

Restless leg syndrome (RLS)

Synonym: Willis-Ekbom disease

What is restless legs syndrome?

The term restless legs syndrome (RLS) was first used in the mid-1940s by Swedish neurologist Karl Ekbom to describe a disorder characterised by sensory symptoms and motor disturbances of the limbs, mainly occurring during rest.

RLS is characterised by an urge to move, usually but not always affecting the legs. Abnormal sensations, including tingling, aching or burning, are usually present in association with restless legs. There may be associated pain, which can be severe. The abnormal sensations tend to be worse in the evenings and are temporarily or partially relieved by movement^[1].

How common is restless leg syndrome? (Epidemiology)^[2]

- Prevalence in the adult population is between 1.9% and 4.6% in Western Europe.
- The prevalence increases with age. Symptoms begin after 40 years of age in most patients but it can occur at any age.
- Over the age of 35 years, the prevalence in women is about double that of men. This is thought to be related to pregnancy. In younger adults, both sexes are equally affected.

What causes restless leg syndrome? (Aetiology)

RLS may be idiopathic or symptomatic of an underlying condition. In most people there is no apparent cause (idiopathic or primary RLS). 18.5–59.6% of patients with idiopathic RLS have a family history, suggesting a genetic component^[1]. It is thought to be related in some way to dysfunction of the dopaminergic system. Iron is important to dopamine metabolism and iron deficiency is one of the causes of restless legs syndrome, so some research has been concentrated on the use of iron. In the absence of iron deficiency, however, iron replacement has not been proven to be efficacious, and aetiology is clearly more complex^[3].

Causes of secondary RLS include:

- Pregnancy (RLS is estimated to affect one in five pregnant women)^[4].
- Stage 5 chronic kidney disease.
- Iron deficiency (RLS is estimated to be present in about 24% of people with iron-deficiency anaemia)^[5].
- Adverse effects of medication. Causative agents include beta-blockers, neuroleptics, lithium, antihistamines and antidepressants. Also dopamine receptor blocking agents such as metoclopramide and prochlorperazine.

Associations have also been found with:

- Folate deficiency, B12 deficiency and magnesium deficiency.
- Polyneuropathy.
- Endocrine: diabetes mellitus, hypothyroidism.
- Spinal disorders.
- Parkinsonism.
- Rheumatoid arthritis, Sjögren's syndrome.
- Amyloidosis.

- Excessive intake of caffeine, alcohol or chocolate (possibly) and sleep deprivation.
- Obesity.

Restless legs syndrome symptoms

- Patients have characteristic difficulty in trying to depict their symptoms of RLS. They may describe creeping, crawling or other uncomfortable feelings in the legs and arms, relieved by rubbing or moving the affected limb.
- They may report sensations such as an almost irresistible urge to move the legs.
- Patients often complain of pain in their legs, which can be severe. Some patients describe a deep painful feeling in their legs.
- The sensations are usually worse during inactivity and often interfere with sleep, leading to chronic sleep deprivation and stress.
- It can lead to significant physical and emotional difficulties.

RLS diagnostic criteria^[6]

Diagnostic criteria should be met as set out by the International Restless Legs Syndrome Study Group (IRLSSG). The latest version was released in 2014. All five essential criteria must be met for a positive diagnosis.

- Essential criteria:
 - An urge to move the legs, usually (but not always) accompanied by uncomfortable or unpleasant (and difficult to describe) sensations in the legs.
 - The urge to move and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
 - The urge to move and any accompanying unpleasant sensations are partly or totally relieved by movement such as walking, bending, stretching, etc, at least for as long as the activity continues.
 - The urge to move and any accompanying unpleasant sensations are worse in the evening or at night rather than during the day, or only occur in the evening or night.
 - The above symptoms cannot be accounted for as symptoms primary to another medical or a behavioural condition. Examples given in the criteria are myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, or habitual foot tapping.
- Supportive criteria:
 - Positive response to dopaminergic treatment.
 - Periodic limb movements during wakefulness or sleep.
 - Positive family history of RLS amongst first-degree relatives.
 - Lack of profound daytime sleepiness.
- Clinical course may be:
 - Chronic-persistent: untreated, symptoms have occurred at least twice per week for the past year.
 - Intermittent: untreated, symptoms have occurred on average less than twice per week for the past year, with at least five lifetime occurrences.

- Associated features to be considered when making the diagnosis:
 - Age: it can begin at any age but most patients seen in clinical practice are middle-aged or older.
 - Gender: twice as common in women as it is in men.
 - Clinical course of the disease: most patients seen in the clinic have a progressive clinical course but a static clinical course is sometimes seen. Remissions of a month or more are sometimes reported.
 - Sleep disturbance: 75% report sleep disturbance. The leg discomfort and the need to move often result in insomnia and associated reduced quality of life.
 - Degree of pain vs discomfort.
 - Part of the body involved: usually the lower limbs, around the calf area.
 - Daily pattern of symptoms and activity levels.
 - History of pregnancy and iron deficiency.

Differential diagnosis^[2] ^[6]

- RLS may be triggered by peripheral neuropathy or radiculopathy but a distinction should be made between these disorders. In pure peripheral neuropathy and radiculopathy, patients do not have the compelling need to move to relieve leg discomfort and the RLS symptoms are not consistently worse at rest or at night.
- Neuroleptic-induced akathisia: motor restlessness induced by antipsychotic agents that block dopamine receptors. Patients feel compelled to move because of an inner sense of restlessness rather than a need specifically to move the legs.
- Positional discomfort: if the only movement needed is a small brief positional change to relieve pressure - eg, on an arthritic hip.
- Myalgia.

- **Peripheral arterial disease:** intermittent claudication is usually worse on exercise and improves with rest..
- **Nocturnal leg cramps.** Usually these are unilateral and require stretching of the muscle to ease the pain, rather than nonspecific movements.
- **Parkinsonism.**
- Venous insufficiency. Oedema or venous stasis.
- **Attention deficit hyperactivity disorder (ADHD) in children.**

Investigations

- Serum ferritin: RLS is frequently associated with iron deficiency.
- Renal function: RLS may be associated with end-stage chronic kidney disease.
- Other investigations for underlying possible cause include fasting blood glucose, magnesium, TSH, vitamin B12 and folate.
- If the neurological examination suggests an associated peripheral neuropathy or radiculopathy, electromyography and nerve conduction studies should be undertaken.

Disorders associated with restless leg syndrome

Periodic limb movement disorder (PLMD) [7] [8]

PLMD is a disorder characterised by periodic episodes of repetitive involuntary limb movements during sleep, usually in the lower limbs. It causes sleep disturbance and daytime sleepiness. Sometimes the person with PLMD is unaware the movements are happening but may still experience tiredness during the day. It differs from RLS in that movements are involuntary, whereas in RLS there is voluntary movement in response to an unpleasant sensation. On its own, it is much less common than RLS, although it may co-exist with RLS or other syndromes. There is little in the literature on management, which usually is along the same lines as RLS. Indeed the 2012 European guidelines on RLS deleted mention of PLMD as there had been no new studies [9] .

Restless legs syndrome treatment and management^[1] ^[2]

- Treat any underlying cause, including supplementation to correct vitamin, electrolyte or iron deficiency. Give iron supplementation if serum ferritin is less than 50 mcg/L. If the cause is pregnancy, reassure that this should settle spontaneously shortly after delivery. Medication is not recommended in pregnancy.
- Consider medications which may be aggravating the situation and stop where possible.
- Reassurance.

Self-help advice

- Advice on improving sleep - eg, avoiding caffeine before bed, not getting too hot, avoiding sleep deprivation.
- Advice on reducing alcohol and caffeine consumption where relevant.
- Regular moderate exercise.
- Stop smoking if a smoker.
- Warm baths before bedtime.
- Measures during an episode of RLS:
 - Stretching affected limbs.
 - Walking about.
 - Relaxation exercises.
 - Massaging affected limbs.
 - Distraction techniques.

RLS medication^[9]

- RLS treatment is needed only in the moderate-to-severe forms of the disorder and where symptoms are having a significant negative impact on quality of life.

- Guidelines advise that non-ergot dopamine agonists should be first-line treatment. Specifically, rotigotine, pramipexole and ropinirole are recommended and have been proven effective in RLS^[10]. Rotigotine is available as a transdermal patch for daytime symptoms^[2]. Some ergot-derived dopamine agonists were shown to be effective, particularly cabergoline and also pergolide; however, these are not advised due to the high incidence of severe adverse effects. Dopaminergic treatment with levodopa (L-dopa) has been shown to be effective but is no longer advised due to the higher risk of augmentation when compared with dopamine agonists.
- The anti-epileptics gabapentin and pregabalin have also been demonstrated to be effective in RLS. Evidence suggests they are more effective than dopamine agonists with less risk of augmentation and they may replace dopamine agonists as advised first-line treatment in future guidelines^[11]. They are used off-licence in this context.
- Alternative options include a weak opioid such as codeine, or a hypnotic such as a benzodiazepine or Z-drug; however, consider the risk of dependence.
- Management options which have been investigated but NOT found to be conclusively effective, and which are not currently advised, include:
 - Folate, B12 or magnesium therapy.
 - Iron (in the absence of low serum iron levels, although if serum ferritin is below 50 mcg/L, supplementation should be used)^[1]^[12].
 - Acupuncture^[13].
 - Aerobic exercise.
 - Physiotherapy.
 - Infrared light

Long-term therapy^[14]

Long-term therapy may be a problem due to loss of efficacy and augmentation. Loss of efficacy over time is an issue encountered with all medication used in the treatment of RLS. Doses may need to be gradually increased, or a change made to a different class of medication.

Augmentation is a problem with dopaminergic treatments and is characterised by a worsening of symptoms some length of time (months or years) into successful therapy. In this scenario, symptoms become more severe, or start earlier in the day, or spread to other parts of the body which were previously unaffected. The higher the dose and the longer the duration of treatment, the higher the risk of augmentation. Treatment should be stopped and specialist advice sought if this occurs. Gabapentin or pregabalin may be preferred for long-term treatment as they do not cause augmentation.

Most medication for RLS is only recommended for a relatively short period of time, usually between six months and two years.

Referral^[1]

Refer to a neurologist or sleep specialist if:

- There is insufficient initial response despite adequate duration and dose of treatment.
- Response to treatment becomes insufficient despite an increased dose.
- Side-effects are intolerable.
- The maximum recommended dosage is no longer effective.
- Augmentation develops (onset of symptoms earlier in the day, increased severity of symptoms, or the spread of symptoms to different parts of the body, such as the arms, trunk or face).

Children with RLS should not be treated in primary care.

Complications

- [Insomnia](#).
- Significant negative effect on quality of life^[1].

- Anxiety and depression. (People with RLS have a higher risk of anxiety and depression than the general population.)^[15]

Restless legs syndrome prognosis

- RLS is usually a chronic disorder that worsens with time but does fluctuate. It may worsen over time, stabilise, improve, or remit.
- Periods of remission are common, especially in younger adults.
- If RLS is secondary to another condition, it may resolve once that condition is treated.

Further reading

- [RLS-UK](#)

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