



**Spectrum
A Drug Information Newsletter
For Pharmacists**

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Restless Legs Syndrome

It is Wednesday morning at your pharmacy when a very tired looking elderly gentleman comes to the counter asking about OTC sleep aids. He wants to know which is the “strongest”. Being the thorough pharmacist you are, you inquire as to why he is having trouble sleeping. He informs you that it is not him that is having the problem, it is his wife, she is constantly moving around in bed. “It seems like she is walking 10 miles in her sleep every night, her legs never stop moving.” Consequently, neither of them sleeps well, and they are considering sleeping in separate beds. You think this sounds familiar and then you remember the Spectrum Newsletter you read on Restless Legs Syndrome.

What is it?

Restless Legs Syndrome (RLS) was first identified in the medical literature over 300 years ago.¹ For many years the condition was believed to be a peripheral disorder of the lower extremities; however, recent improvements in imaging modalities and response to specific pharmacotherapy has lead researchers to conclude that this is more likely a neurological disorder.² Estimates of prevalence of RLS vary but appear to be approximately 5-15%.¹ However, there is significant geographic disparity in prevalence with studies in Singapore and Hong Kong showing rates below 1%.¹ There appears to be no gender difference in prevalence. The syndrome has been recognized in patients as young as 18 years old (3% estimated rate in ages 18-29) and rates rise modestly with age.²

The International Restless Leg Study Group have determined the minimum diagnostic criteria of RLS to be:¹

- a distressing desire to move the legs, usually associated with akathisia (distressing, irritable need to move the legs)
- motor restlessness
- symptoms should be brought on by rest or worsen by rest and there should be at least a partial (but temporary) relief with activity
- symptoms should worsen in the evening or at night

In addition to these diagnostic criteria, patients often report involuntary limb movement while awake and periodic limb movement (PLM) while asleep (seen in about 80% of patients with RLS).¹

Patients with the syndrome are categorized into 2 different pathological groups, primary (idiopathic) and secondary RLS. The pathogenesis of the primary syndrome is unknown. Although, recent functional imaging studies of patients with RLS have demonstrated dysfunction in the binding and uptake of dopamine in the basal ganglia of the brain.² The efficacy of exogenous dopamine and dopamine agonists in treatment of RLS also solidifies the presumption that the pathology is related to

dopamine in the central nervous system. Forty percent of patients with primary RLS have a family history which suggests a genetic predisposition to the disorder.²

Secondary Restless Legs Syndrome is brought about by a number of different conditions. One important secondary cause is uremia; hence patients on dialysis must be closely monitored for this condition. The prevalence of RLS in patients on dialysis have been reported as high as 62%.³ There seems to be no difference in rates between hemodialysis and peritoneal dialysis patients.³ Another condition linked to RLS is iron deficiency anaemia. A number of case reports and studies have linked RLS with low serum and spinal fluid levels of ferritin.² Other secondary causes include diabetic neuropathy², rheumatic diseases², pregnancy², venous insufficiency² and use of certain medications (ex. metoclopramide, lithium and tricyclic antidepressants) that affect dopamine in the brain.¹

What can be done?

Lifestyle and non-pharmacological activities can improve RLS. Reduction or removal of caffeine and alcohol intake as well as smoking cessation have been shown to help reduce symptoms.⁴ Elevating the legs when at rest, massage therapy (including the use of vibrating massage devices), flexion-extension exercises should also be considered part of RLS management.⁴ Whether these activities impact the pathology of RLS or just improve sleep in general is not know.

The cornerstone of management of secondary RLS is dealing with the secondary causes. Removal or reduction of medications that exacerbate RLS should be considered. If patients have iron deficiency, correction of the deficiency with oral or IV iron therapy has been found effective in symptom reduction.³ In patients with end-stage renal disease, dialysis itself does not improve symptoms, but kidney transplant may eliminate RLS.³ For those who remain on dialysis, those who have secondary causes that cannot be modified or removed and those who have primary RLS, pharmacological intervention often required. Please see Appendix 1 for a summary chart of drugs and doses used in the management of RLS.

Dopamine Analogues

The use of levodopa plus a peripheral decarboxylase inhibitor (carbidopa or benserazide) have long been considered the “gold-standard” in the treatment of RLS. Levodopa used at doses between 50-200mg/day have been shown to reduce periodic leg movements and improve sleep.¹ A problem with the use of regular release levodopa is a “wearing-off” affect where symptoms return after approximately 4 hours after the patient goes to bed.¹ This phenomenon can be alleviated by giving a short acting plus a long acting levodopa preparation at the same time before going to bed⁵ or by giving a second dose of regular-release if symptoms recur during the night.¹ A further problem with the use of levodopa is the development of augmentation symptoms with prolonged use. Development of more severe RLS symptoms, return of symptoms earlier in the day and spread of symptoms to different parts of the body (ex. to upper limbs) despite increasing doses of levodopa are all common manifestations of augmentation.³ In a recent 1-year prospective study of levodopa for restless legs syndrome, over 50% of patients discontinued therapy before the end of the trial due to augmentation symptoms.⁶

Dopamine Agonists

Because of problems with long-term efficacy of dopamine analogues, the use of dopamine agonists has become more popular in the management of RLS. The first dopamine agonists studied for this indication was ergotamine derivative, pergolide (Permax[®]). Several placebo controlled trials have shown pergolide’s superiority in both subjective and objective measures of sleep.² However, side effects of the ergot-derivatives dopamine agonists (pergolide and cabergoline - Dostinex[®]) such as nausea/vomiting and orthostatic hypotension, and the risk of pulmonary fibrosis (with pergolide) limits the usefulness of these agents.² The non-ergot dopamine agonists ropinirole (ReQuip[®]) and pramipexole (Mirapex[®]) have also shown promising activity in RLS with less dose-limiting side-

effects.² Recently, the value of ropinirole was tested in the largest placebo-controlled trial to date conducted for treatment of RLS.⁷ Over the course of this 12 week trial, ropinirole was superior to placebo in improving all sleep measures and patient quality of life.⁷ The risk of augmentation from long-term therapy with dopamine agonists still exists but appears to be lower than with levodopa. In a 1 year study with pergolide, augmentation symptoms were seen in 25% of subjects.¹

Other Treatment Options

Benzodiazepines have proven efficacious in RLS management in a few, small open labelled trials. Diazepam and clonazepam have both been shown to improve symptoms and sleep quality.¹ However, long term use of benzodiazepines can lead to concerns of dependence, and long term use in the elderly, carries with it risk of falls and fractures.⁸ The trials examining benzodiazepines in the management of RLS also identified over-sedation and “hang-over” effects as potential problems with long-term use.¹

Opioids, including codeine, methadone and oxycodone have all been found to be helpful in management of RLS.² They positively impact number of sleep arousals, PLM frequency and sleep efficiency.² In addition, long-term sleep studies have shown that narcotics maintain their efficacy.¹ However, concerns over side effects and the potential for dependence and abuse of these agents make them a second-line therapy for those patients who have failed on, or do not tolerate safer alternatives.²

Gabapentin and carbamazepine are the final group of agents that can be used in the management of RLS. Both these agents have been studied in placebo-controlled trials.¹ Although both improved subjective and objective measures of sleep quality, over-sedation was a concerning side-effect, especially with carbamazepine.¹

A common misconception is that quinine is effective in managing symptoms of restless legs syndrome. While there has been at least one case report of its use in one person with this condition,⁹ its value has never been shown in any placebo-controlled or open label trials. Quinine has been found useful in the management of leg cramps which is very different from RLS. Leg cramps are an involuntary, painful contraction of muscles in the legs (usually the calf) that is believed to be caused by an over-excitation of motor neurons in the legs or spine.¹⁰

The Bottom Line

Restless legs syndrome is a common condition that adversely affects patients sleep and sleep-related quality of life. The pathology is either idiopathic or secondary to a number of other medical conditions. The identification of the syndrome as well as any factors that may be causing or worsening the condition is key to appropriate management. Pharmacotherapeutic management is often required, with new dopamine agonists being the preferred therapy.

References

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Appendix 1

Drugs Used in the Management of Restless Legs Syndrome[†]

| Drug | Initial Dose | Recommended Maximum Dose | Common Side Effects |
|---------------------------------------|--------------|-------------------------------|---|
| <i>Dopamine Analogues</i> | | | |
| Levodopa (+ carbidopa or benserazide) | 50 mg | 400mg, in divided doses* | Nausea/vomiting, orthostatic hypotension, hallucinations, augmentation of symptoms, insomnia |
| <i>Dopamine Agonists</i> | | | |
| Pergolide | 0.025mg | 0.5mg, in 2-3 divided doses** | Same as levodopa plus nasal congestion and fluid retention. Health Canada Advisory: sudden onset of sleep, “sleep attacks”*** |
| Pramipexole | 0.125mg | 1.5mg, in 2-3 divided doses** | Same as pergolide without sudden onset of sleep |
| Ropinirole | 0.25mg | 3 mg, in 2-3 divided doses** | Same as pergolide without sudden onset of sleep |
| <i>Other Options</i> | | | |
| Clonazepam | 0.25mg | 2mg, at bedtime | Tolerance, over-sedation |
| Diazepam | 2 mg | 10mg, at bedtime | Same as clonazepam |
| Gabapentin | 300mg | 3600mg, in 3 divided doses | Sedation, dizziness, fatigue, somnolence, ataxia |
| Codeine | 30mg | 180mg, in 2-3 divided doses | Sedation, pruritus, constipation, nausea/vomiting, dry mouth, dependence |
| Oxycodone | 5mg | 20-30mg, in 2-3 divided doses | Same as codeine |
| Oxycodone – extended release | 10mg | 20-30mg, in 2-3 divided doses | Same as codeine |
| Methadone | 2.5mg | 20mg, in 2 divided doses | Same as codeine |

[†] Table adapted from: Early, CJ. Restless legs syndrome. NEJM 2003; 348: 2103.

* Information from Trenkwalder et al. One-year Treatment with Standard and Sustained-Release Levodopa: Appropriate Long Term Treatment of Restless Legs Syndrome. Movement Disorders 2003; 18(10): 1188.

** Evening dose to be taken at least 2 hours before bedtime

*** Health Canada, Advisories for Health Professionals. Important Safety Information Regarding the Antiparkinson Drug Permax[®]: Sudden Onset of Sleep. February 2004.

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