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Restless legs syndrome

Restless legs syndrome (RSL) is a common movement disorder and many patients with the condition complain of disturbed sleep. Nonpharmacological management approaches alone may be appropriate for patients with milder RLS but those with more severe disease require pharmacological management. Non-ergot derived dopamine agonists are regarded as first-line treatment for patients with moderate to severe daily symptoms of RLS.

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'...Wherefore to some, when being in bed they betake themselves to sleep, presently in the arms and legs. Leaping and contractions of the tendons and so great a restlessness and tossing of the members ensure, that the diseased are no more able to sleep, than if they were in the place of greatest torture ...'

Thomas Willis, *Instructions for Curing the Watching Evil* (a chapter in *'The London Practice of Physick'*), 1685

So wrote the great English neurologist Sir Thomas Willis, of Circle of Willis fame and a physician to King Charles II. In the 19th century, this condition was called 'impatience musculaire' by the French and 'anxietas tibiarum' by the Germans and was believed to be a form of hysteria. The modern term 'restless legs syndrome' (RLS) was coined in 1945 by the Swedish neurologist Karl Ekbom, who characterised the disease and presented eight cases in his classic paper on the condition.[1]

Description and epidemiology

The modern definition of RLS has changed little since the time of Thomas Willis. It is a sensorimotor disorder clinically defined by:

- an urge to move the legs, with or without unpleasant sensations
- improvement during movement
- worsening while at rest
- worsening in the evening and night.

IN SUMMARY

- **Restless legs syndrome (RLS) is a common movement disorder and can be distressing for patients.**
- **Diagnosis is clinical and based on clear diagnostic criteria.**
- **Secondary causes of RLS such as iron deficiency and medications precipitating symptoms should be sought and treated.**
- **Nonpharmacological management options should be explored.**
- **Non-ergot derived dopamine agonists are the treatment of choice if the patient has moderate to severe daily symptoms of RLS.**
- **When using dopaminergic therapy, the lowest dose possible should be used to prevent augmentation.**

These four features are the essential diagnostic criteria for RLS listed by the International Restless Legs Syndrome Study Group (IRLSSG); other features, such as family history, are supportive features (Table 1).[2] Although it is called 'restless legs syndrome', the disorder may also involve arms and other body parts. Patients use various descriptive terms for the unpleasant sensations, such as 'crawling', 'searing', 'jittering', 'internal itch', 'burning' and 'tight feeling', and up to 50% describe their sensations as painful.[3]

RLS is common. Population surveys in the past decade have shown that mild symptoms occur in 5 to 15% of the general western population.[4] A large study that surveyed over 15,000 adults in the USA and Europe reported an overall prevalence of RSL of 7.2%, with 2.7% of patients suffering symptoms at least twice a week with moderate or severe distress.[5] The prevalence is even higher in outpatients attending primary care clinics; studies in this population found 10 to 20% of patients reported symptoms that fulfilled IRLSSG diagnostic criteria at least once a week.[6,7] Ethnic variations have been observed, with generally lower rates of this disorder in non-Caucasian populations; for example, a recent study reported a prevalence of 1.6% in Taiwanese adults.[8] This is not surprising given the large influence of genetics in primary RLS.

The prevalence of RLS increases with age. In most epidemiological studies, there is a two to threefold increase in prevalence from a young age (20 to 29 years) to older age (60 to 69 years), regardless of the absolute prevalence.[4] This can only partly be attributed to increased comorbidities with age that predispose to secondary RLS. There also appears to be a female predominance, with women generally being affected about twice as often as men.[5]

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Figure. The symptoms of restless legs syndrome in children may be misinterpreted as attention deficit hyperactivity disorder, growing pains or other sleep disorders.

Restless legs and sleep disruption

Many patients with RLS complain of disturbed sleep. Most report difficulty falling asleep because

Table 1. Diagnostic criteria and supportive features of restless legs syndrome*[2]

Essential features

- Urge to move the legs, usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs
- Urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting
- Urge to move or unpleasant sensations partially or totally relieved by movement, such as walking or stretching, for at least as long as the activity continues
- Urge to move or unpleasant sensations worse in the evening or night than during the day, or only occur in the evening or night

Supportive or associated features

- Family history
- Response to dopaminergic therapy
- Periodic limb movement (during sleep or wakefulness)
- Sleep disturbance
- Variable clinical course but usually chronic and may be progressive
- Normal physical examination in primary/idiopathic form

* Adapted from consensus criteria developed by the Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health in collaboration with the International Restless Legs Syndrome Study Group.[2]

Table 2. Common conditions associated with secondary restless legs syndrome

- Chronic venous insufficiency
- Diabetes mellitus
- End-stage renal disease and dialysis
- Excess caffeine intake
- Hypothyroidism
- Iron deficiency
- Multiple sclerosis
- Obesity
- Parkinson's disease
- Peripheral neuropathies (in particular Charcot-Marie-Tooth and amyloid neuropathy)
- Pregnancy
- Rheumatoid arthritis
- Spinal stenosis and lumbar sacral radiculopathy

the symptoms typically worsen in the evening and night and with immobility. Some, however, fall asleep rapidly but wake frequently with symptoms that force them to get up and walk around in an attempt to relieve the discomfort. As a group, patients with RLS have severe nocturnal sleep disruption compared with normal controls, with reduced total sleep time, reduced sleep efficiency and longer sleep latency. Disturbed sleep is the primary morbidity for most patients seeking treatment for RLS.

RLS is also associated with periodic limb movements of sleep (PLMS), which may further disrupt sleep.

Aetiology and pathophysiology

Most cases of RLS occur as a primary idiopathic disorder and 40 to 60% of these patients report a family history of the condition.[4,9] Secondary RLS may also occur in association with a variety of medical disorders, as listed in Table 2.

Primary RLS and genetic factors

The exact neural structures and mechanisms involved in the pathogenesis of RLS are still debated. Peripheral nerve conduction abnormalities, thalamic, basal ganglia and cerebellar activation defects, dopaminergic and opiate receptor dysfunction and central nervous system iron deficiency have all been implicated.[3,10,11] The reality is that the pathogenesis of RLS is probably multifactorial.

Familial and twin studies suggest a significant genetic contribution.[12-14] Both autosomal dominant and recessive modes of inheritance have been observed, with variable penetrance even within individual families.[15-17] To date, seven candidate genes (RLS1 to RLS7) have been found to be associated with increased RLS susceptibility in linkage studies.[18-25] Six of these (RLS1 to RLS6) have been mapped. Genome-wide association studies have also identified multiple other loci associated with RLS.[26] Thus, the current understanding of RLS is that it is a complex multigenic disorder where carriers of susceptibility alleles are at increased risk of developing symptoms, and this risk is further modified by other genetic and/or environmental factors, resulting in the heterogeneity of the disease spectrum seen clinically.

Patients with a family history of RLS tend to develop symptoms earlier than those with sporadic primary RLS.[14] Although RLS is generally thought to be a disease of adulthood, it may also occur in children, in whom the symptoms may be misinterpreted as attention deficit hyperactivity disorder (ADHD), growing pains or other sleep disorders.[27,28] The interaction between ADHD and RLS is complex; sleep disruption due to RLS may lead to daytime inattentiveness, moodiness and paradoxical overactivity, and diurnal manifestations of RLS may mimic ADHD symptoms. There is also increasing evidence that RLS and idiopathic ADHD may coexist independent of sleep disruption, suggesting a common pathway through dopaminergic dysfunction.[3,29,30]

Table 3. Common differential diagnoses of restless legs syndrome[44]

Akathisia
- Most commonly associated with neuroleptic medications
- Urge to move not necessarily associated with discomfort in legs
- Symptoms do not worsen at night

Nocturnal leg cramps
- Sudden involuntary muscle contractions rather than voluntary movements due to discomfort
- Palpable tightening of leg muscles

Peripheral neuropathy
- Sensory disturbance usually also present
- Not typically relieved by activity
- Primary aetiology such as trauma, nerve root compression, diabetes usually evident

Peripheral vascular disease/ claudication
- Cramping type pains exacerbated by activity and improved with rest
- Symptoms not worse at night

Secondary RLS

Iron deficiency (with or without anaemia) is associated with secondary RLS. Patients with RLS tend to have lower serum and spinal fluid ferritin concentrations compared with age-matched controls.[31,32] MRI for regional brain iron content and autopsy studies have also found reduced iron content in the substantia nigra of patients with RLS.[33] In addition, several other established causes of secondary RLS, such as end-stage renal disease and pregnancy, often result in iron deficiency. Further, iron replacement can alleviate symptoms of RLS in some

Table 4. Common medications that may exacerbate symptoms of restless legs syndrome[45]

Antihistamines – cimetidine
Antipsychotics – haloperidol, olanzapine
Caffeine
Dopamine antagonists
Lithium
L-thyroxine
Mirtazapine
Selective serotonin reuptake inhibitors – fluoxetine, citalopram
Tramadol
Tricyclic antidepressants
Venlafaxine

patients.[31,34] This implies that central nervous system iron deficiency may have a causative role for some patients with this disorder.

There is a strong association between RLS and pregnancy. Some 26% of pregnant women report RLS symptoms in the third trimester, with symptoms frequently resolving after delivery.[35] Interestingly, the number of past pregnancies correlates with risk of RLS. Nulliparous women do not have significantly increased risk compared with men.[36] These observations have led to the hypothesis that in addition to the effects of iron deficiency, pregnancy-related transitory hormonal changes may precipitate symptoms in genetically predisposed patients.

Secondary RLS is also common in patients with end-stage renal disease. Symptoms are reported by 20 to 70% of patients requiring dialysis and are not alleviated by dialysis.[37,38] However, kidney transplantation may resolve these symptoms dramatically.[39] Iron deficiency is likely to play a role in these patients because low-dose erythropoietin and iron replacement have been shown to be helpful in this population.[40,41]

Dopamine and its agonists are effective in the treatment of both Parkinson's disease and RLS, implicating a common pathogenic pathway involving dopamine activity.[42] Iron is again implicated as it is a cofactor in the synthesis of dopamine from tyrosine. Unlike in patients with Parkinson's disease however, there is no apparent loss of dopaminergic neurons in the substantia nigra and other regions in patients with RLS.[43]

Making a diagnosis

The diagnosis of RLS is clinical; there is no definitive laboratory test or pathognomonic finding. All four of the essential features of the IRLSSG diagnostic criteria are required to make the diagnosis (Table 1).[2]

Details of symptoms, exacerbating factors and possible secondary causes can be elicited by a careful history and examination that considers the questions listed below.

- Do the symptoms fit the essential criteria for RLS? Should another diagnosis be considered?
- What are the frequency and severity of the symptoms?
- How do the symptoms impact sleep initiation and maintenance? Is there any history suggestive of periodic limb movements in sleep?
- What are the current medications, and are any of them likely to exacerbate the symptoms?
- Has any treatment for RLS been tried?
- Is there a family history of RLS?
- What are the patient's current alcohol and caffeine intakes?
- Are there any symptoms or signs that suggest a secondary cause of RLS (see Table 2)?

Common differential diagnoses are listed in Table 3, and common medications that may exacerbate RLS symptoms are listed in Table 4.[44,45]

Iron studies and renal function tests are useful to exclude secondary causes of RLS. A ferritin level less than 50 μg/L (even though the haemoglobin level may be normal) is considered clinically significant in the context of RSL symptoms, and iron replacement should be considered.[46] People who frequently donate blood may be at higher risk of developing RLS symptoms, and stopping or reducing the frequency of donations may be helpful.[47,48] A recent large survey of UK blood donors did not find increased risk of RLS with fewer than three donations per year.[49]

Patients with existing RLS may experience peri- and postoperative exacerbation of symptoms because of a combination of immobility, blood loss and change in medications (such as a sudden cessation of usual treatment or the addition of dopamine antagonist agents for nausea).[50] Spinal anaesthesia and parenteral opiates have been associated with the development of transient RLS.[51] Most patients' symptoms return to pre-operative levels by six weeks.

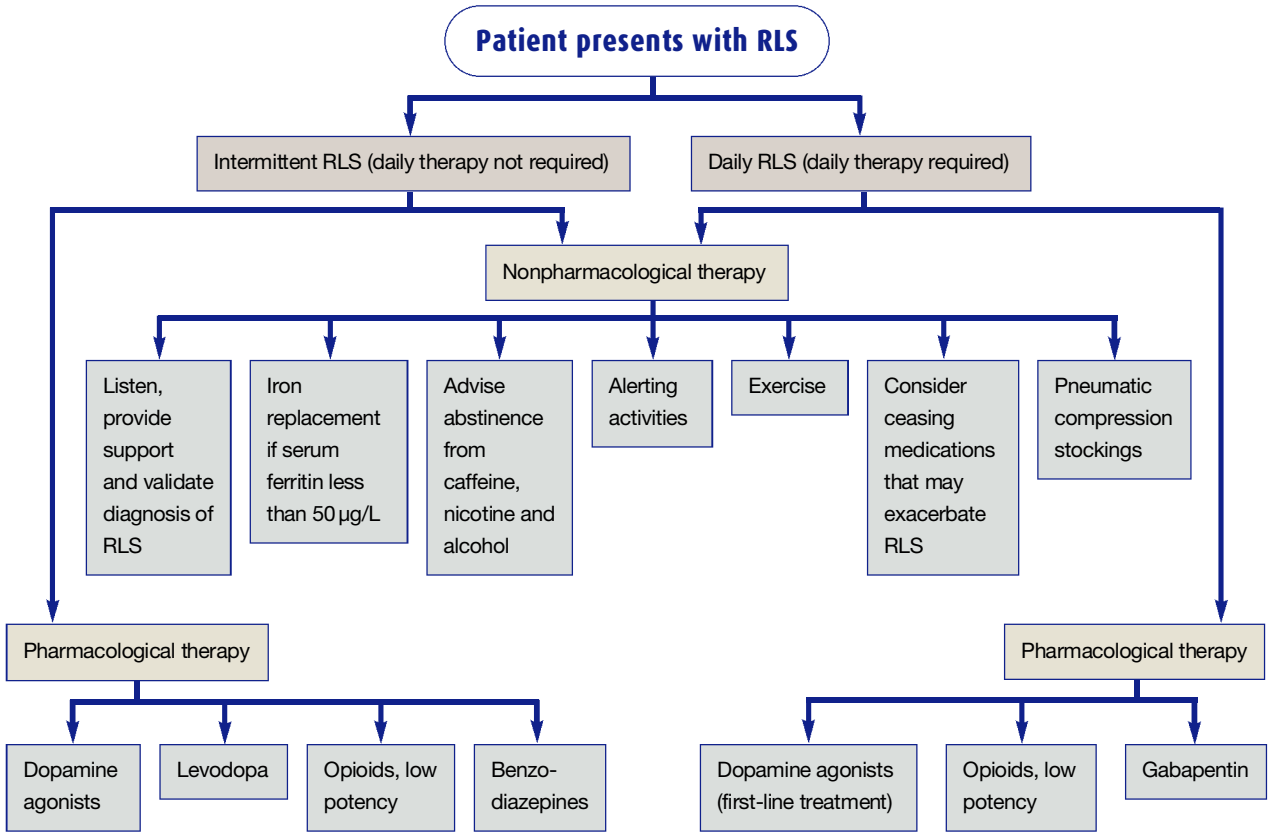
Polysomnography is not routinely required for patients with RLS but may be useful to evaluate sleep quality, such as sleep fragmentation, and the presence of other concurrent sleep disorders, such as obstructive sleep apnoea (Table 5).

Table 5. Sleep studies and restless legs syndrome

Perform sleep studies in patients with diagnosed or suspected restless legs syndrome when:

- diagnosis suspected in children or adolescents
- diagnosis uncertain
- sleep apnoea suspected
- minimal restless legs syndrome but nightly sleep disruption
- continuing sleep disruption despite apparent good treatment of restless legs syndrome

An approach to the management of restless legs syndrome (RLS)[57]



Periodic limb movements of sleep

PLMS are sudden jerking leg movements (typically involving extension of the big toe and flexion of the ankle, knee and sometimes hip) that are repetitive at intervals of five to 90 seconds during non-REM sleep. PLMS are observed in more than 80% of patients with RLS, but their significance in the absence of sleep disruption is debated.[3,52] PLMS is also associated with other sleep disorders such as narcolepsy, obstructive sleep apnoea and insomnia, and with medications such as selective serotonin reuptake inhibitors (SSRIs), and is also common in the general elderly population in the absence of any sleep pathology.[3,53-55] Overall, although the presence of PLMS is not specific to RLS, an elevated PLMS index on polysomnography is supportive of the diagnosis of RLS.

Management options

The management of patients with RLS involves nonpharmacological and pharmacological approaches, depending on symptom frequency, severity and impact. Nonpharmacological approaches alone may be appropriate for patients with milder RLS. It is important to note that most pharmaceutical agents are used 'off-label' for RLS. Although all of the pharmaceutical agents discussed below are registered and approved for use by the Therapeutic Goods Administration (TGA) in Australia, only pramipexole and ropinirole have RLS as listed treatment indication.[56]

Treatment algorithms originally proposed by the Medical Advisory Board of the US Restless Legs Syndrome Foundation in 2004 have been widely adopted for use.[57] The flowchart on this page is based on these algorithms.

The IRLSSG has developed a subjective symptoms rating scale – the International Restless Legs Scale (IRLS) – to assess the severity and impact of symptoms on sleep, mood and daily function.[58] This scale has been validated in various clinical and research cohorts and has proven to be reliable and responsive.[59] Clinically, this scale may be useful to follow the secular evolution of a patient's symptoms and assess the response to treatment.

Table 6. Drugs commonly used in the treatment of patients with restless legs syndrome[60]

Dopamine precursors

- Levodopa (with benserazide or carbidopa)*
  - Initial levodopa dose, 50 mg; usual daily levodopa dose, 100 to 200 mg at bedtime
  - Common side effects: nausea, vomiting, orthostatic hypotension, hallucination, augmentation of symptoms, insomnia

Dopamine agonists

- Pramipexole
  - Initial dose, 0.125 mg; usual daily dose, 0.5 to 1.5 mg in two or three divided doses
  - Common side effects: as for levodopa plus nasal congestion and fluid retention
- Ropinirole
  - Initial dose, 0.25 mg; usual daily dose, 0.5 to 3 mg in two or three divided doses
  - Common side effects: as for levodopa plus nasal congestion and fluid retention
- Pergolide*
  - Initial dose, 0.025 mg; usual daily dose, 0.5 mg in two or three divided doses
  - Common side effects: as for levodopa plus nasal congestion and fluid retention; also risk of valvular heart disease and retroperitoneal or pleuropulmonary fibrosis

Nondopaminergic medications

- Clonazepam*
  - Initial dose, 0.25 mg; usual daily dose, 0.25 to 2.0 mg
  - Common side effects: sedation, tolerance
- Gabapentin*
  - Initial dose, 300 mg; usual daily dose, 600 to 2400 mg in divided doses
  - Common side effects: sedation, dizziness, fatigue, somnolence, ataxia
- Oxycodone*
  - Initial dose, 2.5 mg; usual daily dose, 2.5 to 30 mg in divided doses
  - Common side effects: constipation, sedation, nausea, vomiting, dependence

* Not TGA approved for the treatment of patients with restless legs syndrome.

Nonpharmacological management

The following strategies may be used alone or in combination with pharmacotherapy in patients with RLS. They are listed in a suggested order of approach for clinicians.

- Listening, providing support and validating the diagnosis of RLS, and offering support networks such as RLS Australia (www.rls.org.au).
- Assessing for iron deficiency. All patients with RLS should be assessed for iron deficiency, and those with serum ferritin levels less than 50 μg or reduced iron saturation should receive iron replacement even if they do not have anaemia. The cause for iron deficiency should also be investigated if appropriate.
- Encouraging reduced intakes, and preferably abstinence from, caffeine, alcohol and nicotine. The evidence linking these substances to RLS is predominantly epidemiological but reducing intake is likely to lead to overall improved sleep quality.
- Encouraging participation in activities that distract or provide mental stimulation. This may reduce symptoms at times of inactivity.
- Encouraging exercise. A small randomised controlled trial showed an improvement in RLS symptoms after a 12-week lower body training and aerobic exercise program.[60]
- Considering cessation of medications that may exacerbate RLS (see Table 4).
- Encouraging use of pneumatic compression stockings. A recent randomised controlled trial showed improved symptom and quality of life scores with pneumatic compression devices; one-third of the subjects experienced complete resolution of their RLS symptoms.[61]

Pharmacological management

Medications commonly used in the management of patients with RLS are listed in Table 6.[62] They are usually given one to three hours before bedtime as guided by the onset of symptoms.

Dopamine precursors

Levodopa in combination with benserazide or carbidopa (its peripheral breakdown inhibitors) is effective in the treatment of patients with RLS.[63,64] The duration of action of these drug combinations is typically between two and four hours so the therapeutic effect tends to wear off early in the night. Longer-acting controlled-release formulations may be effective in patients with persistent symptoms. Intermittent levodopa plus benserazide or carbidopa is primarily used in patients with intermittent RLS because of the rapid onset of action of these drug combinations and the occurrence of augmentation (an increase in symptom severity with chronic treatment).

Up to 70% of patients with RLS receiving levodopa plus benserazide or carbidopa eventually develop augmentation.[65] Augmentation may manifest as:[66]

- earlier onset of symptoms in the afternoon or evening
- more rapid onset of symptoms following rest
- increased intensity of symptoms
- a spread of symptoms to different body parts (usually the arms but

also the trunk and even the face)
- a shorter duration of medication effect.

Augmentation is usually progressive and is more likely to develop with higher doses of levodopa plus benserazide or carbidopa (particularly above 200 mg levodopa per day) and longer duration of treatment.[67] Patients who develop augmentation on this drug combination should be switched to another treatment agent.[68] Rebound symptoms may occur with drug discontinuation and therefore tapering or overlap of treatments is recommended.

Augmentation should be distinguished from tolerance (a reduction in effectiveness of the medication over time necessitating an increase in dosage to maintain the same relief of symptoms) and early morning rebound (reappearance of symptoms in the morning corresponding to the end of drug action). Early morning rebound is more common in patients treated with immediate-release preparations of levodopa (20 to 35%).[69]

Levodopa, carbidopa and benserazide are not approved by the TGA for the treatment of RLS.

Dopamine agonists

Dopamine agonists are the treatment of choice for patients with daily RLS symptoms.[3,64,70] Their onset of action is too long for them to be suitable for treating patients with intermittent RLS.

- **Pramipexole and ropinirole.** Non-ergot derived dopamine agonists such as pramipexole and ropinirole have higher affinities for the dopamine D3 receptor, which appears to be involved in the modulation of locomotor activity.[71] These drugs are considered first-line treatment for moderate to severe RLS because of their relatively benign side effect profiles and increasing evidence of efficacy. Currently, pramipexole and ropinirole are the only medications indicated by the TGA for the treatment for RLS.

  A meta-analysis published in early 2010 identified five double-blind randomised controlled trials that examined the effectiveness of ropinirole in RLS.[72] The pooled results (n=1212) showed that ropinirole significantly reduced RLS symptoms (as assessed by the IRLSSG severity rating scale [the IRLS]), and improved reported sleep quality and quality of life compared with placebo. The same meta-analysis also identified six double-blind randomised controlled trials for pramipexole (n=1019), and these had similar positive effects.

  Side effects with pramipexole and ropinirole are usually mild, transient and limited to nausea, lightheadedness and fatigue. They typically resolve within 10 to 14 days. Less common side effects include nasal congestion, constipation, insomnia and leg oedema, and these usually resolve when the medication is ceased.[57] Interestingly, like Parkinson's disease, dopaminergic treatment in patients with RLS is associated with a small risk of developing dopamine dysregulation syndrome, a disorder characterised by impulse control disorders such as gambling, eating disorders, compulsive shopping and hypersexuality.[73,74] Patients should be appropriately counselled before treatment is commenced.

  Augmentation is less common with dopamine agonists (30% of patients) than with levodopa (60 to 70% of patients).[68] With dopamine agonists, dividing the treatment dose or changing the dosing time may alleviate augmentation. It is also worth trying an alternative dopamine agonist as augmentation does not necessarily redevelop.[66,68]
- **Rotigotine.** For persistent day and night symptoms of RLS, continuous transdermal rotigotine (a non-ergot derived dopamine agonist) has recently completed phase III trials and has demonstrated good clinical efficacy.[72,75] The rotigotine patch is now indicated for RLS treatment by the European Medicines Agency and is currently under review by the US Food and Drug Administration and the Australian Drug Evaluation Committee. This formulation may potentially alleviate some of the difficulties associated with dosing patients with RLS. Unfortunately, it is relatively expensive and requires cold storage and transport.
- **Bromocriptine, cabergoline and pergolide.** Ergot derived dopamine agonists such as bromocriptine, cabergoline and pergolide are also useful in the treatment of RLS (but are not approved by the TGA for such use).[64] However, these drugs are now infrequently used because they are associated with rare but significant side effects, namely valvular heart disease and retroperitoneal and pleuropulmonary fibrosis.[76-78] Pergolide was voluntarily withdrawn from the US market in 2007 although it is still available in Australia.[79] Commencement of these medications should be undertaken in conjunction with specialist involvement.

Opioids

A variety of opioid agonists, including codeine, methadone, oxycodone and tramadol, have been reported to be helpful and are used as alternative medications for intermittent RLS. Despite relatively common off-label use in RLS, there is a paucity of controlled studies regarding their efficacy in the condition.[64] Common adverse effects include constipation and nausea. Existing follow-up data suggest long-term use is associated with low rates of adverse events, including dependence and dose escalation.[80] Although prescribers need to be aware of the potential for abuse, this class of medications should not be overlooked because of historical concerns.

Benzodiazepines

Benzodiazepines may be helpful in patients with intermittent RLS with concurrent sleep-onset insomnia (but none are approved by the TGA for treatment of

RLS). Clonazepam is the most studied in this class but most trials are small and have not been performed using recent diagnostic standards or objective measures of therapeutic benefit.[81,82] There has been little research into the effect of benzodiazepines on RLS in the past two decades. Again, caution should be taken regarding tolerance and dependence with the use of these agents.

Gabapentin

A 2008 systematic review identified four randomised controlled studies examining the effect of gabapentin in RLS.[64] This review concluded that gabapentin is efficacious for the treatment of RLS both alone and in combination with dopamine agonists. Gabapentin (off-label use) may be particularly useful in patients who perceive their symptoms as painful. Doses between 800 and 1800 mg per day may be required for symptomatic benefit of RLS, but often the use of very low doses (such as 100 to 300 mg at night) together with dopamine agonists provide a synergistic therapeutic effect. Gabapentin is usually well tolerated.

Referral of patients

GPs can diagnose primary RLS, investigate for and recognise secondary cases and commence management in all patients. Referral of the patient to a sleep physician or neurologist should be considered if:

- the diagnosis is unclear or symptoms are atypical
- there is significant sleep disturbance or likely coexisting sleep pathology such as obstructive sleep apnoea
- there are excessive side effects to medications
- the symptoms are refractory to treatment.

Conclusion

RLS is a common disorder that may be distressing to patients and may significantly impact on their quality of life. The diagnosis is clinical and secondary causes such as iron deficiency need to be ruled out.

Nonpharmaceutical approaches to treatment should be considered initially, prior to instigating pharmacological therapies. Advances in understanding the underlying pathophysiology have broadened drug treatment options. MT

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