may lessen comorbid disease burden. Therefore, it is important that physicians are aware of the presence of RLS when treating patients with conditions that commonly co-occur with the disorder.

Introduction

Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is a chronic neurosensorimotor disorder, characterized by an urge to move the legs which is often accompanied by uncomfortable or unpleasant sensations. These symptoms can result in considerable discomfort and distress, and are recognized as having a significant health-related impact in patients with moderate-to-severe disease[1]. Epidemiological studies have suggested that the prevalence of RLS in the general population may range from 5% to 15%[1]. As many as one in 25 people may suffer from RLS symptoms that cause some degree of distress, and one in 100 may experience symptoms which seriously impact quality of life[1]. In addition, patients with RLS may have an increased risk of diabetes, cardiovascular disease, and stroke[2]. The clinical importance of RLS is further underlined by the results of a large-scale prospective cohort study. Among 18,425 US men followed for 8 years, RLS was associated with a 39% increased risk of mortality (age-adjusted hazard ratio [HR]: 1.39, 95% confidence interval [CI]: 1.19–1.62; $P<0.0001$)[3].

Although the pathophysiology of RLS is not fully understood, evidence exists for both iron/transferrin and dopaminergic abnormalities being factors in its etiology. As iron is a major cofactor in dopaminergic neurotransmission, iron deficits may produce dopaminergic changes that exacerbate RLS symptoms[4]. Among patients with idiopathic/primary RLS, there is evidence for genetic predisposition[5]. Genome-wide association studies have identified six different genes (BTBD9, MEIS1, MAP2K5/LBXCOR1, PTPRD, TOX3) with allelic variants that convey RLS risk[5]. A familial pattern is seen in over 50% of patients with idiopathic RLS, and onset of symptoms before the age of 45 years indicates an increased risk of the disorder occurring among first- and second-degree family members[6].

Although RLS is relatively common in the general population, it often remains undiagnosed[7]. A large cohort study involving 62 primary-care practices in six Western European countries found that 91% of patients with RLS had not been previously diagnosed[8]. Physicians play a pivotal role in the diagnosis and initial management of RLS; therefore, it is important that there is awareness of RLS comorbidities when a patient presents with a condition for which there is a high probability that RLS may be comorbid. The intent of this narrative review is to discuss appropriate diagnosis, recognition of comorbid conditions, and management of RLS.

Methods

Relevant studies published before November 2013 were identified via a comprehensive PubMed search using 'restless legs syndrome' in combination with the following terms: anxiety, arthritis, attention-deficit hyperactivity disorder, cardiac, cardiovascular disease, comorbidities, depression, end-stage renal disease, erectile dysfunction, fibromyalgia, insomnia, kidney disease, liver disease, migraine, mood disorder, multiple sclerosis, narcolepsy, neuropathy, obesity, pain, Parkinson's disease, polyneuropathy, pregnancy, psychiatric disorder, sleep disorder, somatoform pain disorder, and uremia. Additional papers were identified by reviewing reference lists of relevant publications. Case reports, studies that were not conducted in humans and non-English-language publications were excluded. A systematic approach to study selection was not implemented. Instead, data were extracted on the basis of their relevance to the topic.

Diagnosis and caveats to diagnosis of RLS

Diagnosis of idiopathic RLS is made by patient history as there are no physical characteristics or markers for the disorder. Patients may have difficulty describing their symptoms, variously complaining of 'pain', 'creepy-crawlies', 'electric current', 'jittery', 'burning', 'throbbing', and 'tearing' inside the muscles of the extremities, primarily deep in the legs[6]. RLS symptoms predominantly occur in the lower limbs, although any area from the hips to the feet can be impacted. In more severe cases, the upper extremities (shoulder to wrists) may be affected[9] and some instances of facial symptoms have been reported[10].

A patient's description of RLS symptoms may vary; however, the disorder can be confirmed or ruled out on the basis of essential criteria defined by the International RLS Study Group (IRLSSG) using the acronym URGED: (1) Urge to move the legs usually but not always accompanied by unpleasant/uncomfortable sensations, (2) Rest worsens symptoms, (3) Gyration or movement partially/totally relieve symptoms, (4) Evening/nighttime onset or worsening of symptoms[6]. The IRLSSG added a fifth criterion in 2011: occurrence of features 1–4 is not solely accounted for as symptoms primary to another medical/behavioral condition[11] leading to the 'D' of URGED, (5) Denial of another primary causation of the symptoms. The DSM-5 criteria for RLS are consistent with the five IRLSSG criteria, and include the following additional specifications: RLS symptoms occur at least three times per week and have persisted for at least 3 months; symptoms cause significant distress or impairment on social, occupational, educational, academic or behavioral functioning; and the disturbance cannot be explained by the effects of a drug or abuse of medication[12]. Supportive clinical features for RLS include a positive family history, positive response to dopaminergic therapy, and presence of periodic limb movements in sleep (PLMS)[6]. These features do not occur in every patient, but are particularly useful in diagnosing complicated or uncertain cases[6]. In addition, the potential presence of RLS should be considered in patients who complain of early insomnia and paresthesias or dysesthesias of the legs[13].

PLMS are repetitive involuntary limb movements that are found in several sleep disorders, including narcolepsy, sleep apnea and RLS, and may also be present in healthy individuals. As these movements occur in at least 80% of patients with RLS[6,14], they are considered to be a sign of the disorder. PLMS are characterized by extensions of the big toe and flexion at the ankle, knee, and hip as in a retraction response. They typically occur every 20–40 seconds and last for 0.5–5.0 seconds[6]. PLMS can be accompanied by nighttime awakenings or transient arousals resulting in significant sleep disruption, although they can also represent an epiphenomenon. The sleep of the bed partner may also be disturbed due to the patient trembling or kicking out whilst asleep. Whereas RLS can be diagnosed on the basis of clinical symptoms using the

IRLSSG criteria, PLMS can only be diagnosed during a sleep study via polysomnography or actimetry.

Patients with RLS generally do not need to be referred for diagnostic purposes; however, in ambiguous cases, patients may be referred to a neurologist or sleep specialist for further investigation[13]. A diagnostic test completed in research settings, the Suggested Immobilization Test (SIT), can be used to assess severity of leg restlessness and therapeutic response. During SIT, the patient is asked to lie or sit with their legs outstretched and attempt to remain still for 30–60 minutes, during which leg movements are monitored by an electromyogram. In 80% of cases, a SIT index score of over 40 involuntary leg movements per hour can be used to differentiate between patients with or without RLS[13]. One important aspect of diagnosis is delineation between idiopathic and secondary RLS. In the majority of cases, early-onset RLS (before the age of 45 years) is idiopathic[15]. Secondary RLS tends to start after the age of 45 years and is associated with more rapid progression than idiopathic RLS[15]. The three major secondary causes of RLS (iron deficiency, pregnancy, and end-stage renal disease [ESRD]) all compromise CNS iron availability[4].

Two major challenges in the differential diagnosis of RLS may contribute to the high proportion of patients who remain undiagnosed[16]. Firstly, RLS may be comorbid with other disorders. Physical examinations are generally normal in patients with idiopathic RLS, but can be used to detect comorbidities or secondary causes[6]. Secondly, other disorders can mimic the IRLSSG criteria (Table 1). The inner urge to move the limbs is often the key to distinguishing between RLS and mimic conditions that cause discomfort[16]. In addition, many RLS mimics do not have a circadian rhythmicity and are not relieved by movement. Patient history directs the process to determine potential mimics that can then be ruled out based on specific physical findings. Complications in diagnosis arise as mimics such as neuropathy, arthritis, venous stasis, and positional discomfort may coexist with RLS; this further underscores the importance of awareness among medical providers of conditions that are commonly comorbid with RLS.

Comorbidities

Insomnia

RLS has been identified as the fourth leading cause of insomnia[17] and sleep disturbance is often the primary reason for patients with RLS seeking medical attention. Approximately 50–85% of RLS patients experience troubling insomnia affecting sleep onset and maintenance[7,8,14,18–23]. The impact of RLS on health appears to be closely related to the frequency and severity of sleep disturbances. A European primary-care study found that individuals whose RLS had a 'high' negative impact on health had a significantly greater frequency of sleep disturbances (58% $\geq$4 nights/week) compared with patients whose RLS had 'moderate' (47% $\geq$4 nights/week), or 'little/no' negative impact (35% $\geq$4 nights/week) ($P<0.001$)[8]. Several controlled studies have shown a significant association between RLS and insomnia[20–23], and polysomnographic studies have demonstrated that patients with RLS experience reduced sleep efficiency, increased arousals, and reduced total sleep time[24–26]. Data from the Sleep Heart Health Study ($n=535$) showed participants with RLS ($n=71$) had a higher prevalence of insomnia (22.7% vs. 5.7%, $P=0.009$) and higher sleep latency (49.47 ± 62.23 min vs. 27.34 ± 32.2 min, $P=0.014$) than those without the disorder[27]. Collectively, these data highlight the high prevalence of insomnia comorbid with RLS. It is especially important to determine whether RLS is the underlying cause of insomnia as RLS symptoms are often exacerbated by over-the-counter sleep medications that contain antihistamines[28]. Patients with insomnia often use these agents to self-medicate. Furthermore, prescription of medications with no effect on the underlying disorder will often be inadequate in managing insomnia in patients with RLS.

Depressive and anxiety disorders

Population-/community-based studies[22,23,29–40] and clinic-based studies[18,25,41–45] have consistently demonstrated an increased prevalence or risk of depression and/or anxiety in

Table 1. Confounds in the differential diagnosis of RLS.

Confound	How many IRLSSG criteria are met?	Differentiate from RLS	Coexist with RLS
Leg cramps	4 of 4	Muscle spasm easily identified	+
Neuropathy/radiculopathy	0–4 of 4	Numbness, burning, and tingling; morning symptoms	+++
Arthritis	2–3 of 4	Discomfort in and around joints; stiffness on arising	++
Vascular	2–3 of 4	Varicosities and PVD; relief from movement slow; rub helps more; walking is worse	++
Positional discomfort	1–2 of 4	Foot or leg 'asleep' from compression; shift and it's gone	–
Exacerbation of RLS	Pregnancy, blood loss, renal disease, antidepressants, dopamine blockade, Parkinson's disease, axonal neuropathy		

IRLSSG = International RLS Study Group; PVD = peripheral vascular disease; RLS = restless legs syndrome.

patients with RLS, although in two studies an increased risk of depression was seen in men but not in women[29,31]. It should be noted that the majority of these studies did not adjust for antidepressant use. A prospective study of 56,399 women with no history of depression or regular antidepressant use found that participants with physician-diagnosed RLS at baseline had a higher risk of developing clinical depression (multivariate-adjusted relative risk [RR] = 1.5 [95% CI: 1.1, 2.1]; $P = 0.02$) and clinically relevant depressive symptoms (1.53 [1.33, 1.76]; $P < 0.0001$) over 6 years of follow-up than women without RLS[46]. Another prospective study showed an increased 12 month risk of anxiety and depressive disorders, particularly panic disorder (odds ratio [OR] = 4.7 [95% CI: 2.1–10.1]), generalized anxiety disorder (OR = 3.5 [95% CI: 1.7–7.1]), and major depression (OR = 2.6 [95% CI: 1.5–4.4]) among patients with RLS ($n = 130$), compared with a community sample of patients with somatic illness ($n = 2265$)[44]. In the majority of cases, the onset of RLS occurred prior to that of the psychiatric disorder. Antidepressant use was not reported.

Diagnosis of mood disorders in patients with RLS is complicated by symptom overlap. Fatigue, sleep disturbance, diminished concentration, and psychomotor agitation are common to both RLS and depressive disorders[47,48]. Causality between RLS and depression is unclear and seems to be bidirectional and multidimensional[48,49]. In two prospective cohort studies (Dortmund Health Study [DHS], $n = 1122$, median follow-up: 2.1 years; Study of Health in Pomerania [SHIP], $n = 3300$, median follow-up: 5 years), clinically relevant depressive symptoms were associated with new-onset RLS (DHS, adjusted OR = 1.94 [95% CI: 1.09–3.44]; SHIP, adjusted OR = 2.37 [1.65–3.40])[50]. Conversely, RLS at baseline was a risk factor for clinically relevant depression in the SHIP study (OR = 1.82 [95% CI: 1.1–3.0])[50]. In both studies, sensitivity analyses that excluded participants on antidepressants yielded similar results to those listed above. Sleep disruption and fatigue due to RLS may be causal factors for depression or depressive symptoms. Sleep deprivation, poor nutrition, and lack of exercise may increase the risk of developing RLS[48]. In a cross-sectional study of patients with ESRD ($n = 949$ [55 patients had 'probable' RLS])[51], multivariate analyses indicated that the presence of RLS symptoms was independently associated with depression (OR = 3.96 [95% CI: 2.21–7.1]). This relationship remained significant after adjusting for insomnia (OR = 2.9 [95% CI: 1.55–5.43]), indicating that the association of RLS with depression cannot be fully explained by sleep impairment in ESRD. Consistent results were obtained when patients on antidepressants, antihistamines or dopaminergic treatment were excluded. It is possible that RLS severity may be influenced by the degree of renal failure; thereby indirectly influencing depression and sleep quality. An unknown pathophysiological factor, or factors, common to both disorders (such as an abnormality in dopaminergic transmission or a genetic association) could falsely suggest a causal association between RLS and depression[48]. The possibility also exists that epidemiological association may, at least partly, be a result of overlap in the symptoms of two disorders which are both prevalent in the population.

Treatment of comorbid depression in patients with RLS must be carefully considered as antidepressants have been reported to trigger or exacerbate RLS symptoms (Table 2). Patients receiving the serotonin–noradrenalin reuptake inhibitor (SNRI) venlafaxine, and the selective serotonin reuptake inhibitors (SSRIs) citalopram, fluoxetine, paroxetine, and sertraline have been shown to have an elevated PLMS index in comparison with controls and patients taking bupropion[52]. In an observational study ($n = 271$), RLS was recorded as a side-effect of antidepressant administration in 9% of patients and typically occurred during the first few days of treatment[53]. Mirtazapine induced or exacerbated RLS in 28% of patients, and SSRIs (citalopram, escitalopram, sertraline, paroxetine, and fluoxetine) and SNRIs (duloxetine and venlafaxine) induced RLS in around 5% of patients. Other epidemiological studies have reported conflicting results[47]. In a retrospective chart review of 200 patients presenting with insomnia, no association was seen between RLS and use of antidepressants[54]. Similarly, antidepressant use was not shown to be a major risk factor for developing RLS in an observational study of 243 patients with affective and anxiety disorders[55].

Table 2. Medications and substances that may exacerbate RLS symptoms.

Medication	
Antidepressants (TCAs, SSRIs, and SNRIs)	Used to treat depression, anxiety, and pain disorders
Antiemetics	Used to treat nausea, including motion sickness and morning sickness
Antihistamines	Used to treat allergies Often found in over-the-counter sleep medications
Calcium channel blocking antihypertensives	Used to treat hypertension
Excessive caffeine	Found in coffee, tea, energy drinks, and other beverages Also found in chocolate
Excessive alcohol	Consumption of excessive alcohol at bedtime may exacerbate RLS

RLS = restless legs syndrome; SNRIs = serotonin–noradrenalin reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

As patients with RLS appear to have higher rates of disorders commonly treated with SSRIs and SNRIs[48], prescribers should be aware of the potential for treatment-related exacerbation of RLS symptoms. Antidepressants with probable lower rates of exacerbation of RLS include buproprion, desipramine, trazodone, and nefazodone[48].

Cardiovascular disease

The potential mechanisms for an association between RLS and cardiovascular disease (CVD) have been extensively discussed in previous review articles[56,57]. RLS may be associated with vascular risk factors such as hypertension, diabetes and obesity. In addition, PLMS, with or without central nervous system microarousals or awakenings, are associated with transient rises in pulse rate and blood pressure[58]. This sympathetic hyperactivity associated with PLMS may be an underlying factor in the increased risk for hypertension and CVD among patients with RLS[57].

A systematic review by Innes *et al.* identified 14 cross-sectional studies published between 1995 and 2010 with data for RLS and CVD[2]. Of these, 11 studies reported significant associations between RLS and CVD with ORs ranging from 1.4 (1.1–1.9) to 2.9 (1.2–7.2) following adjustment for confounders[30,33,38,59–66]. One study did not show an association between RLS and CVD[67], and two studies reported positive but non-significant[68]/marginally significant associations[22]. The results of two cross-sectional studies indicated that CV risk may be related to the frequency of RLS symptoms[33,66], and one study reported stronger associations between RLS, CAD and CVD among participants with 'severely' bothersome RLS symptoms (RLS and CAD, OR: 2.12 [95% CI: 1.2–3.75]; RLS and CVD: 2.33 [1.37–3.97]) than among those with 'moderate' RLS bothersomeness (1.98 [1.17–3.37]; 1.88 [1.14–3.09])[66]. More recently, Winter *et al.* investigated the associations between RLS, vascular risk factors and CVD in two large-scale cross-sectional studies: one in female health care professionals ($n = 30,262$)[69], and one in male physicians ($n = 22,786$)[70]. Hypercholesterolemia, diabetes and BMI were each associated with RLS in women[69], whereas diabetes was the only vascular risk factor associated with RLS in men[70]. In the female cohort, no significant relationships were observed between RLS and prevalent CVD (major CVD, myocardial infarction, and stroke)[69]; however, in the male cohort, prevalent stroke was associated with an increased risk of RLS (1.40 [1.05–1.86) and prevalent myocardial infarction was associated with a decreased risk of RLS (0.73 [0.55–0.97])[70]. The authors suggest that RLS may be a marker for increased prevalence of vascular risk factors, rather than an independent risk factor for CV events.

The potential relationship between RLS and CVD has also been investigated in prospective studies. In a cohort of older men (aged 55–69 years; $n = 1986$) followed up for 10 years, RLS was associated with ischemic stroke (adjusted OR = 1.67 [95% CI: 1.07–2.06]; $P = 0.024$). Men with RLS also had a slightly increased risk for an ischemic heart disease event; however, this was not statistically significant (OR = 1.24 [95% CI: 0.89–1.74), $P = 0.206$)[71]. Li *et al.* carried out a prospective study of RLS and coronary heart disease (CHD) among women in the Nurses' Health Study ($n = 70,977$; mean follow-up: 5.6 years)[72]. Women with a duration of RLS of ≥3 years had an elevated risk of developing CHD (multivariable-adjusted HR = 1.72 [95% CI: 1.09–2.73]; $P = 0.03$), non-fatal MI (1.8 [1.07–3.01]) and fatal CHD (1.49 [0.55–4.04]) in comparison to women without RLS[72]. In contrast to these results, no associations between RLS and CVD were observed in a large-scale study involving two cohorts: 29,756 female health professionals (aged ≥45 years; mean follow-up 6 years), and 19,182 male physicians (aged ≥40 years, mean follow-up 7.3 years)[73]. Following adjustment for vascular risk factors, RLS (diagnosed according to the IRLSSG) was not associated with an increased risk for major CVD, stroke, myocardial infarction, CVD death or coronary revascularization[73].

To date, most prospective studies have investigated the relationship between baseline RLS and incident CVD. However, Szentkiralyi *et al.* evaluated whether CV risk factors and vascular diseases predict the development of RLS based on data from the Dortmund Health Study (DHS, $n = 1312$, median follow-up: 2.1 years) and the Study of Health in Pomerania (SHIP, $n = 4308$, median follow-up: 5 years)[74]. Obesity was a risk factor for incident RLS in the DHS study (OR = 2.06 [95% CI: 1.22–3.47]; $P < 0.01$), and diabetes (1.89 [1.18–3.03]; $P < 0.01$), hypertension (1.41 [1.02–1.94]; $P = 0.04$) and hypercholesterolemia (1.4 [1.02–1.92]; $P = 0.04$) were each associated with incident RLS in the SHIP study. A history of MI or stroke was not a predictor of RLS. When the analysis was reversed, the presence of RLS at baseline was not associated with an increased risk of developing a CV risk factor or vascular disease. However, the authors note that the short follow-up periods of the two studies may have been insufficient to detect RLS-related CV risk.

Although most of the relevant studies have supported an association between RLS and CVD, some have had conflicting results. Further investigation is needed in order to fully elucidate the relationship between RLS and CVD.

Pain

Sleep disturbances may have a role in increasing and prolonging pain and fatigue[75]. Many patients with RLS describe their symptoms as painful; this may be due, at least in part, to dopaminergic dysfunction as dopaminergic pathways may be involved in pain modulation and analgesia[76].

Polyneuropathy

The paresthesias and dysesthesias associated with polyneuropathy are very similar to RLS symptoms and may result in misdiagnosis of RLS[77]. Differentiating features include a more frequent distal extremity 'burning' complaint in polyneuropathy and/or the circadian intensification of RLS later in the day, normally higher in the calf or thigh. Polyneuropathy may be comorbid with RLS, and patients with both conditions can often distinguish between neuropathic and RLS discomfort.

Studies investigating the prevalence of RLS in polyneuropathy have varied considerably in terms of their design and the subtypes of polyneuropathy present within the patient population[78–81]. In a prospective study that used the IRLSSG diagnostic criteria, the prevalence of RLS among 28 patients with chronic inflammatory demyelinating polyneuropathy was 39%, in comparison to 7% among 28 age- and gender-matched controls ($P<0.01$)[80]. In contrast, a case–control study found no difference in the prevalence of confirmed RLS (determined by a movement disorder specialist) between 245 patients with peripheral neuropathy and 245 age- and gender-matched controls (12% vs. 8%, $P=0.14$); however, an increased prevalence of RLS was found among patients with hereditary neuropathy ($P=0.016$)[79]. In another study, the prevalence of RLS (according to the IRLSSG criteria) among 97 patients with polyneuropathy (30%) exceeded the estimated prevalence in the general population (7–10%), and was significantly greater than in other neurologic patients. Small-fiber sensory neuropathy was significantly more common among patients with RLS, suggesting that abnormal sensory inputs related to polyneuropathy may play a role[78]. Studies of RLS among diabetic neuropathy patients have shown a prevalence ranging from 9% to 33%[82,83]. Among a cohort of 99 patients with diabetic neuropathy, small-fiber neuropathy and symptoms of 'burning feet' were more common among the 33 patients with RLS[83]. The frequent occurrence of RLS in association with thermal dysesthesias may be due to the involvement of small sensory fibers; abnormal sensory inputs from small fibers may trigger RLS[83].

Polydefkis *et al.* used skin biopsies to investigate the prevalence of large-fiber neuropathy and small sensory fiber loss (SSFL) in 22 patients with RLS[84]. Neuropathy was identified in 8 patients (36%): 3 had pure large-fiber neuropathy, 2 had mixed large-fiber neuropathy and SSFL, and 3 had pure SSFL. Patients with SSFL had a later age of RLS onset ($P<0.009$), tended to have no family history of RLS ($P<0.078$), and were more likely to report painful symptoms ($P<0.001$) compared to patients without SSFL. These authors suggest that a distinct subform of RLS may be triggered by the painful dysesthesias associated with SSFL.

The relationship between neuropathic pain and RLS (diagnosed according to the IRLSSG criteria) was specifically investigated in two studies[85,86]. Firstly, a retrospective study reported a significantly higher frequency of RLS among patients with painful or dysesthetic polyneuropathy ($n=102$) compared with patients with non-painful neuropathy ($n=178$) (40% vs. 16%, $P<0.001$). RLS was significantly associated with decreased small fiber input. The second study prospectively evaluated 58 patients with distal symmetric polyneuropathy (DSP) and symptoms of neuropathic pain or dysesthesia[86]. The prevalence of RLS among patients with DSP (36.2%) was higher than among age- and gender-matched healthy controls (3.6%; $P<0.0001$). No significant differences were seen between DSP patients with and without RLS in terms of the cause, pattern (small fiber neuropathy/mixed small–large fiber neuropathy) and sensory profile of painful neuropathy[86].

Somatoform pain disorder

Patients with sleep disorders have an increased risk of developing somatoform symptoms[75,87]. An RLS prevalence of 42% was reported among 100 patients with somatoform pain disorder attending an outpatient clinic[75]. Those with somatoform pain disorder and RLS experienced longer periods of pain and were more likely to experience continuous pain than those without RLS. Pain duration and pain parameters (maximal, medium, and minimal pain) increased with RLS severity. Several possible connections between RLS and somatoform pain have been described in the literature[75]. Disturbance of the monoaminergic system due to glucocorticoid induced monoamine depletion occurs as a result of chronic pain. Monoaminergic dysfunction of the dopamine system may play a role in the pathophysiology of RLS, as dopamine is required for the synthesis of noradrenaline[75]. Pathophysiologic mechanisms link sleep disturbances, which are common among RLS patients, to pain. The use of non-opioid analgesics in conjunction with antidepressants is common among patients with somatoform pain disorder and may increase the risk of developing RLS (Table 2)[55,75].

Rheumatoid arthritis

A high prevalence of RLS has been observed among patients with rheumatoid arthritis (RA)[88–90]. In a questionnaire survey, 28% (41/148) of respondents with RA and 24% (11/45) of respondents with osteoarthritis met all four IRLSSG diagnostic criteria for RLS[90]. Although 52 (27%) respondents met all four IRLSSG criteria, only 5 (3%) had a previous RLS diagnosis. This suggests that RLS symptoms may be misinterpreted as symptoms of arthritis. Interestingly, 91% (69/76) of patients with RLS symptoms (patients meeting ≥ 1 of the IRLSSG criteria) felt that they could distinguish between RLS and arthritic symptoms, yet only 13 (17%) had sought medical attention for RLS.

Fibromyalgia

Fibromyalgia and RLS are both more prevalent among women than men, share in the complaint of sensory abnormality, and are associated with PLMS, fatigue, and insomnia[91,92]. Fibromyalgia may be misdiagnosed as RLS or vice versa[92]. Studies of patients with fibromyalgia have shown a prevalence of RLS of 20–66%; however, in many of these studies the criteria for diagnosing RLS and/or fibromyalgia were poorly defined[92]. Fibromyalgia and RLS may share a similar dopaminergic pathophysiology[91,92], and dopaminergic treatment has been shown to be beneficial in improving fibromyalgia symptoms[93]. Furthermore, the paresthesias associated with fibromyalgia may share a similar pathogenetic mechanism to those associated with RLS[94]. Antidepressants are commonly prescribed to treat patients with fibromyalgia; as previously discussed, the use of these medications may exacerbate RLS symptoms[92].

Secondary RLS

Iron deficiency

As previously mentioned, iron/transferrin abnormalities are implicated in the pathophysiology of RLS, and iron deficiency is widely recognized as a major secondary cause of the disorder[4]. In a prospective study of patients with RLS attending a sleep disorders clinic ($n = 302$), 31% were found to have low serum ferritin levels (<50 µg/l)[95]. High incidences of secondary RLS have been reported among populations at increased risk for iron insufficiency, for example pregnant women and patients with ESRD (as discussed later in this article). A hospital-based study in patients with iron-deficiency anemia reported a prevalence of RLS of 41%; however, these data were limited by small sample sizes and the absence of standardized assessment criteria[96]. A more stringent study[97] included 251 patients with both anemia (Hgb < 14 for males and <12 for females) and iron deficiency (serum ferritin <20 µg/l or transferrin saturation <19%) attending a community-based hematology practice. Clinically significant RLS (diagnosed via a validated questionnaire[98]) was present in 23.9% of anemic patients[97], considerably higher than the prevalence of 2.7% reported within the general population[19]. A high prevalence of RLS has also been reported among blood donors[99–101] who may have donation-induced iron depletion[102]. However, several studies have failed to show an association between RLS, donation frequency[99,100,103] and donor iron status[99,104].

Pregnancy

Although RLS is the most common movement disorder in pregnancy, it is poorly recognized by obstetricians[105]. Data from epidemiological studies indicate that RLS affects 10–34% of pregnant women[105–116]. Two prospective studies have examined RLS in pregnancy using the IRLSSG criteria. The prevalence of RLS among 500 pregnant women completing a mailed questionnaire was 17% in the first trimester, 27.1% in the second trimester, and 29.6% in the third trimester[115]. In the second study, 501 pregnant women were assessed for RLS by their attending physician and diagnosis was confirmed by an experienced neurologist. The reported prevalence of RLS was 12%[111]. Among the women with RLS, 51% experienced RLS symptoms 5–7 times per week.

Factors associated with RLS in pregnancy include anemia (iron and folate deficiency), a history of childhood growing pains, and a family history of RLS and growing pains[105]. Estrogen has also been implicated in pregnancy-related RLS[117]. This is supported by data from a community-based cohort study ($n = 535$) that showed increased odds of developing RLS among estrogen users (OR = 2.5 [95% CI: 1.17–5.10]; $P = 0.017$)[27]. Patients with pre-existing RLS tend to experience worsening of symptoms during the third trimester, and women with new-onset RLS tend to experience transient symptoms which appear during the third trimester and normally end within days after delivery[113]. Iron and folate supplementation may improve RLS symptoms in women with low serum ferritin levels; if symptoms are severe, treatment with opiates, gabapentin, or benzodiazepines may be considered as these drugs have an extensive safety record in pregnancy[118].

End-stage renal disease

Most studies examining the association between RLS and kidney disease have focused on dialysis-dependent patients with ESRD. A wide variability in rates of RLS (7–83%) has been observed among patients undergoing dialysis[119]. This is likely to be due to differences in patient numbers, dialytic strategies, and criteria used to diagnose RLS[119]. Four large-scale studies used the IRLSSG criteria and found a prevalence of RLS of 12–29%[119–122]. In one study, few patients reported symptoms prior to dialysis and/or had a family history of the disorder, suggesting that hemodialysis may be associated with a distinct secondary form of RLS[120]. Presence of RLS was associated with anemia[121], high serum phosphate levels[121], lower hemoglobin levels[120], insomnia[119], anxiety[119,121], depression[119,120], emotion-orientated coping with stress[121], obstructive sleep apnea[120], poor sleep quality[120], and excessive daytime sleepiness[120]. As reported earlier, the significant association between RLS and depression has been shown to be partly independent of insomnia in patients with ESRD[51].

Few studies have evaluated RLS in patients with non-dialysis-dependent chronic kidney disease (CKD).

A case–control study found that non-dialyzed patients with chronic renal function ($n = 138$) had an almost five-fold increased risk of RLS occurrence than controls with normal renal function ($n = 151$) (OR = 4.9 [95% CI: 1.6–14.7]; $P = 0.004$)[123]. Another study investigated the prevalence of RLS among 500 nephrology patients with varying degrees of kidney function. A similar RLS prevalence was observed among patients with ESRD on dialysis (26%), patients with non-dialysis dependant CKD (estimated glomerular filtration rate [eGFR] < 60: 26%), and patients with normal renal function (eGFR ≥ 60: 18.9%) ($P = 0.27$)[124]. Patients were recruited from nephrology clinics; therefore, patients included in the 'normal' group (eGFR ≥ 60) likely had some form of renal abnormality. In this study, RLS was not correlated with the severity of kidney disease. In contrast, two studies of non-dialyzed patients have reported an association between RLS and worsening severity of CKD[125,126]. In a Japanese study, a higher prevalence of RLS was observed among 514 patients with CKD than among 535 matched controls (3.5% vs. 1.5%, $P = 0.029$), and RLS prevalence increased with increasing CKD stage (stage 1 [eGFR: > 90]: 0%; stage 2 [60–89]: 1%; stage 3 [30–59]: 4.2%, stage 4 [15–29]: 3.2%; stage 5 [<15]: 7.4%) ($\chi^2 = 8.08$, $P = 0.09$)[125]. Renal failure (CKD stage >3) was present in 94% of CKD patients with RLS, compared with 70% of CKD patients without RLS ($P = 0.016$)[125]. Similarly, a study of 301 hospital patients (aged ≥50 years) showed an increasing prevalence of RLS with worsening renal function (no significant CKD: 15.5%; stage 3: 20.4%; stage 4: 35.3%; stage 5: 28.6% (χ^2 for trend = 5.3, $P = 0.04$)[126]. None of the patients with CKD were on dialysis. Patients with stage 4 CKD had a three-fold higher risk of RLS than those without CKD (adjusted OR = 3.08 [1.10–10.28]; $P = 0.05$). Together, these studies indicate that RLS is a common comorbidity among non-dialyzed patients with CKD.

Uremic RLS may be associated with more rapid disease progression, greater subjective disease severity, and a higher severity of sleep disturbance compared with idiopathic RLS[127]. In addition, patients with uremic RLS may have a poorer response to dopaminergic treatment than patients with idiopathic RLS[127]. Intravenous iron administration has been associated with a reduction in RLS symptoms in patients with ESRD[128]. Oral iron administration may be less suitable for patients with chronic renal disease, as their intestinal iron absorption is often impaired due to disorders of hepcidin/ferroportin regulation and inflammation[129]. The presence of RLS among dialyzed uremic patients does not seem to be associated with cause of ESRD[119], transplant history[119], or type of dialysis[119,130,131]. Two studies have shown a relationship between RLS and time on dialysis[119,132], and one study has shown an increased risk of insomnia among patients undergoing dialysis treatment for over 12 months[133]; however, other studies have had conflicting results[130,131]. RLS symptoms have been shown to improve in patients with ESRD following kidney transplantation[134].

In patients on dialysis, RLS has been shown to be associated with lower quality of life[135,136] and severe RLS symptoms have been associated with increased mortality[136,137]. A study of 804 kidney transplant recipients reported significantly greater mortality after 4 years among patients who had RLS at baseline (univariate HR for the presence of RLS: 2.53 [95% CI: 1.31–4.87]) compared with those without the disorder. RLS was a significant predictor of mortality (HR = 2.02 [95% CI: 1.03–3.95])[138]. RLS is also associated with poor sleep, insomnia, and impaired quality of life among patients receiving a kidney transplant[139]. Sleep disturbances associated with RLS may contribute to the development of cardiovascular complications and infections, which are significant causes of mortality in patients with ESRD[119]. In a prospective, observational study of 100 patients on dialysis, a higher severity of RLS (intermittent vs. continuous) was associated with a higher risk of new cardiovascular events and higher short-term mortality[140]. Similarly, PLMS are an independent predictor of higher cardiovascular and cerebrovascular risk in patients with chronic kidney disease[141].

Other comorbidities

RLS has been linked in the literature with a number of other medical conditions, including narcolepsy, obesity, migraine, and Parkinson's disease. Since the evidence for these associations comes mainly from epidemiologic studies (Table 3), more research is needed. Dopaminergic dysfunction has been implicated in many potential comorbidities. For example, modification of dopaminergic pathways has been reported in narcolepsy[188], obesity has been shown to decrease D2 receptor availability in the brain[189] migraine has been associated with dysfunctions in dopamine and iron metabolism[156], and the involvement of dopamine deficiency in the pathophysiology of Parkinson's disease is well established[190]. Determining the prevalence of RLS among patients with PD is particularly challenging due to the difficulty in discriminating between PD-related akathisia and the sensory symptoms of RLS. As dopaminergic treatment for PD is efficacious in ameliorating RLS symptoms, the incidence of RLS among patients with PD may be underestimated[191]. Conversely, long-term dopaminergic therapy may contribute to the emergence of RLS in patients with PD due to dopaminergic-related augmentation (exacerbation) of previously subclinical symptoms[191].

Table 3. Comorbidities which may be associated with RLS based on epidemiological data.

Comorbidity	Study type	RLS assessment	Main results
ADHD			
Pullen *et al.*, 2011[142]	Retrospective review of medical records (374 patients with child-onset RLS)	IRLSSG criteria	Prevalence of ADHD: 25%
Picchietti *et al.*, 2007[143]	Cross-sectional survey (10,523 households with children aged 8–17 years)	IRLSSG criteria for childhood RLS	Prevalence of ADD/ADHD among children with definite RLS: 8–11 year age group, 14.8%; 12–17 year age group, 17.6%
Kotagal and Silber, 2004[144]	Retrospective chart review (32 children with RLS)	IRLSSG criteria for childhood RLS	'Inattentiveness' seen in 25% of children with RLS
Wagner *et al.*, 2004[145]	Cross-sectional study (62 RLS patients, 32 insomnia patients, 77 controls)	IRLSSG criteria	Prevalence of 'highly probable' ADHD: RLS patients, 24%; insomnia patients, 3%; controls, 4% ($P<0.01$)
Chervin *et al.*, 2002[146]	Cross-sectional survey (866 children aged 2–14 years)	RLS item of the Pediatric Sleep Questionnaire	Prevalence of hyperactivity: children with RLS, 18%; children without RLS, 11%
Picchietti *et al.*, 1998[147]	Controlled cohort study (69 children with ADHD, 38 controls)	Modified 1995 IRLSSG criteria designed to minimize misdiagnosis in children	Prevalence of RLS: children with ADHD, 12%; controls, 3%
Chervin *et al.*, 1997[148]	Cross-sectional study (70 children attending psychiatric clinic, 73 children attending general pediatrics clinic)	Pediatric Sleep Questionnaire	Prevalence of RLS symptoms: children with ADHD, 15%; children with a non-ADHD psychiatric disorder, 5%; and general pediatric patients, 10%
ED			
Li *et al.*, 2013[149]	Prospective cohort study (10,394 men)	IRLSSG criteria	Men with RLS had a higher risk of developing ED over 6 years of follow-up (RR = 1.38 [95% CI: 1.14–1.68]; $P=0.001$) Higher frequency of RLS symptoms associated with increased risk of ED (Ptrend = 0.001)
Gao *et al.*, 2010[150]	Cross-sectional study (23,119 men)	IRLSSG criteria (patients were required to have symptoms $\geq$5 times/month)	Prevalence of ED: RLS patients, 53%; patients without RLS, 40% (age-adjusted OR = 1.47 [95% CI: 1.3–1.7]) Higher frequency of RLS symptoms associated with increased risk of ED
Liver disease			
Franco *et al.*, 2008[151]	Cross-sectional study (141 patients with chronic liver disease)	IRLSSG criteria	Prevalence of RLS: 62%. Prevalence of RLS in patients without known risk factors (e.g., kidney disease, iron deficiency, and anemia): 56%
Migraine			
Winter *et al.*, 2013[152]	Cross-sectional study (22,926 men participating in the Physicians' Health Study)	IRLSSG criteria	Prevalence of migraine: 12.3%; prevalence of RLS: 7.5% Migraine was associated with an increased risk of having RLS (multivariable-adjusted OR = 1.20 [95% CI: 1.04–1.38])
Schürks *et al.*, 2012[153]	Cohort study (31,370 women participating in the Women's Health Study)	IRLSSG criteria	Prevalence of migraine: 21.9% Women with migraine had an increased risk for RLS (multivariable-adjusted OR = 1.22 [95% CI: 1.13–1.32])
Seidel *et al.*, 2012[154]	Case–control study in children and adolescents aged 5–18 years (111 migraine patients, 73 headache-free controls)	IRLSSG criteria	Prevalence of 'definite' RLS: migraine, 22%; controls, 5% (OR = 3.9 [95% CI: 1.4–10.9], $P<0.001$)
Lucchesi *et al.*, 2012[155]	Case–control study (277 patients with migraine [episodic: 175; chronic: 102], 200 healthy controls)	IRLSSG criteria	Prevalence of RLS: migraine patients, 22.7%; controls, 7.5% ($P<0.0001$). RLS was more common with chronic than episodic migraine (34.3% vs. 16%; $P=0.0006$)
Chen *et al.*, 2010[156]	Cross-sectional study (1041 patients attending a headache clinic)	IRLSSG criteria	Higher prevalence of RLS in patients with migraine (11%) versus patients with tension type headache (5%) or cluster headache (2%) ($P=0.002$)
d'Onofrio *et al.*, 2008[157]	Case–control study (200 patients with headache, 120 controls)	IRLSSG criteria	Prevalence of RLS: headache patients, 22%; controls, 8% ($P=0.002$)
Rhode *et al.*, 2007[158]	Case–control study (411 patients with migraine, 411 controls)	IRLSSG criteria	Prevalence of RLS: migraine patients, 17%; controls, 6% ($P<0.001$; OR = 3.5 [95% CI: 2.2–5.8])

(continued)

Table 3. Continued.

Comorbidity	Study type	RLS assessment	Main results
Young *et al.*, 2003[159]	Cross-sectional study (50 patients with severe headache [41 had migraine])	IRLSSG criteria	Prevalence of RLS: 34%
MS			
Li, 2012[160]	Cross-sectional study (65,544 women [aged 41–58 years])	IRLSSG criteria (RLS symptoms ≥5 times/month)	Prevalence of RLS: women with MS, 15.5%; without MS, 6.4% (adjusted OR = 2.72 [95% CI: 1.89–3.93]) Prevalence of severe RLS: women with MS, 9.9%; without MS, 2.6% (adjusted OR = 4.12 [2.65–6.42]) Over 4 years of follow-up, women with MS had a higher risk of severe RLS compared with those without MS (adjusted RR = 3.58 [95% CI: 1.53–8.35])
Vavrova *et al.*, 2012[161]	Cross-sectional study (765 patients with MS)	IRLSSG criteria	Diagnosis of RLS: 32.1%
Aydar *et al.*, 2011[162]	Case–control study (98 patients with definite MS and 129 healthy volunteers)	IRLSSG criteria	Prevalence of RLS: MS patients, 27.6%; controls, 10.1% (OR = 2.55; *P* = 0.018)
Fragoso *et al.*, 2011[163]	Case–control study (80 MS patients, 180 controls)	IRLSSG criteria	Prevalence of RLS: MS patients, 58%; controls, 18% (OR = 6.02 [95% CI: 3.36–10.78]) Average severity of RLS symptoms was higher in MS patients
Deriu *et al.*, 2009[164]	Case–control study (202 MS patients, 212 controls)	IRLSSG criteria	Prevalence of RLS: MS patients, 14%; controls, 3% Risk of RLS was 5 times higher in MS patients (OR = 5.76; *P* = 0.00002)
Manconi *et al.*, 2008[165]	Case–control study (861 MS patients, 649 controls)	IRLSSG criteria (RLS symptoms ≥2 times/month)	Prevalence of RLS: MS patients, 19%; controls, 4% Risk of RLS was 5.4 times higher in MS patients (OR = 5.4 [95% CI: 3.56–8.26])
Moreira *et al.*, 2008[166]	Cross-sectional study (44 MS patients)	IRLSSG criteria	Prevalence of RLS: 27%
Manconi *et al.*, 2007[167]	Cross-sectional study (156 MS patients [100 females, 56 males])	IRLSSG criteria (RLS symptoms ≥1 time/week)	Prevalence of RLS: 32.7% RLS preceded clinical MS onset in 8.5% of cases
Gómez-Choco *et al.*, 2007[168]	Case–control study (135 MS patients, 118 controls)	IRLSSG criteria	Prevalence of RLS: MS patients, 13%; controls, 9% (*P* = not significant)
Auger *et al.*, 2005[169]	Case–control study (200 MS patients, 100 controls)	IRLSSG criteria	Prevalence of RLS: MS patients, 38%; controls, 16%
Narcolepsy			
Plazzi *et al.*, 2012[170]	Case–control study (17 patients with narcolepsy and RLS, 68 age- and gender-matched controls [34 with narcolepsy, 17 with idiopathic RLS, and 17 healthy controls])	IRLSSG criteria (RLS symptoms recurring ≥2 times/week during preceding 6 months)	Age at onset of RLS in patients with narcolepsy: 34.2 years In the majority of cases (12/17), the onset of narcolepsy preceded RLS symptoms Structure of PLMS in narcolepsy with RLS was similar, but not identical, to that of PLMS in idiopathic RLS
Plazzi *et al.*, 2010[171]	Case–control study (184 narcolepsy patients, 235 controls)	IRLSSG criteria (RLS symptoms ≥2 times/week)	Prevalence of RLS: narcolepsy patients, 15%; age-matched controls, 3% (OR = 5.6 [95% CI: 2.38–13.18])
Ferri *et al.*, 2007[172]	Cross-sectional study (521 patients attending neurology clinic [9 narcolepsy patients])	Single question based on IRLSSG criteria	Prevalence of RLS in narcolepsy patients: 2 of 9 patients
Obesity			
Gao *et al.*, 2009[173]	Cross-sectional study (65,554 women, 23,119 men)	IRLSSG criteria (patients were required to have restless legs ≥5 times/month)	Obesity (BMI ≥30 vs. <23 kg/m^2) (OR = 1.42 [95% CI: 1.30–1.55; *P* trend <.0001]), higher waist circumference (OR = 1.60 [95% CI: 1.45–1.78; *P* trend <.0001), greater BMI in early adulthood (OR = 1.24 [95% CI: 1.01–1.52; *P* trend <0.004]), and weight gain (OR = 1.41 [90% CI: 1.28–1.55; *P* trend <0.0001]) were all associated with a higher prevalence of RLS
Kim *et al.*, 2005[36]	Cross-sectional study (5228 women, 4711 men)	Single question	RLS significantly associated with obesity in women (BMI ≥25 vs. <25 kg/m^2; OR = 1.19 [95% CI: 1.10–1.39; *P* < 0.05]) but not in men (OR = 1.1 [95% CI: 0.89–1.37; *P* = not significant])

Ohayon and Roth, 2002[63]	Cross-sectional study ($n = 18,980$)	Minimal criteria for RLS as defined by the International Classification of Sleep Disorders	OR for RLS was 1.22 (95% CI: 1.03–1.45) for BMI of >27 versus <27 kg/m^2
Phillips *et al.*, 2000[174]	Cross-sectional study ($n = 1803$)	Single question based on IRLSSG criteria	Higher BMI (per increased increment of 5 kg/m^2) correlated with RLS (OR = 1.31 [95% CI: 1.11–1.53])
PD			
Bhalsing *et al.*, 2013[175]	Case–control study (187 patients with parkinsonian disorders [134 with PD], 172 healthy controls)	IRLSSG criteria	Prevalence of RLS: all Parkinsonian patients, 9.6%; patients with PD, 11.9%; controls, 2.9%
Rajabally and Martey, 2013[176]	Case–control study (37 patients with PD, 37 age- and gender-matched controls)	IRLSSG criteria (patients were required to have RLS symptoms for ≥2 days/week)	Prevalence of RLS was comparable in patients with PD (16.2%) and controls (10.8%; $P = 0.30$)
Shin *et al.*, 2013[177]	Cross-sectional study (151 drug-naive PD patients)	IRLSSG criteria	Prevalence of RLS: 16.5%
Angelini *et al.*, 2011[178]	Case–control study (109 *de novo* PD patients, 116 controls)	IRLSSG criteria	Overall lifetime prevalence of RLS: PD patients, 6%; controls, 4% (P = not significant) No significant difference in prevalence of current/previous RLS in PD patients or controls
Gjerstad *et al.*, 2011[179]	Case–control study (200 drug-naive patients with early PD, 173 age- and gender-matched controls)	IRLSSG criteria	Leg restlessness: PD patients, 40.5%; controls, 17.9% (RR = 2.26 [95% CI: 1.57–3.24], $P < 0.001$) Prevalence of RLS: PD patients, 15.5%; controls, 9.3% (RR = 1.68 [95% CI: 0.95–2.96], $P = 0.07$)
Gao *et al.*, 2010[180]	Cross-sectional study (23,119 men)	IRLSSG criteria	OR for PD was 1.99 (95% CI: 1.1–3.6; $P = 0.02$) for men with RLS symptoms compared with men without RLS
Guerreiro *et al.*, 2010[181]	Cross-sectional study (48 PD patients)	IRLSSG criteria	Prevalence of RLS: 19%
Lee *et al.*, 2009[182]	Cross-sectional study (447 consecutive patients with PD attending a hospital)	IRLSSG criteria	Prevalence of RLS: 16.3% Duration of anti-Parkinson therapy (per year increase) was a contributing factor to the development of RLS (OR = 1.199 [95% CI: 1.014–1.419], $P = 0.034$)
Calzetti *et al.*, 2009[183]	Case–control study (118 outpatients with PD attending a movement disorders clinic, 110 age- and gender- matched controls)	IRLSSG criteria	Prevalence of current/previous RLS: PD patients, 12.7%; controls, 6.3% ($P = 0.16$)
Gómez-Esteban *et al.*, 2007[184]	Cross-sectional study (114 PD patients)	IRLSSG criteria	Prevalence of RLS: 22%
Nomura *et al.*, 2006[185]	Case–control study (165 PD patients, 131 controls)	IRLSSG criteria	Prevalence of RLS: PD patients, 12%; controls, 2% ($P < 0.01$)
Krishnan *et al.*, 2003[186]	Case–control study (126 PD patients, 128 controls)	IRLSSG criteria	Prevalence of past/current RLS: PD patients, 8%; controls, 1% ($P = 0.01$)
Ondo *et al.*, 2002[187]	Cross-sectional study (303 PD patients)	1995 IRLSSG criteria	Prevalence of RLS: 21%

ADD = attention-deficit disorder; ADHD = attention-deficit hyperactivity disorder; BMI = body mass index; CI = confidence interval; ED = erectile dysfunction; IRLSSG = International Restless Legs Syndrome Study Group; MS = multiple sclerosis; OR = odds ratio; PD = Parkinson's disease; RR = relative risk; RLS = restless legs syndrome.

Table 4. Presenting symptoms of RLS in children.

Symptom	
Leg discomfort	Limb pain/discomfort arising during periods of inactivity and primarily occurring during the evening and at night. Unexplained limb discomfort may be attributed to 'growing pains'
Urge to move	Difficulty sitting still particularly in the late afternoon or evening (fidgeting, running, stretching, walking, rocking, etc.)
Behavioral problems at bedtime	Reluctance to go to bed, difficulty staying in bed and falling asleep
Sleep disruption	Restless sleep, nighttime awakenings, child may get out of bed and move around during the night
Daytime sleepiness	Difficulty waking in the morning, falling asleep at school/inappropriate times, increased need for naps
Behavioral problems during the day	Reduced academic performance, irritability, moodiness, aggression, lack of concentration, and/or hyperactivity

Pediatric RLS

Approximately 40% of adults with RLS first experience symptoms as children or adolescents[14]. Symptoms may remit and then reappear when the patient is 30–40 years of age. A large epidemiological study (10,523 families) found a prevalence of RLS of 1.9% among 8–11-year-olds and 2.0% among 12–17-year-olds[143]. Clinical diagnosis is complicated as younger children in particular may struggle to describe subjective symptoms. Children with RLS may present with different symptoms to adults, and may exhibit mood and behavioral problems as a result of disrupted sleep (Table 4)[192].

The IRLSSG has developed specific criteria for the diagnosis of pediatric RLS[6]. These criteria are stricter than those required for a diagnosis of adult RLS in order to prevent over-diagnosis and to account for high levels of motor activity exhibited by children[6]. For a diagnosis of 'definite' RLS, children (aged 2–12 years) must fulfill all of the adult diagnostic criteria and describe symptoms consistent with leg discomfort. If a child is unable to describe their symptoms, they must fulfill two of the following three supportive criteria: (1) sleep disturbance atypical for their age; (2) biological parent or sibling with definite RLS; (3) polysomnographically documented periodic limb movement (PLM) index of at least 5 PLM/hour of sleep. Criteria for 'probable' and 'possible' RLS have also been developed for use in children up to the age of 18 years[6].

An epidemiological survey performed in the United States and United Kingdom found that only 11% (9/81) of children (aged 8–11 years) and 11% (14/125) of adolescents (aged 12–17 years) who fulfilled IRLSSG criteria for definite RLS had previously been diagnosed with the disorder[143]. Many confounds in the differential diagnosis of RLS (Table 1) occur in children as well as in adults. In addition, childhood onset RLS may be misdiagnosed as growing pains[193]. A high prevalence of comorbid conditions has been observed in pediatric RLS patients. In a retrospective assessment of 18 children and adolescents with RLS, attention-deficit hyperactivity disorder (ADHD), anxiety, depression, parasomnia, and oppositional defiant disorder were each found in >20% of patients[194]. Up to 25% of patients with RLS may suffer from ADHD[142] (Table 3), and the two disorders share similar features. For example, sleep deprivation due to RLS may result in behavior consistent with ADHD, and iron deficiency and dopamine dysfunction have been implicated in the pathophysiology of both conditions[192].

As previously discussed, RLS may occur secondary to CKD. Studies of pediatric patients with CKD have reported an RLS prevalence ranging from 10% to 35%[195–199]. This range includes both dialysis-dependent and non-dialysis-dependent patients. The wide variation in reported RLS prevalence is likely due to differences in the severity of CKD within the patient populations, the study methodologies and the criteria that were used to diagnose RLS. The most rigorous study was a controlled cross-sectional investigation of CKD patients aged 8–18 years who were recruited from outpatient clinics and a hemodialysis unit. The NIH criteria were applied for diagnosis of RLS and patients with mimic conditions were systematically excluded[199]. An RLS prevalence of 15.3% was observed among children with CKD, in comparison to 5.9% among healthy controls ($P = 0.04$)[199]. Of the 19 children with CKD and RLS, only five had told a healthcare provider about their RLS symptoms; one child had received a diagnosis of RLS, one had been diagnosed with growing pains, and one with muscle cramps[199]. These results illustrate the importance of screening and differential diagnosis of RLS in children who may be at increased risk of the disorder due to the presence of potential comorbidities.

Management of RLS symptoms

Once correctly diagnosed, management strategies for RLS are defined by the severity and frequency of symptoms. In mild cases, symptoms may be improved by lifestyle changes and self-help measures[200]. Education, improvements in sleep hygiene, cognitive behavioral therapy and distracting techniques such as reading, stretching, massage, and exercise may help patients to cope with their symptoms[200,201]. Improvements in RLS-related quality of life, mental health status, and subjective ratings of RLS symptom severity have been observed in patients receiving

cognitive behavioral therapy to improve their coping strategies[201]. Medications such as SNRIs, SSRIs, and dopamine blockers should be reviewed by the patient's medical team and avoided if possible, as should caffeine and excessive alcohol in the afternoon and evening (Table 2)[200]. Possible secondary causes of RLS should be identified and treated whenever possible.

Treatment with oral iron reduces RLS symptoms in many, but not all, patients with low peripheral iron stores[4]. Patients with low serum ferritin levels (10–50 ng/mL) should be given oral iron supplementation. The standard supplement is 325 mg of ferrous sulfate, taken orally three times per day in combination with vitamin C to aid absorption[202]. Unfortunately, gastrointestinal symptoms, particularly constipation, often limit the successful use of iron supplements. Formulations of iron that attempt to reduce constipation may be better tolerated by patients. Intravenous iron has been proposed as a method to reduce the gastrointestinal side effects, but evidence for its efficacy is limited. Low-to-moderate responder rates have been reported[203–205], with few responders experiencing a sustained therapeutic effect past 6 months[204]. Blood transfusions can be considered for severely anemic patients[200].

Patients with moderate-to-severe symptoms of RLS show disturbance of daily activities, quality of life and/or sleep, and benefit from pharmacologic therapy[200]. A number of effective treatment options are available (Table 5). Three non-ergot dopamine agonists, pramipexole, ropinirole, and rotigotine transdermal system, are approved for the treatment of moderate-to-severe idiopathic RLS by the US Food and Drug Administration and the European Medicines Agency. In addition, the α-2-δ calcium-channel ligand gabapentin enacarbil is approved for the treatment of moderate-to-severe RLS in the United States and Japan[206,210].

Treatment guidelines recommend non-ergot dopamine receptor agonists for initial treatment of patients with very severe RLS symptoms, excessive weight, comorbid depression, increased risk of falls or cognitive impairment[202,207]. Randomized controlled trials have demonstrated the efficacy of pramipexole, ropinirole and rotigotine versus placebo in improving RLS symptom severity, as assessed by the International Restless Legs Syndrome Study Group rating scale[206–208]. Based on the available evidence, all three agents are considered 'effective' in treating RLS for up to 6 months[207]. Longer-term studies are limited; ropinirole and pramipexole have been established as 'probably' effective for up to 1 year, and rotigotine as 'probably effective' for up to 5 years[207]. No head-to-head comparisons have been performed. Pramipexole and ropinirole are administered orally, and should be taken 1–3 h before bedtime, or upon symptom onset. Extended release formulations are available but have not been evaluated in RLS. Rotigotine is administered via a transdermal patch which is applied once daily, and worn for 24 hours before being replaced. This 24 hour coverage may be particularly beneficial for patients who experience RLS symptoms during the day[202]. Doses of all three medications should be kept low in order to minimize potential side effects. Dopaminergic adverse events include nausea, fatigue, headache, dizziness, orthostatic hypotension and daytime somnolence[206–208]. Hypersomnia and sleep attacks may occur at higher doses. Skin reactions related to rotigotine patch application were reported in 58% of patients with RLS participating in a 5 year open-label study[211]. Impulse control disorders (ICDs) such as compulsive shopping, pathologic gambling and punding may develop in 6–17% of patients taking dopamine receptor agonists[207].

Augmentation (treatment-induced exacerbation of RLS symptoms) is the main complication of long-term dopaminergic therapy and was first reported with the dopamine precursor levodopa, the first dopaminergic therapy to be used for RLS. Characteristic features of augmentation include an increase in RLS symptom intensity, the onset of symptoms earlier in the day, a shorter time to symptom onset during periods of rest, spread of symptoms to previously unaffected body parts, and a shorter period of relief following the administration of medication[212]. Affected patients experience a worsening of RLS symptoms beyond baseline levels and a paradoxical response to treatment; symptoms worsen following an increase in dose and improve following a dose reduction[212]. In order to reduce the risk of augmentation, dopaminergic therapy should be maintained at the lowest possible dose. As augmentation is associated with iron deficiency[213], serum ferritin levels should be monitored and iron treatment initiated if appropriate[212]. Augmentation appears to be less common with the dopamine agonists than with levodopa, although incidences cannot be directly compared due to a lack of comparative studies. Reported 6-month incidences were 60% with levodopa[214], 9.2% with pramipexole[215], 3.5% with ropinirole[216] and 1.5% with rotigotine[217]. The short-term efficacy (up to 6 weeks) of levodopa has been demonstrated in clinical trials[206] and occasional use may be beneficial for patients with intermittent RLS symptoms (Table 5). However, this medication is not recommended for chronic therapy due to the high risk of developing augmentation[202,206–208].

The α-2-δ ligands are recommended as initial treatment for patients whose sleep disturbance outweighs their sensory symptoms, comorbid insomnia, anxiety, or pain, or for patients with a history of anxiety or ICDs (Table 5)[202,207]. Gabapentin enacarbil is the only non-dopaminergic therapy approved by the FDA for the treatment of moderate-to-severe RLS. Its efficacy in improving RLS symptoms, as assessed by the IRLS, has been demonstrated in placebo-controlled trials of up to 52 weeks in duration[206]. Improvements in sleep architecture and mood have also been reported[206]. Long-term treatment guidelines consider gabapentin enacarbil 'probably effective' for 1 year of

Table 5. Pharmacological therapy for restless legs syndrome[202,206–209].

Medication	Dosing	Level of evidence	Choice of therapy	Potential side effects
Intermittent RLS symptoms				
Levodopa	**Carbidopa/levodopa**: titrate from 25 mg/100 mg to a maximum of 75/300 mg (12.5/50 mg increments every 4–7 days)	Short-term efficacy demonstrated in controlled trials	Not recommended for long-term therapy due to risk of developing augmentation	Nausea, fatigue, somnolence, augmentation
Low potency opioids or opioid agonists	**Codeine** (30–60 mg), **tramadol** (50–100 mg) or **oxycodone** (5–20 mg) taken as needed at bedtime, or during the day if breakthrough symptoms occur	Few controlled trials in RLS	Fast onset of action; useful for treating intermittent daytime symptoms	Constipation, nausea, respiratory depression; seizures and augmentation may occur with tramadol
Benzodiazepines/benzodiazepine agonists	**Temazepam** (15–30 mg), **zolpidem** (5–10 mg), **zaleplon** (5–10 mg), **eszopiclone** (1–3 mg)	No adequate controlled trials in RLS	Useful for patients with sleep disturbances	Morning drowsiness/unsteadiness may occur with long-acting agents
Daily RLS symptoms				
Non-ergot dopamine agonists	**Pramipexole**: 0.125–1 mg daily, taken 1–3 h before symptom onset; titrate in 0.125 mg increments every 2–3 days **Ropinirole**: 0.5–4 mg daily, taken 1.5 h before symptom onset; titrate in 0.25–0.5 mg increments every 2–3 days **Rotigotine**: 1–3 mg/24 h; titrate in 1 mg increments every 7 days	Efficacy of all three agents well established in randomized placebo-controlled trials	Recommended for very severe RLS, patients with comorbid depression or dysthymia, or obesity/metabolic syndrome; rotigotine 24 h patch may be advantageous for patients with daytime symptoms	Nausea, fatigue, somnolence, headache, augmentation, impulse control disorders, hypotension Skin reactions occur with rotigotine patch
Calcium channel α2δ ligand	**Gabapentin enacarbil**: 600–1200 mg taken once daily at 5 pm **Gabapentin**: 300–1200 mg daily, administered in once or twice daily doses; titrate in 300 mg increments every 7 days **Pregabalin**: 100–300 mg daily, administered in once or twice daily doses; titrate from 50 mg in 50 mg increments every 7 days	Efficacy of gabapentin enacarbil well established in randomized placebo-controlled trials; low level of evidence for pregabalin and gabapentin	May be useful for patients with comorbid pain, anxiety or insomnia, or for those who have previously experienced an impulse control disorder/addiction	Somnolence, dizziness, depression Weight gain and suicidal ideation reported with pregabalin
High potency opioids	**Oxycodone**, **hydrocodone** or **methadone** at low doses (~5–20 mg)	Evidence largely based on class III and IV studies; one 12 week controlled study showed superiority of oxycodone over placebo	May be useful for patients with an unsatisfactory response to therapy with dopamine agonists or α-2-δ ligands	Constipation, nausea, dizziness, sedation and respiratory depression Potential for addiction/tolerance

treatment[207]. Two other α-2-δ ligands, gabapentin and pregabalin, may be used off label (Table 5). Low-level evidence supports their use in RLS[206]. Common side effects of all three α-2-δ ligands include somnolence and dizziness[206,207]. There are no reports of augmentation with these medications. Weight gain and suicidal behavior and ideation may occur with pregabalin[206].

High potency opioids can be considered for patients whose RLS symptoms do not respond to therapy with dopamine agonists or with α-2-δ ligands (Table 5)[202]. Oxycodone, hydrocodone or methadone may be used as monotherapy, or in combination with a dopamine agonist or anticonvulsant. Clinical evidence for the effectiveness of these medications in RLS is limited[206–208]. Doses should be kept low (~5–20 mg) due to the potential for addiction and tolerance. Patients with intermittent RLS symptoms may benefit from occasional use of codeine, tramadol or oxycodone. These medications may be taken at bed-time or during the day if breakthrough RLS symptoms occur. Side effects of opioid therapy include constipation, nausea, dizziness, sedation and respiratory depression. Patients should be monitored for the development or worsening

of sleep apnea, as opioids are known to cause respiratory depression. Augmentation has been reported with tramadol[218,219].

Intermittent therapy with benzodiazepines may be considered for patients with RLS and comorbid insomnia, or patients for whom RLS-related sleep disturbances outweigh their sensory symptoms (Table 5). Zaleplon may be useful for inducing sleep, zolpidem may improve both sleep onset and maintenance, and temazepam and eszopiclone may be beneficial in reducing RLS-related awakenings as their half-lives are compatible with 8 hours of sleep[202]. Evidence for the efficacy of these agents in RLS is lacking, but it is likely that they act by improving sleep rather than by reducing the sensory and motor symptoms of RLS[202].

No medications have been approved to date by the Food and Drug Administration for the treatment of RLS in children; however, medications which are accepted for usage in the pediatric population such as clonidine, clonazepam, and gabapentin have been prescribed off label[220]. Dopaminergic agents are also used, although their effects in children have not been extensively studied[220].

Conclusions

RLS is a common sensorimotor disorder which can cause considerable morbidity and have a significant impact on quality of life. RLS is a clinical diagnosis based on an interview; however, it is frequently unrecognized in medical practice largely due to comorbidities that can mimic its symptoms. Although other conditions share similar characteristics, the differential diagnosis of RLS is generally possible via careful consideration of the IRLSSG criteria and supportive features. RLS can be comorbid with a variety of other conditions and the relationship between RLS and these conditions is not fully elucidated (Figure 1). Identification of patients with RLS is particularly important, as many medications which are used to treat common comorbidities, such as antihistamines and antidepressants, may exacerbate RLS symptoms (Table 3). Despite potential difficulties in differential diagnosis, correct identification and management are crucial in order to prevent the potential clinical consequences of RLS. A number of treatments are available that allow RLS to be effectively managed.

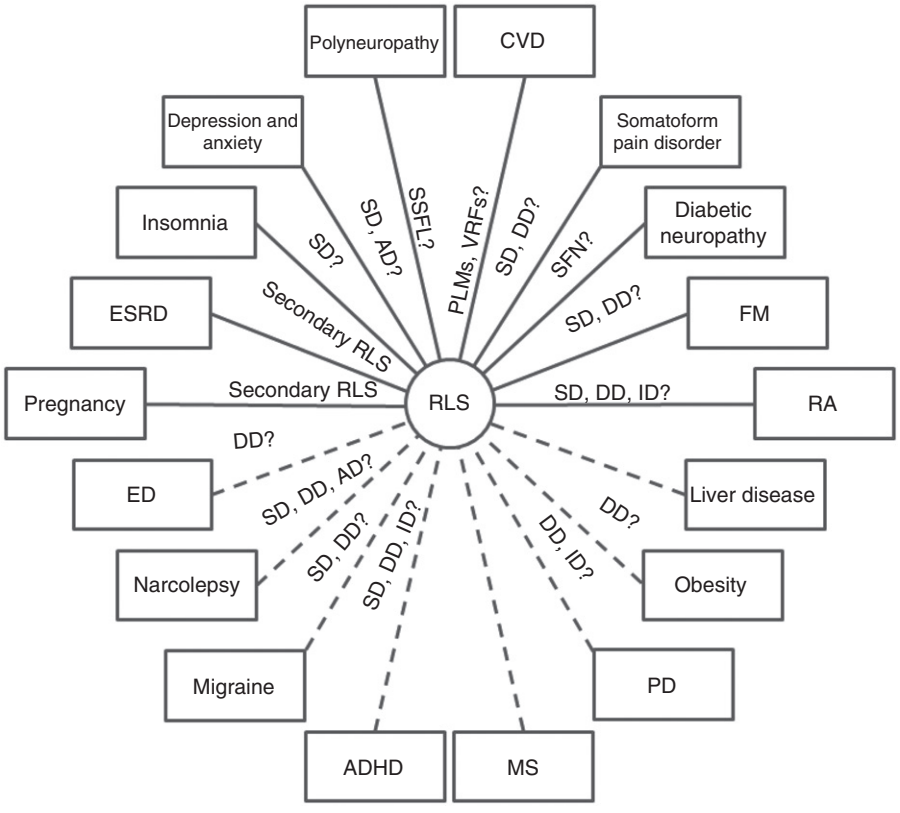

Figure 1. Possible associations between RLS and comorbidities. Dotted lines indicate comorbidities for which the evidence for the association comes from epidemiologic studies. AD = use of antidepressants; ADHD = attention-deficit hyperactivity disorder; CVD = cardiovascular disease; DD = dopaminergic dysfunction; ED = erectile dysfunction; ESRD = end-stage renal disease; FM = fibromyalgia; ID = iron deficiency; MS = multiple sclerosis; PD = Parkinson's disease; PLMs = periodic limb movements; RA = rheumatoid arthritis; RLS = restless legs syndrome; SD = sleep disruption; SFN = small fiber neuropathy; SSFL = small sensory fiber loss; VRFs = vascular risk factors.

Transparency

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P.M.B. has disclosed that he has consulted for UCB, GlaxoSmithKline, and Xenoport and has been a research investigator for Pfizer, Sanofi-Aventis, and Sensory Medical. M.N. has disclosed that she has no significant relationships with or financial interests in any commercial companies related to this study or article.

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