Restless legs syndrome: Treatment overview

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ABSTRACT

Restless Legs Syndrome (RLS) is a neurological movement disorder which affects a significant proportion of the general population. This article reviews the neurochemical basis and diagnosis of RLS, and reviews pharmacologic treatment options for the disorder.

KEYWORDS

restless legs syndrome (RLS), treatment, neurology

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INTRODUCTION

Restless Legs Syndrome (RLS) is a neurological movement disorder characterized by a distressing urge to move the legs and in some cases, other parts of the body, such as arms. RLS symptoms most often begin during rest or inactivity and can be relieved by movement. RLS follows a circadian pattern with symptoms most intense in the evening and nighttime hours. Restless legs syndrome is a common cause of insomnia. RLS symptoms can range from relatively mild to severe, and from only rarely experienced to an intense daily torture. When severe, RLS may have profoundly disruptive effects on sleep quality and daily life. Recognition of the condition and appropriate treatment therefore has a large impact on morbidity and quality of life. This article aims to give clinicians an overview of pharmacological treatment of RLS. The neurochemical basis of such treatment and recent guidelines for treatment of RLS are reviewed.

BACKGROUND

Restless leg syndrome [RLS] prevalence range from 1.9% to 15%, depending on case ascertainment, and it affects all age groups, although prevalence increases with age. Prevalence is about twice as high in women as in men.[1] RLS is less common among African American then Caucasians.[1] RLS is more common in older adults, although it can occur as early as during the pre-school years.[2] RLS usually progresses slowly to daily symptoms and severe disruption of sleep after age 50 years. Familial RLS tend to have an earlier age of onset (<45y) and slower disease progression.

NEUROCHEMICAL BASIS OF RESTLESS LEG SYNDROME

Currently, the most widely accepted mechanism involves a genetic component, along with abnormalities in the central, subcortical dopamine pathways and impaired iron homeostasis.[3] RLS is considered either primary, often occurring within families, or secondary, developing in association with other conditions (such as iron deficiency anemia, pregnancy or end-stage renal disease. There is a high frequency of familial cases of RLS consistent with a genetic origin in primary RLS. RLS seems to have a complex genetic basis, but environmental factor (such as smoking, alcohol abuse, iron or folic acid deficiency, etc.) are also important in provoking RLS.

Dopaminergic drugs alleviate the symptoms and dopamine antagonists can trigger or exacerbate them. Studies in animal models and patients have implied that the syndrome is characterized by up regulation of dopaminergic transmission, with postsynaptic desensitization.[4] Dopaminergic activity shows natural circadian fluctuations, and this is thought to be the underlying mechanism for the characteristic circadian pattern of the symptoms.

RLS has been linked to iron deficiency in the body, particularly within dopamine containing neurons.[5] Magnetic resonance imaging, studies of cerebrospinal fluid, and autopsy specimens of substantia nigra have shown that brain iron stores are reduced in patients with restless legs syndrome.[6] Iron is an essential cofactor for tyrosine hydroxylase and seems to have a crucial role in dopamine metabolism. Despite the involvement of the dopamine pathway, RLS and Parkinson's disease (PD) seem to have very different underlying biology, and there is no solid evidence that RLS can lead to PD.

Pregnancy is also considered a contributing factor in RLS, with the disorder thought to affect 25-40% of pregnant women. The syndrome usually subsides within weeks after delivery.[11] RLS also occurs in as many as 25-50% of patients who have end-stage renal disease; these patients find their

symptoms to be particularly bothersome during hemodialysis. RLS may improve after transplantation.7

THE DIAGONOSIS OF RLS

The diagnosis of RLS is based primarily upon interview with the patient. A clinical diagnosis of RLS can only made if patients complain of four key symptoms which constitute the essential criteria.

Currently, there are no lab tests that can definitively confirm or deny the presence of RLS. The use of sleep studies or a suggested immobilization test may occasionally be helpful in difficult cases by demonstrating the presence of periodic limb movements.[8] It has been proposed that response to a dopaminergic medication can be formalized as a confirmatory test.[9]

Essential criteria:

- Urge to move the legs with or without dysesthesias. Sometimes the arms or other body parts are involved in addition to the legs.
- Onset or exacerbation with rest.
  The motor and sensory symptoms most often begin or worsen during periods of rest or inactivity, particularly when lying down or sitting. Rest includes both lack of motor activity and decreased mental activation.
- Relief with movement.
  RLS symptoms are partially or totally relieved by movements such as walking or stretching; symptoms are relieved for at least as long as the activity continues. Mental activation also reduces symptoms.
- Circadian pattern. RLS symptoms usually occur or worsen in the evening or at bedtime.
  Symptoms are usually quiescent in the morning.

TREATMENT GUIDELINES

Treatment comprises the recognition and reversal of causes and symptom control. For patients with mild or infrequent symptoms, non-drug based options may be sufficient to provide symptom relief.

Measure serum ferritin in all patients with symptoms of restless legs syndrome. Anemia is not sufficiently sensitive a marker for iron deficiency. Patients with a serum ferritin of less than 112 pmol/L (50 µg/L) should be started on iron supplements. Take a drug history to screen for exacerbating agents, such as antipsychotics, antidepressants (especially selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors), antihistamines, dopamine receptor blocking agents such as metoclopramide and prochlorperazine, and diphenhydramine.[3]

Treatment for restless legs syndrome may not be necessary for patients with mild symptoms or symptoms without significant impairment. Spontaneous remission is possible in some cases. In patients with mild RLS, non-pharmacological measures should be tried before prescribing medications.

Nonpharmacological Management

Sleep hygiene (e.g., reserving bed for sleep and intimacy, avoiding stimulating substances near bed time, ensuring bedtime is quiet and dark) measures should be recommended to all patients.

Some patients benefit from different physical modalities before bedtime, such as a hot or cold bath, a whirlpool bath, limb massage, or vibratory or electrical stimulation of the feet and toes, or any age appropriate engrossing mental activity (e.g., video games, crossword puzzles).

Sedentary activity, such as going to the theatre or taking a long airplane flight may be better suited to the morning, whereas activities like walking, housework or exercise, may help relieve RLS symptoms in the evening.

It is useful to avoid substances (e.g., smoking, caffeine) that may exacerbate symptoms, including both over the counter and prescription medications.

Pharmacologic Management:

Medication management should be considered in patients with symptoms that seriously impair quality of life, sleep, or daytime functioning despite reversal of iron deficiency, removal of possible exacerbators, and exclusion of secondary restless legs syndrome.[10] See Table 1 for an overview of treatment options.

Pharmacologic therapy of idiopathic RLS is designed to relieve the patient's sensory and motor symptoms and sleep disturbances. Such therapy is symptomatic; it does not cure RLS but merely suppresses the disorder's unwanted manifestations. Curative therapy may be available to treat the underlying disorder in secondary RLS, such as iron deficiency or renal failure.

Choice of agent should be guided by the nature of the symptoms, but the dopamine agonists—ropinirole, pramipexole, and rotigotine, and a slow release preparation of gabapentin enacarbil, a prodrug of gabapentin.—are the only FDA approved agents in the United States.

Medications used in the treatment of RLS.

- Dopaminergic agents
- Anticonvulsants

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- Benzodiazepines
- Opioids
- Presynaptic alpha 2 adrenergic agonists
- Iron salts

The first step in selecting RLS treatment is to characterize symptoms according to intensity, persistence (intermittent/persisting for most days), circadian pattern of onset, and etiology (primary or secondary).

Patients with RLS are divided into different treatment categories:

1. **Intermittent RLS:**
   RLS that is troublesome enough when present to justify treatment, but does not occur frequently enough to necessitate daily therapy.
2. **Daily RLS:**
   RLS that is frequent and troublesome enough to require daily therapy.[2]
3. **Refractory RLS:**
   Refractory RLS is daily RLS that has been unsuccessfully treated with two classes of drugs (one dopaminergic and one non-dopaminergic) at the correct dose and for an adequate length of time.[11]

Table 1: Overview of Treatments

Drug	Starting dose and maximum recommended dosage	Time to full effective therapeutic dose	Side-effects
Levodopa	50 mg 200 mg	At first dose	Augmentation Rebound
Ropinirole*	0.25 mg 4 mg	4-10 days	Nausea, low blood pressure, dizziness, headache, nasal congestion
Pramipexole*	0.125 mg 0.54 mg	At first dose	Nausea, low blood pressure, dizziness, headache, nasal congestion
Rotigotine transdermal patch*	1 mg 3 mg	1 week	Skin irritation, nausea, low blood pressure, dizziness, headache, nasal congestion
Pregabalin	25mg 300 mg	3-6 days	Sleepiness, dizziness, headache, fluid retention
Clonazepam	0.50 mg 2.0 mg	First dose: effect mainly on sleep	Sleepiness, dizziness, morning drug hangover
Gabapentin	300 mg 2700 mg	3-6 days	Sleepiness, dizziness, fluid retention

Source: Garcia-Borreguero et al. BMC Neurology 2011,11:28
*FDA approved medications for moderate to severe RLS

Pharmacologic therapy varies with the patient's form of RLS.

Patients with mild and intermittent symptoms may not require pharmacologic treatment or may only need an occasional nocturnal dose of a sedative-hypnotic agent to help them sleep.[12]

Although no treatments have been approved for intermittent RLS, the intermittent use of levodopa or pramipexole can be considered to be most appropriate if an off-label treatment is warranted. Other off-label treatment options include low-potency opioids, or if symptoms mainly disturb sleep, a hypnotic such as clonazepam, although its use is off-label. Levodopa and opioids may be useful when symptoms are unpredictable (e.g., an airplane trip, a long car ride, a theatrical event) because they do not require dose titration to be effective.

Continuous pharmacological treatment should be considered if patients complain of having RLS symptoms at least 3 nights each week. Daily treatment is necessary for patients with moderate to severe RLS that has a negative impact on their lives either every day or on most days of the week. In such cases the dopamine agonists (pramipexole, ropinirole,and rotigotine) are the first-line treatment choice. Dopamine agonists need to be started with a low dose and then titrated up to an effective dose to minimize side effects. When the main problem is sleep disruption (either difficulty initiating or maintaining sleep), a sedative hypnotic may be useful. The alternate agents should be considered only if there is some contra-indication or a specific clinical situation (e.g., painful RLS with neuropathy which may be addressed with an anti-convulsant such as gabapentin).Ergot derived dopamine agonists are not recommended because of the risks of

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cardiac valvular fibrosis and other fibrotic side effects.[13] Pergolide, an ergot agonist that was quite successful in treating RLS, has been withdrawn from the U.S. and Canadian markets because of the risk of serious damage to patients' heart valves.

However, in addition to nighttime symptoms, the patient might describe symptoms during the daytime. Such daytime symptoms are not uncommon and can particularly break through during immobilization or any other changes in lifestyle. Such cases should be treated preferentially with transdermal rotigotine due to its longer duration of action.[14] Second line treatment consists of opioid-like drugs (e.g., tramadol, tilidine, codeine) but their use over the long term could be problematic due to addiction issues.[15] Alpha-2-delta ligands (pregabalin, gabapentin and gabapentin enacarbil) might constitute a promising alternative if their efficacy is confirmed in long-term trials.[16] The U.S. Food and Drug Administration (FDA) has approved Horizant(TM) (gabapentin enacarbil) Extended-Release Tablets for the treatment of moderate-to-severe primary Restless Legs Syndrome in adults

Refractory RLS should be referred to the appropriate RLS specialist.

Children & RLS

A few case reports and one case series have assessed treatment specific to children. These case reports have indicated individual response to strict limit setting in enforcing the child's sleep schedule, restricting caffeine consumption, and using medications such as clonazepam, carbidopa/levodopa, and clonidine. In general, it is best to start with behavioral, sleep-schedule, and sleep hygiene interventions before considering pharmacological treatments in children with RLS.

SUMMARY

RLS affects a significant proportion of the general population. The diagnosis is generally simple if one is familiar with the syndrome. Recent advances in the treatment of RLS have significantly improved the available treatment options. As a result, patients can in all likelihood find effective relief from this debilitating disease. Further efforts in educating the medical community of this disorder will help to make therapeutic advantages available to the vast majority of patients.

Substance use disorder programs, such as buprenorphine programs, continue to grow and can benefit from clinical pharmacy involvement. The needs of each individual program should be assessed to determine the most appropriate roles for the pharmacist. Even with limited prescriptive authority, clinical psychiatric pharmacists can improve patient care and clinical outcomes in buprenorphine programs.

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