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Restless legs syndrome

Background
Restless legs syndrome (RLS) is a common, but frequently undiagnosed, chronic, sensorimotor disorder. In western countries, it is seen in approximately 10% of the general population, with a higher prevalence in women and the elderly (10–20%).

Objective
This article outlines the epidemiology, aetiology, diagnosis and management of RLS. Information that is most relevant to general practice is presented, with an emphasis on practical management.

Discussion
Restless legs syndrome is divided into primary and secondary forms. There is a strong genetic influence in primary RLS. Secondary forms are associated with iron deficiency, pregnancy, and renal failure. Diagnosis is essentially by clinical history using simple diagnostic criteria. Management depends on severity, and ranges from nonpharmacologic to pharmacologic measures. Recent research has provided insights into the pathophysiology of RLS and provided an evidence base for some of the newer treatments.

Case study

Mrs MM was 48 years of age when initially referred to the clinic because of insomnia. She described difficulties with sleep initiation and maintenance insomnia. She also mentioned that she was bothered with difficulties keeping her legs still, particularly at rest and in the evening. This had worsened over the past few years and was a major contributor to her sleep difficulties. She derived some benefit from moving her legs or walking when the leg symptoms were particularly severe.

Mrs MM had a history of mild snoring, but no witnessed apnoeas or excessive day time sleepiness. She had no history of renal disease, diabetes or peripheral neuropathy. She was taking no regular medications.

Examination findings were unremarkable. Investigations revealed a mild iron deficiency with a ferritin of 13 µg/L (15–200).

She was subsequently treated with iron replacement, which corrected her iron deficiency over a period of 1 month. Despite this, her symptoms persisted.

Mrs MM was then commenced on carbidopa/levodopa 100/25 mg two tablets at night. Within a week she had significant improvement in her symptoms. She described a restful sleep without any difficulties.

After 12 months of therapy there was a return of her symptoms. She noticed her leg symptoms were occurring earlier during the day and there was little or no relief with her nocturnal carbidopa/levodopa.

What would be the next step in Mrs MM's management?

Restless legs syndrome (RLS) is a common, distressing movement disorder, yet many sufferers are not diagnosed or managed adequately. Restless legs syndrome has detrimental effects on sleep, daily function and quality of life. It is characterised by discomfort of, and urge to, move the legs, primarily during rest or inactivity. Relief of symptoms is gained with movement. Symptoms are mostly present or worsen in the evening.[1]

Treatment ranges from eliminating aggravating factors (eg. iron deficiency and certain medications), through other nonpharmacologic measures (eg. abstinence from caffeine, nicotine and alcohol) to pharmacotherapy (eg. dopamine agonists, levodopa, opioids,

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and benzodiazepines). In recent years, pharmacotherapy for RLS has been enhanced by new agents, supported by well designed published studies.[2–4]

The high prevalence of RLS requires that general practitioners familiarise themselves with the condition and take a leading role in its management.

Epidemiology

In the past decade, several studies have been published from different populations examining the prevalence of RLS. In a study of the general population in Kentucky,[5] where 1803 adults were interviewed, the age adjusted prevalence for RLS was 10%. The prevalence increased with age, with 19% of subjects over 80 years of age reporting frequent RLS symptoms. Similar prevalence rates in the general population have been reported in Canada.[6] The prevalence of the condition in patients attending primary care clinics is even higher (15–25%),[7] most likely as a consequence of the increased health care needs of these patients. There appears to be a female predominance, although this is not consistent in all studies.[8] Recent Asian surveys indicate a lower prevalence in these populations.[9,10] Ethnic variations in prevalence would not be surprising given the large influence of genetics in primary RLS. However, more studies are needed to confirm these findings.

Aetiology

Primary and secondary forms of RLS are recognised. Within the primary category, 40–60% of patients report a family history. Secondary causes include iron deficiency, pregnancy, renal failure, peripheral neuropathy, diabetes mellitus, thyroid disorders, fibromyalgia and rheumatoid arthritis.

Family and twin studies report a substantial effect of genetic factors[11,12] and have proposed both autosomal dominant[13,14] as well as recessive[15] modes of inheritance. Genetic studies suggest several candidate loci associated with RLS. To date, five chromosomal loci (RLS1-5) have been mapped for RLS in single families, and three susceptibility loci have been identified in a genome wide association study.[16–19] Although RLS is generally thought to be a disease of adulthood, it may also occur in children, where it is often misinterpreted as attention deficit hyperactivity disorder (ADHD), growing pains or other sleep disorders.[20,21]

Iron deficiency is associated with symptoms of restless legs[22,23] and replacement can alleviate these symptoms. Pathological and imaging studies have shown iron depletion in dopaminergic neurons in the substantia nigra.[24,25] This suggests a problem with iron transport within the central nervous system in RLS.

Table 1. Diagnostic criteria and supportive features of RLS[1]

Required diagnostic criteria for RLS

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night

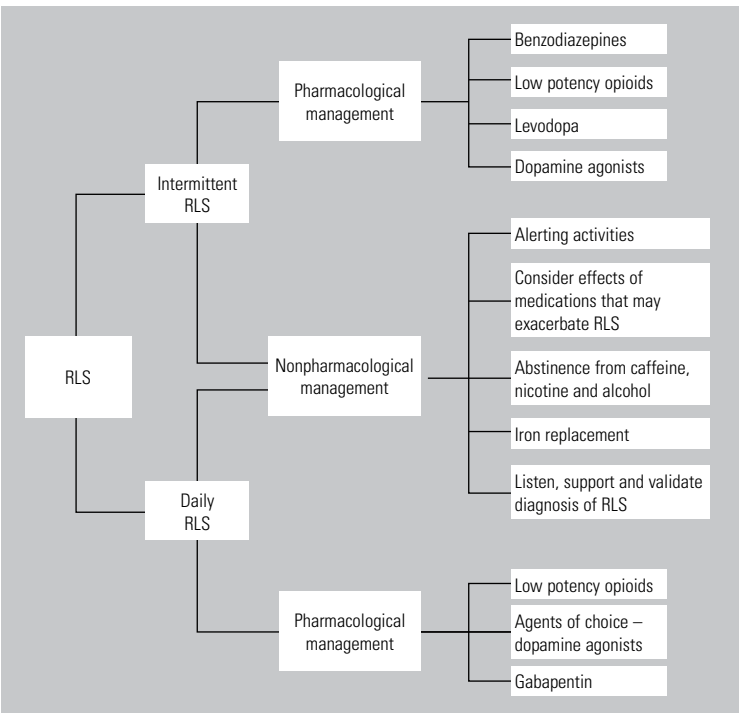
Supportive or associated features of RLS

1. Family history
2. Response to dopaminergic therapy
3. Periodic limb movements (during wakefulness or sleep)
4. Disturbed sleep

Twenty-six percent of pregnant women have RLS symptoms in the third trimester of their pregnancy, which frequently resolve after birth.[26] Twenty to seventy percent of dialysis requiring patients report RLS.[27–31] Symptoms are not alleviated by dialysis, but kidney transplantation may dramatically resolve symptoms.[32,33] It is unclear how pregnancy or renal failure are linked to RLS, but both conditions can be associated with anaemia.

The effectiveness of dopamine and its agonists to treat RLS implicates a problem with dopamine activity in RLS. It is interesting

Figure 1. Algorithm for the management of daily and intermittent RLS[40]



that iron is a cofactor in dopamine synthesis. Studies point to a defect in iron metabolism or dopamine pathways in the brain, but small autopsy studies show that unlike Parkinson disease, there is no loss of dopaminergic neurons.[34]

Diagnosis

The diagnosis of the RLS is clinical. Current diagnostic criteria[1] refer to four essential features and other supportive features of RLS (*Table 1*).

The symptoms of RLS should be distinguished from paraesthesia and peripheral neuropathy, and arthritis pain and muscle cramps. A detailed clinical history will elicit the symptoms, the impact of these symptoms on sleep initiation and sleep maintenance, and the presence of periodic limb movements in sleep. The history is also important to evaluate other exacerbating factors, such as drugs that may increase leg restlessness. Physical examination may identify secondary causes, such as a peripheral neuropathy or anaemia. Iron studies are important, with a ferritin level <50 µg/L considered significant in the context of RLS symptoms.

Polysomnography is not routinely required, but may be useful to evaluate sleep quality (eg. poor sleep initiation or sleep fragmentation from restless legs/periodic limb movements) and the presence of concurrent sleep disorders, such as obstructive sleep apnoea. Periodic limb movements (episodes of limb movements that typically recur at intervals of 5–90 seconds during non-REM sleep) can be readily identified in a sleep study, but these are common in the general population in the absence of symptoms of RLS, and there is debate as to their importance.[35] Questionnaire symptom scales, including a severity rating scale, and other sleep laboratory tests such as the suggested immobilisation test (which measures subjective leg discomfort and limb movements while the patient is still), have been used mainly in research studies to monitor response to treatment.[36,37]

Management

Management of RLS involves both pharmacological and nonpharmacological approaches (*Figure 1*). It is important to note that as the severity and frequency of RLS is variable, nonpharmaceutical therapies alone may be appropriate for milder forms of RLS. It is also important to point out that most pharmaceutical agents are used in an off label basis for RLS. In Australia, only ropinirole and pramipexole have RLS as a listed treatment indication, and pramipexole now has a restricted PBS listing. However, the other dopamine precursors and agonists have been utilised for many years for RLS.

Nonpharmaceutical management

- Listen, support and validate the diagnosis of RLS and offer support networks such as RLS Australia (www.RLS.org.au)
- Assess iron deficiency in all RLS patients. If iron deficiency is established either by a low ferritin (<50 µg/L) or low percentage iron saturation, a cause for iron deficiency should be investigated and iron replacement started[22]
- Mental alerting activities such as video games may reduce symptoms at times of boredom
- Reduce or abstain from caffeine, nicotine and alcohol
- Consider ceasing medications that may exacerbate RLS such as antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs) or the serotonin norepinephrine reuptake inhibitors (SNRIs), neuroleptics, dopamine blocking agents (eg. anti-emetics), and sedating antihistamines
- There is recent evidence that compression stockings may improve symptoms and therefore quality of life.[38]

Pharmacological management

Commonly used drugs in the management of RLS are listed in *Table 2*. The medications are usually given 1–3 hours before bed time, as guided by the onset of symptoms.

Table 2. Commonly used drugs used for restless legs syndrome

Drug	Initial dose	Usual daily dose range	Common adverse effect
Dopamine precursors			
Levodopa (+ carbidopa or benserazide)	50 mg	100–200 mg	Nausea, vomiting, orthostatic hypotension, hallucination, augmentation of symptoms, insomnia
Dopamine agonists			As for levodopa plus nasal congestion and fluid retention
Ropinirole	0.25 mg	0.5–3.0 mg	
Pramipexole	0.125 mg	0.5–1.5 mg	
Pergolide	0.025 mg	0.5 mg	Also risk of valvular heart disease and retroperitoneal or pleuropulmonary fibrosis
Nondopaminergic medications			
Gabapentin	300 mg	600–2400 mg	Sedation, dizziness, fatigue, somnolence, ataxia
Clonazepam	0.25 mg	0.25–2.0 mg	Sedation, tolerance
Oxycodone	2.5 mg	2.5–30.0 mg	Constipation, sedation, nausea, vomiting, dependence

Adapted from: Earley C. Restless legs syndrome. N Engl J Med 2003;348:2103–9

Dopamine precursors

Levodopa plus dopa-decarboxylase inhibitor (DDI) is useful to treat intermittent RLS symptoms. Because the effect of levodopa can wear off early in the night (duration of action 2–4 hours), longer acting forms may also be useful. An important side effect of levodopa, which limits its use to intermittent therapy, is augmentation. Augmentation is an increase in severity of symptoms with regular long term therapy. Typically, symptoms start to occur earlier in the day compared to the start of therapy. Often the symptoms are more intense or spread to the trunk and arms.[39] Up to 70% of patients taking levodopa develop augmentation, and the risk increases with higher doses.[40]

Importantly, increasing the levodopa dose may make augmentation worse and if it occurs, levodopa should be stopped and another agent trialled. Rebound, the recurrence of RLS in the early morning, also occurs in 20–35% of patients taking levodopa.[41] Rebound probably reflects the end of the drug action of the dopamine precursor.

Dopamine agonists

These agents have a longer onset of action than levodopa (90–120 minutes) and therefore are not ideal for intermittent use once symptoms have started. They are the drugs of choice for daily RLS.[42,43] Augmentation is less common (30%) compared to levodopa (70%).[44] Unlike dopamine precursors, augmentation with dopamine agonists (DA) may be treated by giving divided doses and/or increasing the dosage. Dopamine agonists are either ergot derived or nonergot derived:

- Ergot derived DA such as pergolide, cabergoline and bromocriptine, are indicated to treat Parkinson disease or endocrine disorders. Low dose cabergoline (1 mg) was shown to be effective in moderate to severe RLS.[45] However, ergot derived DA are associated with rare but significant side effects, namely valvular heart disease and retroperitoneal or pleuropulmonary fibrosis.[46] Hence, these drugs are not commonly used or recommended for RLS
- Nonergot DA, including ropinirole and pramipexole, are becoming more popular as first line treatment options for moderate to severe RLS because of their more attractive side effect profile compared to the ergot agents as described above.[47] Ropinirole has been studied in the largest double blind, placebo controlled trial in RLS supporting its effectiveness in reducing RLS symptoms.[3,4] Pramipexole has only recently been introduced in Australia, despite widespread use elsewhere. Interestingly, there have been several reports of unusual compulsive behaviours occurring in those taking dopamine agonists, including pathological gambling and hypersexuality.[48] Encouragingly very recent studies have confirmed the efficacy of a 24 hour transdermal patch using the dopamine agonist rotigotine to relieve both night and day time symptoms.[49] This drug is not currently available in Australia, but may have a great potential to alleviate many of the difficulties associated with dosing patients with RLS.

Low potency opioids

Low potency opioids (eg. codeine) or opioid agonists (eg. tramadol) agents are useful for intermittent or daily RLS symptoms. However, daily use may be associated with adverse effects such as constipation or nausea and tolerance may develop.

Benzodiazepines or benzodiazepine agonists

These agents are most useful for intermittent RLS symptoms. Because of their hypnotic effects they may be particularly useful to treat sleep onset insomnia caused by RLS. Most controlled trials have been performed with clonazepam.[43]

Gabapentin

This agent is especially useful in painful variants of RLS. One controlled trial suggests that mean doses of 1300–1800 mg/day are needed, but some patients may benefit from smaller doses.[50]

The role of the GP

General practitioners should be able to diagnose primary RLS, recognise secondary cases and commence management in all patients. General practitioners should consider referral to sleep specialists or neurologists under the following circumstances:

- atypical symptoms
- significant sleep disturbance
- excessive medication side effects, and
- refractory symptoms.

Summary of important points

- Restless legs syndrome is a distressing movement disorder that affects a significant proportion of the adult population.
- Many sufferers do not receive an accurate diagnosis or an appropriate management plan.
- Clear diagnostic criteria for RLS exist.
- Management involves both pharmacological and nonpharmacological options.

Conflict of interest: none declared.

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