The night time hustle: managing **restless legs syndrome** in adults

Restless legs syndrome is a common condition that can significantly affect a patient's quality of life. It is a neurological disorder, which can be diagnosed on the basis of the patient's description of their symptoms. Lifestyle modification is the mainstay of treatment for patients with mild or infrequent symptoms. Pharmacological treatments, starting with dopamine agonists, should be reserved for people with more severe symptoms.

What is restless legs syndrome?

Restless legs syndrome is a neurological disorder characterised by throbbing, pulling, creeping or other unpleasant sensations in the legs and an uncontrollable, usually overwhelming, urge to move them. Symptoms occur primarily in the evening when a person is relaxing, and can increase in severity throughout the night. Both legs may be affected or one may be worse than the other. In more severe cases, the arms and lower trunk may also be affected.

Restless legs syndrome can be a primary condition or secondary to another disorder. It is known to have a genetic basis and a positive family history is a strong risk factor. Despite this, the pathophysiology of restless legs syndrome remains unclear; what is known about the function of the implicated genes does not yet explain the syndrome. Dopaminergic dysfunction and iron deficiency are both thought to have a role in restless legs syndrome.[1] The syndrome is also strongly associated with depression and anxiety disorders, although whether these conditions are caused by restless legs syndrome or are the result of lower sleep quality is not known.[2]

Restless legs syndrome is thought to affect between 7 – 15% of the population.[3, 4] It is twice as common in females as in males and prevalence increases with age in most populations.[2] Most people with restless legs syndrome first report symptoms after middle-age, however, early onset is thought to be associated with increased severity later in life.[3]

Approximately four in five people with restless legs syndrome also experience periodic limb movement of sleep (PLMS). This is characterised by involuntary leg movement while the person is asleep. The condition can cause repeated waking and poor sleep quality. The presence of PLMS in a person with restless legs syndrome is likely to increase the severity of impact on the person's quality of life through the combination of delayed sleep onset from restless legs syndrome and poor quality sleep from PLMS.

A diagnosis is made based on description of symptoms

There is no specific examination or test that will confirm a diagnosis of restless legs syndrome. The patient's description of their symptoms, combined with a brief history, is sufficient to make a diagnosis.

The diagnostic criteria for restless legs syndrome is a history of:[5]

- A strong and often overwhelming urge to move the affected limbs, often associated with an uncomfortable or tingling sensation (paraesthesia or dysaesthesia)
- Sensory symptoms that are triggered by rest, relaxation or sleep and relieved with movement
- Symptoms that are worse at night and are absent or negligible in the morning
- Symptoms that are partially or totally relieved by leg movement

The presence of sleep disruption or sleep onset problems, a positive family history and a history of response to dopaminergic medicines (if previously taken), provide supportive evidence for the diagnosis.

The limb movements associated with restless legs syndrome are characteristic and repetitive – usually repeated dorsiflexing of the big toe or flexion of the ankle, knee or hip, lasting between 5 – 90 seconds and occurring periodically.

Assess whether the cause is secondary to another condition

Restless legs syndrome can occur secondary to one of the following factors or conditions:[6, 7]

- Iron deficiency
- Pregnancy, especially in the last trimester (prevalence of 11 – 26%), resolving after delivery
- Hypothyroidism or hyperthyroidism (can cause night-time restlessness)
- Rheumatoid arthritis
- Uraemia from chronic kidney disease
- Peripheral neuropathies, due to conditions such as diabetes and Charcot-Marie-Tooth disease
- Medicines, including anti-emetics (e.g. prochlorperazine), most antipsychotics (e.g. haloperidol, quetiapine and olanzapine), anti-depressants (TCAs, SSRIs and SNRIs) and some over-the-counter cold and allergy remedies that contain sedating antihistamines (e.g. diphenhydramine)

Further investigation is guided by the suspected secondary cause. Management of the cause, if identified, is likely to eliminate or reduce the severity of restless legs syndrome in most people.

A serum ferritin test should be considered for patients with restless legs syndrome without an obvious secondary cause, as iron deficiency is a common underlying cause.[6] Although iron deficiency alone is not sufficient to cause restless legs syndrome, serum ferritin correlates inversely with symptom severity.[5] MRI, cerebrospinal fluid and autopsy studies have shown that brain iron stores are reduced in patients with restless legs syndrome.[5] Testing is therefore a low cost, low harm way of potentially identifying a commonly implicated factor.

Symptomatic treatment of restless legs

Recommend lifestyle changes

Advice includes improving sleep hygiene (behaviours to enhance sleep), brief exercise, e.g. walking, before bedtime, performing gentle leg stretches for five minutes prior to sleep and eating a healthy diet. Distracting activities, e.g. reading a book, may also reduce the awareness of the discomfort.

Reassurance and support is also important, as many people believe that restless legs syndrome is a precursor condition to Parkinson's disease. There is a large body of evidence showing no link between the two conditions.[5, 8]

Best Practice Tip: Find out if there are any support groups within the community that patients can be referred to for advice and education.

Medicines for severe symptoms

Pharmacological treatment should be limited to people with severe symptoms who are distressed by their condition and whose daytime function is affected by poor sleep quality, despite lifestyle intervention and exclusion of secondary causes. It is estimated that approximately 20% of people with restless legs syndrome have severe symptoms.[5, 9]

Medicines are usually taken one to three hours prior to going to bed, as guided by symptom onset.[8] Because restless legs syndrome fluctuates over time, patients may require only intermittent medicine use.

The choice of medicine should be based on the patient's symptoms and requirements:

- Low-dose dopamine agonists, e.g. ropinirole, are first-line treatment for daily symptoms of restless leg syndrome[8]
- Dopamine precursors, e.g. levodopa, can be trialled if dopamine agonists are not tolerated or if medicine is only required intermittently
- Anticonvulsants (particularly gabapentin) may be considered if treatment with dopaminergic medicines has failed or is contraindicated, or where symptoms are painful

Dopaminergic medicines such as ropinirole and levodopa should never be abruptly stopped, as this can precipitate neuroleptic malignant syndrome, particularly if the medicine has been used for a long time. If cessation is necessary, the dose should be tapered gradually over at least one month. In addition, significant adverse effects, such as sleep attacks and impulse control issues, are possible with dopaminergic medicines. These potential adverse effects should be discussed with patients, and those with a history of addictive or compulsive behaviours should be monitored more closely while taking dopaminergic medicines.

Dopamine agonists

Ropinirole has the most evidence of efficacy for restless legs syndrome (among dopamine agonists).[8, 9] In New Zealand it is fully subsidised, but unapproved for this indication. Ropinirole can be started at 250 micrograms, daily, taken two to three hours before bed, gradually titrated up to a maintenance dose of 0.5 – 3 mg /day.[8]

Pramipexole is subsidised and approved for use in restless legs syndrome.[10] Pramipexole can be started at 125 micrograms, once daily, two to three hours before bed, doubled weekly as needed, to a maximum of 750 micrograms daily.[8, 11]

Bromocriptine is often suggested as a treatment for restless leg syndrome, but there is limited evidence for its use.[12]

Dopamine precursors

Levodopa was traditionally used first-line for the treatment of restless legs syndrome, however, adverse effects and the high occurrence of augmentation with levodopa (see "Augmentation") mean that it is now considered second-line to dopamine agonists. Levodopa is a short-acting medicine, therefore it is recommended in patients with intermittent symptoms or if dopamine agonists are not tolerated.[13] It is fully subsidised, but not approved for this indication.

Levodopa can be started at 50 mg, daily, one to two hours before bed, titrated to a maintenance dose of 100 – 200 mg/day. It is formulated with either carbidopa or benserazide to prolong its actions in the central nervous system and reduce rebound restless legs syndrome that can occur in the early morning.[8] For some patients, symptoms may rebound late at night. If rebound occurs regularly, switch to an alternative long-acting formulation.

Anticonvulsants

There is some evidence that gabapentin is an effective treatment for restless legs syndrome, and is useful where pain is a significant symptom.[5, 8] It can be started at 300 mg, daily, although evidence suggests doses of 1300 – 1800 mg/day are needed for full effect.[8]

Gabapentin is not approved for use in restless legs syndrome and not subsidised for this use, therefore the cost of the medicine should be discussed with the patient.

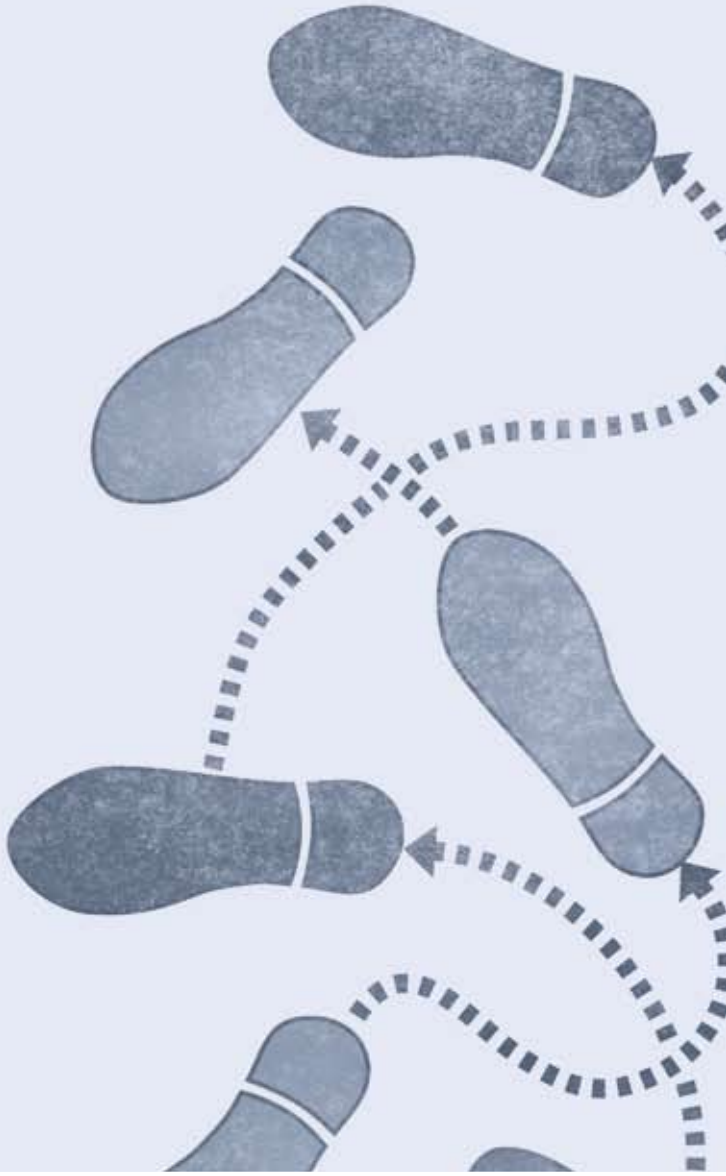
N.B. Gabapentin is fully subsidised under Special Authority for the treatment of neuropathic pain, where a tricyclic antidepressant has previously been trialled and is not tolerated or not effective.

Iron supplementation

Iron supplementation should be considered for patients with a serum ferritin level below 50 micrograms/L.[5, 15] However, there is a lack of quality evidence for the treatment of restless legs syndrome with iron supplementation in patients without an iron deficiency.[1] The underlying cause of anaemia should always be assessed.

Augmentation is a common adverse effect of dopamine treatment

Augmentation is the worsening of restless leg symptoms over time, with symptoms occurring earlier in the day (than before treatment) and may begin to involve the trunk and arms. It occurs in up to 70% of patients three to four weeks after beginning treatment with a dopamine precursor, e.g. levodopa, but can occur with any dopaminergic medicine.[14] Augmentation may be less likely with intermittent treatment. If augmentation occurs, reduce the dose or stop the medicine for a short time (low-dose opioids may be used as an adjunctive medicine, however, the evidence for their use is weak[15]). Alternatively, switch to a longer acting formulation, or if using levodopa, switch to a dopamine agonist such as ropinirole.[14]



Burning feet syndrome

Burning feet syndrome is a condition resembling restless legs syndrome, caused by the dysfunction of peripheral neurons.[17] It is most commonly seen in people aged over 40 years. Symptoms are described as a burning sensation, heaviness, numbness or dull ache in the feet that is worse at night.[17] The sensation is usually limited to the soles of the feet, but may be more widespread. The condition may be idiopathic or secondary to another condition, such as hyperthyroidism or diabetes.[17] An underlying vitamin B deficiency may be present in some people with burning feet.

Neurologic examination may reveal hypoaesthesia (reduced sense of touch), allodynia (the perception of non-painful stimuli as painful) or hyperalgesia (exaggerated pain perception). Objective signs are typically absent: there should be no muscle atrophy, and knee and ankle reflexes should be normal.

Physical deformities such as muscle loss, high medial arch or toe clawing rule out burning feet and suggest other conditions, such as autonomic neuropathy or Charcot-Marie-Tooth disease. The presence of marked erythema and increased skin temperature is characteristic of erythromelalgia, a neurovascular pain disorder in which blood vessels become periodically blocked, rather than burning feet syndrome. Burning feet may rarely co-exist with these conditions, but would be the less significant diagnosis.

Investigation for burning feet syndrome is directed by the suspected secondary cause (Table 1).[17]

Treatment should include advice on symptom control and relief: avoid tight shoes/socks and exposure to excessive heat. During an episode, soaking the feet in water for fifteen minutes may relieve symptoms. Where required, pharmacological management is similar to the management of neuropathic pain; begin with paracetamol and an adjuvant treatment such as capsaicin ointment.[17] Tricyclic antidepressants, carbamazepine or gabapentin may be added if symptoms are more severe.[17]

Table 1: Initial investigations for burning feet syndrome[17]

Suspected condition	Appropriate testing may include:
Diabetes	HbA_{1c}
Alcoholism	Liver function test
Multiple myeloma	ESR, serum free light chain testing (or Bence Jones protein in urine) and serum protein electrophoresis
Nutritional deficiencies	Ferritin / B12 / folate
Hypothyroidism	TSH
HIV infection	HIV status in at-risk patients

Other medicines

Low-dose strong opioids may be used temporarily to permit a lowering of the dose of dopaminergic medicines when augmentation occurs.[6] However, the evidence base for this group of medicines for the treatment of restless legs syndrome is limited.[15]

Clonazepam may be considered for patients who have significant sleep disturbance as a result of restless legs syndrome, particularly difficulty falling asleep. There is modest evidence for the intermittent use of clonazepam for sleep disturbance at 1 mg, daily, before bedtime.[9]

Pharmacological treatment in pregnancy

Reassurance and advice about lifestyle measures is usually sufficient for most women who are pregnant and experiencing restless legs syndrome. Pharmacological treatment should be a last resort.

Restless legs syndrome in women who are pregnant may be associated with iron or folic acid deficiency. Supplementation with iron and folic acid is a safe treatment option, and these supplements are commonly used by women during pregnancy. Where supplementation is ineffective and symptoms are severe, gabapentin (pregnancy safety category B1) or benzodiazepines (category C) may be used, with careful consideration of the risks to the foetus associated with these medicines during pregnancy, such as cleft palate, and neonatal syndromes, e.g. hypotonia, hypothermia and respiratory depression.[16]

Referral if treatment fails

Refer patients to a neurologist or sleep specialist, if:[5, 8]

- There is an insufficient initial response despite adequate duration and dose of treatment
- Response to treatment becomes insufficient despite maximum dosage
- Adverse effects become intolerable
- Significant augmentation develops

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