

# Restless legs syndrome and periodic limb movements of sleep

## Abstract

Restless legs syndrome describes a curious need to stretch and move in response to an unpleasant feeling in the legs. For most people who have this, as they are drifting off to sleep there is a twitch of the toe, foot and ankle followed by another and then another. The limb movements are strikingly periodic and are described as such by frustrated bed partners. The pathophysiology remains debated but is likely to involve dopaminergic dysfunction and ascending arousal systems.

Despite a prevalence of 5–10% in the general population, the variable nature of symptoms and difficulty describing the dysaesthesia often leads to delay in treatment. This article outlines the diagnostic criteria, medication and comorbidities that modify symptoms, the impact of restless legs syndrome on health, and symptomatic management. Several licensed therapies are effective but the dopamine agonists in particular can cause challenging side effects and paradoxically worsen symptoms over time. Case histories are reviewed to guide physicians.

**Key words:** Restless legs syndrome; Periodic limb movements of sleep; Dopamine agonists

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## Introduction

Restless legs syndrome is a sensory motor phenomenon and the diagnosis remains clinical. The current diagnostic criteria for restless legs syndrome were published in 2014 by the International Restless Legs Syndrome Study Group (<http://irlsbg.org/>) (Table 1) (Allen et al, 2014). They emphasise many of the original features first elegantly described by Karl Ekbom in a monograph in 1944 when he wrote that:

**'the sensations appear only when the patient is at rest, most often in the evening and early part of the night, and produce an irresistible need to keep the legs moving. Furthermore, the sensations are not felt in the skin but deep down in the legs.'**

**Table 1. Diagnostic criteria for restless legs syndrome**

A need to move the legs, usually accompanied or caused by uncomfortable, unpleasant sensations in the legs. Any kind of sensation may be a manifestation of restless legs syndrome and a wide variety of descriptions have been used ranging from 'painful' to 'burning' – some people say it feels like they have insects inside their legs or arms. Sometimes the need to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs

The need to move and unpleasant sensations are exclusively present or worsen at rest or during periods of inactivity such as lying or sitting

The need to move and unpleasant sensations are partially or totally relieved by movement such as walking or stretching at least while the activity is continued

The need to move and unpleasant sensations are generally worse or exclusively occur in the evening or night

Symptoms are not solely accounted for by another condition such as leg cramps, positional discomfort, leg swelling or arthritis

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Patients describe a creeping, crawling feeling deep under the skin of the calves and thighs that makes them want to move. The circadian variation is striking with symptom onset late in the evening and into the first half of the night but fewer symptoms in the early hours of the morning. There is a need to differentiate all the other uncomfortable feelings within legs and feet that patients can have. The criteria emphasise the need for a careful history and also highlight how episodic and variable restless legs syndrome can be for the patient over his/her lifetime. The differential diagnosis is listed in **Table 2**. A further scoring system has been developed to measure severity, largely for use in treatment trials.

Sir Thomas Willis first defined restless legs syndrome in 1672 as a restlessness of the limbs alongside ‘a snapping of the tendons’. Around 80% of patients will have associated periodic limb movements of sleep. Periodic limb movements of sleep do have defined physiological parameters using video polysomnography of at least four sequential movements 5–90 seconds apart seen as a rapid, triple flexion of toe, foot and ankle. The characteristic gap is 20–30 seconds between kicks. The number of movements per hour is quantified as a periodic limb movement index. Occasional periodic limb movements are common and are often asymptomatic when seen as an infrequent, isolated phenomenon. However, those who have disturbed sleep and daytime dysfunction are said to have periodic limb movement disorder typically kicking >30 times an hour.

One simple screening question for the presence of restless legs syndrome has been validated with 100% sensitivity and 96.8% specificity as ‘When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?’ (Ferri et al, 2007).

### What else could it be?

A number of conditions may mimic restless legs syndrome. Common differential diagnoses of restless legs syndrome and periodic limb movement disorder are outlined in **Tables 2** and **3**.

Table 2. Common differential diagnosis of restless legs syndrome	
Condition	Differential diagnosis from restless legs syndrome
Leg cramps	Explosive onset of severe muscle pain and tenderness in the muscle
	Usually unilateral
Positional discomfort	Sensory symptoms and the need to move are only located in the limb which has been in an unusual position
	Only this position triggers the symptoms
Peripheral neuropathy	Pain and paraesthesia predominate
	No diurnal variation
	No relief from movement
	Abnormal neurological examination, e.g. reduced pin prick and reflexes
	Peripheral neuropathy can increase the risk of comorbid restless legs syndrome
Akathisia	Stereotyped motor restlessness
	No diurnal variation
	Sensory symptoms usually absent
	Urge to move the whole body in response to an inner feeling of restlessness
	Typically drug-induced, e.g. antidepressants, antipsychotics or dopamine agonists
Attention deficit hyperactivity disorder	Restlessness without diurnal variation
	Sensory symptoms are absent
	Both commonly co-exist, leading to a negative interactive effect

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**Table 3. Common differential diagnosis of periodic limb movement disorder**

Condition	Differential diagnosis from periodic limb movement disorder
Obstructive sleep apnoea	Nocturnal arousals may arise from sleep-disordered breathing – respiratory event-related arousals
	Ask about snoring, apnoeas, nocturia, dry mouth, headache upon awakening, and daytime sleepiness
	Video polysomnography will differentiate
Sleep starts (hypnic jerks)	A single brief myoclonic jerk at sleep wake transition ‘falling off a log’
Rapid eye movement sleep behaviour disorder	Dream enactment behaviours more likely in the second half of the night
	Associated injury to patient or bed partner in 70% of cases
Nocturnal epilepsy	Brief, violent hypermotor activity
	Stereotyped and equally likely to be upper limb

## What causes it?

The pathogenesis remains debated. Structural brain imaging is normal. There is a circadian variation to dopamine secretion and a clear treatment response to both levodopa and dopamine agonists. Dopamine levels show a circadian variation and this has led to a current theory of a spinal cord dopamine dysfunction (Clemens et al, 2006). The proximity of this system to the circadian control centres of the hypothalamus may be the cause of the circadian pattern characteristic of restless legs syndrome.

There is evidence to suggest that a defect in brain iron metabolism contributes to the disease. Iron deficiency as a trigger was initially noted by Ekbom, and restless legs syndrome is increased in pregnancy during physiological iron deficiency. Iron is an essential co-factor for tyrosine hydroxylase, therefore a decrease in iron may affect the availability of dopamine.

In addition, functional imaging studies suggest that thalamic glutamate levels are increased consistent with the hyperarousal and fragmented sleep associated with the condition. Currently restless legs syndrome is best viewed as a multitransmitter neurochemical disorder, resulting in enhanced excitability and decreased inhibition.

## Who gets it?

The majority of cases are idiopathic with a female to male ratio of 2:1. Many sleep disorders increase with age and restless legs syndrome is no exception with only 2% of all patients presenting under the age of 16 years. Population studies screening for any degree of restless legs syndrome show prevalence in the western world of 5–15%, with frequency rising from the third to the seventh decade and then decreasing again. Of these only about 10% have daily, severe symptoms that impact on function. Around 40% of patients have a family history, and those with a family history tend to present younger although no single gene has been identified to date.

Many other medical problems that decrease mobility are associated with an increase in reported symptoms of restless legs syndrome, for example degenerative disc disease and spinal stenosis, multiple sclerosis and peripheral neuropathy. Population studies show that those who smoke have a four-fold increased risk of developing restless legs syndrome over time. Uraemia is also associated with restless legs syndrome and is common in those who require dialysis. In pregnancy 30% of women experience some restless legs syndrome, maximal in the third trimester and at least 70% will have rapid resolution post partum.

## What impact does restless legs syndrome or periodic limb movement disorder have on health?

### Restless legs syndrome

When severe, restless legs syndrome disrupts sleep and is associated with poorer health and a lower quality of life (Winkelman et al, 2006), akin to Parkinson’s disease or stroke

(Happe et al, 2009). Patients with restless legs syndrome experience fragmented sleep, particularly in the first half of the night. Insomnia and hyperarousal is more common than excessive daytime somnolence. Unsurprisingly, patients struggle with employment and social activities (Abetz et al, 2004). The loss of work productivity has been shown to pose a significant financial burden to society (Durgin et al, 2015).

Anxiety, depression, panic disorder, psychosomatic symptoms and post-traumatic disorder are more common in those with restless legs syndrome (Cho et al, 2009; Kim et al, 2013; Yilmaz et al, 2018). In one study, the severity of restless legs syndrome was directly related to depression and anxiety scores (Sevim et al, 2004). Restless legs syndrome is an independent risk factor for self-harm and suicide (Zhuang et al, 2019).

Growing evidence suggests that restless legs syndrome is related to cardiovascular disease. When severe, it is associated with hypertension (Hein et al, 2019), myocardial infarction (Winkelman et al, 2017), ischaemic stroke (Hermann et al, 2018) and increased cardiovascular mortality (Li et al, 2018). It is probably also associated with diabetes and dyslipidaemia (Innes et al, 2012). Chronic overactivation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis increases blood pressure, which may be one mechanism for the association between hypertension and restless legs syndrome (Gamaldo et al, 2009; Innes et al, 2012; Yilmaz et al, 2018).

### Periodic limb movement disorder

There is far less data on the clinical impact of periodic limb movement disorder. Patients with periodic limb movement disorder have worse sleep quality and insomnia symptoms when compared to those without (Byun et al, 2019). Depression and anxiety are both associated with periodic limb movement disorder, and several studies have demonstrated that antidepressants increase periodic limb movements of sleep (Picchietti and Winkelman, 2005). One study reported that the degree of sleepiness, depression and anxiety were similar among patients with restless legs syndrome and those with periodic limb movement disorder (Hardy De Buisseret et al, 2017). While frequent periodic limb movements of sleep are associated with cardiovascular and mortality risk, it remains unknown if this extends into periodic limb movement disorder (Fulda, 2018). The direct health economic burden of periodic limb movement disorder is estimated as 1% of the total sleep disorder cost to society (Hillman et al, 2006).

## How to manage restless legs syndrome and periodic limb movement disorder

### Restless legs syndrome

#### Treat lifestyle factors or secondary causes where possible

Underlying causes such as iron deficiency should be excluded. Any patient with a ferritin level below 75 mcg/litre should be commenced on iron supplementation (Avni et al, 2019). When oral iron replacement fails to raise ferritin levels, intravenous iron can be considered (Trotti and Becker, 2019). Patients should be screened for substances that exacerbate restless legs syndrome, including nicotine, high dose caffeine or excess alcohol. A number of medications aggravate restless legs syndrome including the selective serotonin-reuptake inhibitor and serotonin–noradrenaline reuptake inhibitor antidepressants (in particular mirtazapine), antihistamines, beta-blockers and the dopa-depleting anti-emetics such as metoclopramide. Whenever possible, these should be reduced or withdrawn (Gupta and Pandi-Perumal, 2018; Kolla et al, 2018).

#### Psychological and physical measures

Many describe benefit from relaxation therapy before bedtime, such as yoga, stretching, and massaging the affected limbs (Harrison et al, 2019). Sleep hygiene should be optimised, e.g. avoiding stimulants or high intensity exercise just before bedtime (although increasing exercise during the day is helpful) and reducing cigarette smoking in particular. For those with a comorbid insomnia, cognitive behavioural therapy for insomnia is helpful. Patient education is important, and the RLS-UK charity has a useful website ([www.rls-uk.org/](http://www.rls-uk.org/)).

### Pharmacological treatments

It is important to emphasise that only a minority of patients will require specific pharmacotherapy for symptoms of restless legs syndrome or the associated sleep disturbance. In the UK, only three medications (all dopamine agonists) are licensed for the indication of restless legs syndrome: ropinirole, pramiprexole and rotigotine (a topical patch) (Table 4). Meta-analyses suggest that they are of similar efficacy. Ropinirole and pramiprexole appear to have maximal effect 1.5 hours after consumption, and effectively decrease both symptoms of restless legs syndrome and also periodic limb movements of sleep throughout the night. The rotigotine patch can be used for 24-hour cover for those with daytime symptoms and may have a lower risk of augmentation.

The dopamine agonists have two class-specific side effects: impulse control disorder and augmentation. Symptoms of impulse control disorder include compulsive gambling, eating or shopping, and hypersexuality. It is reported in 7–17% of patients based on case series (Grall-Bronnec et al, 2018). Younger patients, those with novelty-seeking personality traits and patients with a history of substance misuse are at higher risk. Augmentation is a worsening of restless legs syndrome symptoms beyond what is expected as part of its usual trajectory. Symptoms occur earlier in the day, and affect other body parts, e.g. upper limbs. Patients also get less symptom relief following movement, worsening sleep, and a shorter duration of treatment effect. The rate of augmentation is high at 7%/year with at least 50–60% of patients requiring dose increase over time. Augmentation rates tend to be dose-dependent, and so the lowest possible dose of dopamine agonists should be used (Table 4). The risk is increased in patients with low iron stores, so ferritin levels should be monitored during treatment.

Off-label but evidence-based therapies include gabapentin and pregabalin both with positive randomised controlled trials; for pregabalin follow-up data showing sustained

**Table 4. Pharmacological treatment of restless legs syndrome**

Drug	Licensed or typical dose range	Common side effects	Augmentation risk management	Comments
Ropinirole	0.5–4 mg	Nausea, headache	Suggested maximum dose of 4 mg	Risk of impulse control disorder and augmentation (see text)
Pramiprexole	0.88–540 mcg	Nausea, peripheral oedema	Suggested maximum dose of 540 mcg	As per ropinirole
Rotigotine	1–3 mg daily	As per ropinirole; skin irritation from the patch 10%	Suggested maximum dose of 3 mg	Possible lower risk of augmentation
Gabapentin	200–600 mg at night	Sleepiness, dizziness, nausea, peripheral oedema	Lower risk of augmentation	Randomized controlled trial evidence for benefit used once daily. Useful when pain is a prominent feature
Pregabalin	25–300 mg at night	As per gabapentin	Lower risk of augmentation	Better bioavailability than gabapentin. As effective as pramiprexole. Licensed in the UK for generalised anxiety disorder, useful in patients with comorbid anxiety. Rebound insomnia when stopped suddenly
Targinact (prolonged release oxycodone with naloxone)	5 mg/2.5 mg every 12 hours to a maximum of 60 mg/30 mg	Sleepiness, nausea, constipation. May worsen obstructive sleep apnoea. Dependence	Not described	Helpful when there is prominent pain. Can be used when occasional treatment is required, e.g. for meetings, or on a flight. Can cover the withdrawal of dopamine agonists when augmentation has occurred
Clonazepam	0.25–1 mg at night	Daytime drowsiness; risk of dependency; worsens obstructive sleep apnoea; falls risk in the elderly	Not described	Can be helpful for patients with significant comorbid insomnia

benefit after a year. There is much less randomised controlled trial evidence for oxycodone (a single randomised controlled trial with a high number of adverse events) and no trial data for clonazepam although it remains widely used (Table 4).

The treatment of depression with comorbid restless legs syndrome can be challenging, as many antidepressants can worsen restless legs syndrome. Bupropion is an exception, which can be helpful in treating restless legs syndrome and does not worsen severity (Bayard et al, 2011). In the UK, it is only licensed for smoking cessation, so access may be problematic.

### Periodic limb movement disorder

Typically, the same management advice is used for periodic limb movement disorder, although the evidence base is less developed (Fulda, 2018). In isolated periodic limb movement disorder, the authors tend to favour treatments that consolidate sleep (there are no specifically licensed drugs for periodic limb movement disorder). Treatment is usually guided by improvements in self-reported daytime symptoms (e.g. reduction in excessive daytime somnolence) in isolated periodic limb movement disorder, although repeated polysomnography is sometimes required.

Case studies 1 and 2 give some example cases of treating patients with restless leg syndrome or periodic limb movement disorder, discussing some of the issues faced and how these were resolved.

#### Case study 1

A 35-year-old nurse was referred to the sleep clinic with treatment-resistant insomnia. She described difficulty initiating and maintaining sleep, and daytime fatigue. A trial of cognitive behavioural therapy for insomnia was unsuccessful. She reported an aching painful discomfort in her legs most evenings, which was initially attributed to her busy ward job. However, the uncomfortable sensations were associated with an urge to move and worse with rest or lying down. Movement provided short-lived relief. She regularly had to leave the bed to 'walk them off'. When she napped in the day, the sensations did not occur. Her caffeine consumption had significantly increased to 'get through the day'. She recalled that her mother and grandmother suffered with 'jumpy legs'. She had no other medical history and took no prescribed medications.

She was describing restless legs syndrome, which can commonly present as insomnia. Her serum ferritin level was 24 mcg/litre, and so iron therapy was started. She was advised to reduce her caffeine intake. Given her young age, description of pain, and the negative impact of restless legs syndrome on her daytime function, low-dose gabapentin at night was commenced. Review 3 months later revealed she was in remission, with improved sleep and daytime function. Repeat serum ferritin level was 80 mcg/litre, and iron therapy was stopped. Gabapentin was continued long term at unchanged dose with ongoing benefit.

#### Case study 2

A 60-year-old taxi driver with known restless legs syndrome was referred to the sleep clinic with worsening sleep maintenance difficulties and increased daytime somnolence, to the point where he no longer felt safe to drive. He had been prescribed ropinirole 2mg for the past 5 years to treat restless legs syndrome, and denied ongoing symptoms. His GP had recently commenced mirtazapine for new onset anxiety, with the hope of also improving sleep maintenance. However, his sleep deteriorated following this, and so it was stopped. There were no difficulties with sleep initiation. He slept alone, and was not aware of snoring or leg movements.

Inpatient video polysomnography revealed a raised periodic limb movement index of 80 events per hour with no other sleep disorder. He was diagnosed with restless legs syndrome and comorbid periodic limb movement disorder. Augmentation was suspected as ropinirole controlled his evening symptoms of restless legs syndrome but no longer provided cover through the night. Iron studies were normal. Given his comorbid anxiety, ropinirole was cross-titrated to pregabalin 300mg nocte. Review at 6 weeks revealed improved sleep, no daytime somnolence, his anxiety had resolved and he had returned to work. Mirtazapine was discontinued as it was thought to be additionally aggravating his periodic limb movements.

## Key points

- Restless legs syndrome affects 5–10% of the population but of this group only 10% have severe symptoms that disturb sleep. The condition is more common in women and increasingly frequent with age. The condition can be episodic or persistent.
- The pathophysiology remains debated but brain iron metabolism, dopamine dysfunction and ascending arousal systems all seem to play a part.
- Lifestyle advice and in particular nicotine reduction should be first-line treatment alongside review of prescribed medications that can aggravate symptoms.
- Dopamine agonists are highly effective in the short to medium term but 50–60% of patients will develop augmentation and 10–13% will develop some symptoms of impulse control disorder leading to increasing use of both gabapentin and pregabalin used off licence and once daily.
- For those who have persistent symptoms despite treatment, secondary care referral and consideration of video polysomnography is recommended.

## Conclusions

Restless legs are common. When severe they disrupt sleep and have an impact upon daytime function. The best diagnostic test remains an accurate clinical history. Lifestyle measures will help many but for those more severely affected, pharmacotherapy with either dopamine agonists or the gabapentinoids has a good evidence base, albeit with increasing recognition of specific long-term side effects with dopamine agonists which require ongoing monitoring.

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### Conflicts of interest

The authors declare no conflicts of interest.

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