



Choose treatment for restless legs syndrome based on patient and drug characteristics

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Abstract

Restless legs syndrome (RLS; also known as Willis-Ekbom disease) is a common neurological, sensorimotor disorder. RLS is initially managed with lifestyle modifications, elimination of possible iatrogenic contributors and maintenance of normal-high peripheral iron stores. Moderate-to-severe RLS may be treated with pharmacological therapy, which generally involves the use of α -2- δ ligands (e.g. gabapentin enacarbil, pregabalin, gabapentin) and dopamine agonists (e.g. pramipexole, rotigotine, ropinirole), as well as opioids for treatment-resistant RLS. The chosen drug class/specific drug depends on patient factors (e.g. the most prominent symptoms, comorbidities, age-related issues, preferences) and drug factors (e.g. tolerability profile, augmentation risk).

Common and progressive condition

Restless legs syndrome (RLS; also known as Willis-Ekbom disease) is a common neurological, sensorimotor disorder characterized by an irresistible urge to move the legs, usually in response to unpleasant leg sensations (e.g. creeping, crawling, itching, pulling, throbbing) [1–3]. Although the arms and/or other parts of the body may be involved, the legs are usually firstly and most severely affected [4]. RLS symptoms begin or worsen during periods of inactivity or rest, are worse during the evening or night, and are partially or fully relieved by movement [2]. However, symptoms may progress to a point where they are no longer confined to the evening or night and no longer relieved by movement [2].

An estimated 7–10% of the US population have RLS [3]. Although RLS can start at any age, middle-aged or older individuals tend to be more severely affected than younger individuals, and symptoms generally become more frequent and longer lasting with age [3]. It is also more common in Parkinson's disease (PD) patients than in the general population [5].

RLS can reduce sleep quality and quantity, impair daytime functioning, increase the risk of falls (especially in older adults because of night-time ambulation), and decrease

health-related quality of life (HR-QoL) [1, 3]. By the time most patients seek treatment (usually in their fifth or sixth decade of life), daily preventative pharmacotherapy is usually needed [1]. This article summarizes the pharmacological management of RLS [1, 2, 5].

Diagnose based on patient history

RLS is diagnosed based on history alone, without the need for ancillary testing [1]. For a diagnosis of RLS, a patient must meet the five criteria shown in Fig. 1, with these features not able to be solely accounted for as symptoms of another behavioural or medical condition (e.g. arthritis, habitual foot tapping, leg cramps, leg oedema, myalgia, positional discomfort, venous stasis) [2].

Supportive factors should also be considered (Fig. 1) [1, 3, 6]. For example, as many as 20% of RLS patients have a first-degree relative with the disorder [1], and > 80% of experience periodic limb movements during sleep (PLMS), with involuntary jerking or twitching movements in the leg (and sometimes arm) that typically occur every 15–40 s, sometimes throughout the night [3]. As the pathophysiology of RLS involves dopamine dysfunction, patients with RLS should have a positive response to these drugs [3].

RLS has a high prevalence in the geriatric population, and those with cognitive impairment who are unable to verbalize their sensory symptoms (e.g. those with dementia) should be given special consideration (Fig. 1) [1]. Clinicians can

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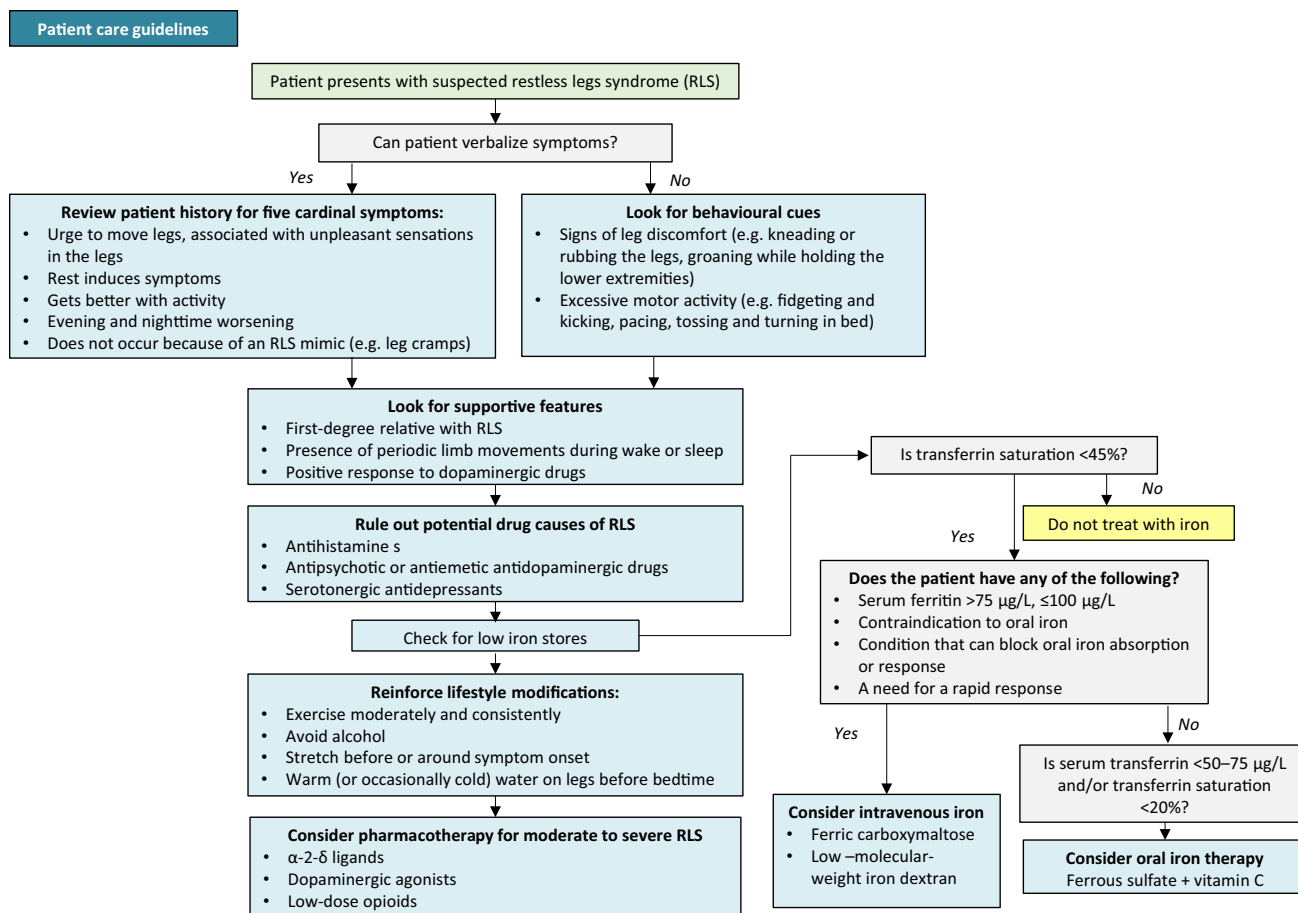


Fig. 1 Suggested management of restless legs syndrome [1–3, 6]

look for specific behavioural cues, such as excessive motor activity (e.g. fidgeting and kicking, pacing, tossing and turning in bed), rubbing or kneading the legs, or groaning while holding the lower extremities. Although these ‘signs’ are not definitive or sufficient, they represent a first step in diagnosing RLS in this patient population [1].

The clinical course of RLS is categorized based on the average frequency of symptoms per week in the past year when RLS was left untreated as follows: intermittent when symptoms occur less than twice weekly on average; and chronic-persistent when symptoms occur at least twice weekly on average [2]. Based on the widely used International RLS Study Group 40-point scale, RLS is also categorized as mild, moderate or severe [1].

Start with non-pharmacological approaches

Treatment of RLS begins with non-pharmacological approaches (Fig. 1), which provide satisfactory outcomes in patients with mild RLS [1].

Lifestyle modifications include moderate, consistent exercise (can worsen RLS if excessive), avoidance of alcohol (can worsen RLS if consumed), and alleviating measures, such as stretching before or around symptom onset, and applying warm (or occasionally cold) water on legs before bedtime [1].

The use of drugs that can worsen RLS needs to be minimized or avoided [1]. Such drugs include:

- All antidopaminergic agents (antiemetics, antipsychotics).
- Histamine-1 (H_1) blockers (anti-allergy drugs, anti-vertigo drugs, over-the-counter sleeping aids)
- Serotonergic agents (antidepressants, except bupropion).

Of note, H_1 blockers and sedative antidepressants are frequently used to treat insomnia, but can worsen RLS symptoms [1].

Treat iron deficiency if necessary

Substantial evidence supports iron deficiency in the brain as part of RLS pathophysiology, with iron therapy aiming to correct this deficiency [6]. Of note, severe iron deficiency to the point of anaemia is associated with a six-fold increase in RLS prevalence [6]. Only peripheral (i.e. serum) iron levels can be measured routinely, and results are rather insensitive and subject to circadian variation [1]. Therefore, transferrin saturation and serum ferritin (ideally collected in the morning after an overnight fast) should be used to assess iron stores [1, 6].

Performing a complete iron panel (serum ferritin, transferrin saturation, iron, total iron binding capacity) is recommended when a patient is initially evaluated for RLS, as well as every time the patient has an unexplained worsening of RLS symptoms [6]. If peripheral iron levels are low (serum ferritin < 100 µg/L and/or transferrin saturation < 20%), the patient may benefit from oral or intravenous (IV) iron therapy (Fig. 1) [1]. Not supplementing iron when iron levels are low but somewhat higher (i.e. transferrin saturation > 45% and/or serum ferritin > 300 µg/L) minimizes the risk of peripheral iron overload [6].

For oral iron treatment, ferrous sulfate 325 mg (65 mg elemental iron) + vitamin C 100 mg twice daily (or the total dose once daily) is recommended for 12 weeks if tolerated, with a repeat iron panel done after 12 weeks [6]. For IV iron treatment, ferric carboxymaltose 1000 mg over 15 min, or 500 mg over 7.5 min twice (5–7 days apart) is recommended. Optionally, low-molecular-weight iron dextran 975 mg can be given over 1–4 h after a 25 mg test

dose. The iron panel should be repeated at 8 and 16 weeks following the infusion [6].

Iron deficiency should probably not be compensated for in PD patients with RLS [5]. PD is associated with increased iron in dopaminergic areas, so iron supplementation in PD could possibly contribute to neuronal death.

Introduce drugs for moderate-to-severe RLS

Pharmacological treatment is usually started when RLS symptom frequency and severity interfere with HR-QoL [2, 7]. RLS is generally treated with α -2- δ ligands (e.g. gabapentin, pregabalin, gabapentin enacarbil), dopamine agonists (e.g. pramipexole, ropinirole, rotigotine) and opioids (e.g. oxycodone, tramadol, methadone) (Table 1) [1].

Initial treatment should be individualized and targeted based on patient (e.g. most prominent symptoms, comorbidities, age-related issues, preferences) and drug (e.g. tolerability profile, augmentation risk) factors (Table 2) [7, 8]. More specifically, PLMS with can be treated with ropinirole (strong evidence), or pramipexole, rotigotine, cabergoline or pregabalin (moderate evidence) [8]. Other objective sleep measures (e.g. sleep efficiency, sleep latency) can be treated with ropinirole, gabapentin enacarbil or pregabalin (moderate evidence), and subjective sleep measures with gabapentin enacarbil or cabergoline (strong evidence), or ropinirole, pramipexole or pregabalin (moderate evidence).

In patients with concomitant psychiatric symptoms, ropinirole can be considered for anxiety and depression. In individuals with moderate-to-severe RLS-related mood disturbance, pramipexole can be used for depression and anxiety,

Table 1 Dosages and adverse events of drugs commonly used to treat chronic restless legs syndrome []

Drug	Dosage (mg/day)		Common AEs in drug class	Additional AEs/comments
	Initial	Usual		
α -2- δ ligands [7, 9, 10]				
Gabapentin	300 (100) ^a	900–2400	Sedation, dizziness, weight gain, led oedema	Excreted renally (use with caution or avoid use in patients with renal impairment)
Pregabalin	75 (50) ^a	150–450		
Gabapentin enacarbil ER	600 (300) ^a	600–1200		
Dopamine agonists [7, 8, 11–13]				
Pramipexole	0.125	0.25–0.5	Sedation, insomnia, hypotension, impulse control disorder, augmentation	
Ropinirole, oral	0.25	0.5–4.0		
Rotigotine, patch	1	1.0–3.0		
Opioids				
Oxycodone	5	10–30	Sedation, constipation, nausea, sleep apnoea	Occasional insomnia
Tramadol	25–50	50–200		Augmentation, seizures
Methadone	2.5	5–20		Prolonged QT interval (recommend ECG)

AE adverse event, ECG electrocardiograph, ER extended release

^aIn patients aged < 65 years (\geq 65 years)

Table 2 Initial treatment for restless leg syndrome (RLS) based on patient-related factors [7]

Patient factors suggesting the use of an α -2- δ ligand	Patient factors suggesting the use of a dopamine agonist
Sleep disturbance disproportional to other RLS symptoms (e.g. severe insomnia)	Increased risk of falls
Comorbid insomnia	Very severe RLS symptoms
Painful restless legs	Excessive weight
Comorbid pain syndrome	Metabolic syndrome
History of impulse control disorder	Comorbid depression
Comorbid generalized anxiety disorder	Symptomatic periodic limb movements during sleep

Consider a long-acting agent for daytime symptoms, iron if risk of pregnancy (avoid α -2- δ ligands and dopamine agonists). Avoid use or reduce dosage of α -2- δ ligand in impaired renal function, and choose a drug that is not hepatically metabolized when there is a high potential for drug interactions

and gabapentin enacarbil for overall mood. To improve HR-QoL, gabapentin enacarbil, ropinirole, pramipexole and cabergoline, as well as pregabalin, rotigotine and IV iron (ferric carboxymaltose), can be used.

Start with an α -2- δ ligand

An α -2- δ ligand (Table 1) can be considered for initial RLS treatment to prevent augmentation, an iatrogenic worsening of RLS symptoms that is commonly associated with the long-term use of dopamine agonist [7]. The α -2- δ ligands have no significant risk of augmentation [7]. There is strong evidence to support the use of gabapentin enacarbil, moderate evidence to support pregabalin, and insufficient evidence to support or refute gabapentin in the treatment of RLS [8].

Good initial response to dopamine agonists

Most patients have a good initial response to dopamine agonists, but treatment efficacy diminishes and/or augmentation develops over time even at low dosages [7]. In a US community-based study of patients treated with dopamine agonists, only 25% of patients had no indication of augmentation [14]. The risk of developing augmentation with dopamine agonists is strongly correlated with treatment dose and duration, and likely related to the specific action of the dopaminergic system. Therefore, avoiding the use of dopamine agonists is the most effective strategy to prevent augmentation [14].

If dopamine agonists are selected for initial RLS treatment, the lowest daily dosage should be used, with the dosage not exceeding that recommended for RLS (Table 1) [7]. If augmentation is mild, the dose of the dopamine agonist can be divided or taken before the onset of RLS symptom. If breakthrough night-time symptoms occurs, the dose can be increased with caution. However, when augmentation is severe, treatment can be switched to the rotigotine patch or an α -2- δ ligand. Of note, long-term use of rotigotine at a high dose can also cause augmentation. In very severe cases, consider switching to an opioid [7].

Strong evidence supports the use of pramipexole, rotigotine and cabergoline, but cabergoline is rarely used because of the risk of fibrotic complications and cardiac valvulopathy at high dosages [8]. Moderate evidence supports the use of ropinirole, and weak evidence supports levodopa [8]. Levodopa was the first dopaminergic drug that was used to treat RLS, but it has a shorter half-life and a shorter time to augmentation than ropinirole, pramipexole and rotigotine [7]. Although it is not frequently used to treat RLS, levodopa is recommended PD patients with RLS who have contraindications to dopamine agonists (e.g. age > 70 years, cognitive dysfunction/hallucinations, impulse control disorder, severe sleepiness) [5].

Consider opioid therapy when other treatments fail

Opioid therapy can be considered for severe, treatment-resistant RLS, and in patients who develop augmentation with other treatments [2]. There is insufficient evidence to support or refute the use of oxycodone in the treatment of RLS [8]. However, oxycodone is likely efficacious on its own in those with daily RLS symptoms [2]. Oxycodone and methadone are commonly used opioids in the treatment of RLS [1]. Tramadol is used as well, but is associated with a risk of augmentation [1]. Prolonged-release oxycodone/naloxone can be considered where available [2, 8]. Prior to initiating opioid therapy, patients should be screened for a history of alcohol or drug abuse because they pose a higher risk of opioid abuse or misuse [1].

Advance nonpharmacological options may help

Patients and clinicians desiring nonpharmacological approaches to treat RLS should consider the use of pneumatic compression before usual symptom onset [8], and may consider near-infrared spectroscopy (NIRS) or repetitive transcranial magnetic stimulation (rTMS). Pneumatic leg compression is likely effective, and NIRS and rTMS are possibly effective, whereas vibrating pads are possibly ineffective and transcranial direct current stimulation is probably

ineffective in treating RLS symptoms. Vibrating pads may work for subjective sleep concerns, but not for RLS symptoms. Evidence is insufficient to either support or refute the use of acupuncture to treat RLS [8].

Take-home messages

- Initially manage RLS by modifying lifestyle, eliminating possible contributors and maintaining normal-to-high iron stores.
- Consider pharmacological therapy for moderate-to-severe RLS if symptom frequency and severity interfere with a patient's HR-QoL.
- Generally treat with α -2- δ ligands, dopamine agonists or opioids, with the drug class specific drug chosen based on patient and drug factors.

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