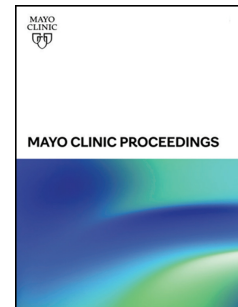


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An Updated Algorithm for the Management of Restless Legs Syndrome

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An Updated Algorithm for the Management of Restless Legs Syndrome

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Abbreviations: RLS, restless legs syndrome; SMAB, Scientific and Medical Advisory Board; PLMS, periodic limb movements of sleep; TSAT, transferrin saturation; ICD, impulse control disorder

Abstract

Restless legs syndrome (RLS) is a common disorder, largely managed by primary care providers. Much has changed in its management since the last version of this algorithm was published in 2021. The Scientific and Medical Advisory Board of the RLS Foundation has written this new paper as a practical algorithmic guide to current treatment based on a review of the literature published since 2020 and consensus expert opinion. This updated algorithm includes management of intermittent RLS, including behavioral approaches; new indications for oral and intravenous iron therapy; the role of medications in exacerbating RLS; gabapentinoids as first line pharmacologic therapy for chronic persistent RLS; the risks of dopamine agonists and the precautions needed if they are used; the management of dopamine agonist augmentation; the important role of low-dose opioids in management and how to safely use them; novel therapies including peroneal nerve stimulation and buprenorphine; and RLS in children, during pregnancy and lactation, in end-stage renal failure and in the perioperative period. Alternative, investigative, and potential future approaches are addressed.

Introduction

Restless legs syndrome (RLS) is a common neurologic disorder with the population prevalence of symptoms occurring at least twice a week and resulting in moderate or severe distress estimated at 1.5-2.7%.^{1,2} It is characterized by an urge to move the legs, associated with discomfort and sometimes pain, occurring at rest especially towards evening and during the night, and relieved by movement such as walking.³ The effects of resultant sleep deprivation can be profound, including daytime sleepiness, impaired quality of life and depression,⁴ sometimes severe enough to induce suicidal ideation.⁵ Much of the pathophysiology is still uncertain, but the condition is inherited in approximately 60% of patients with a relationship to multiple genes demonstrated by genome-wide association studies.⁶ Low iron stores in the basal ganglia appear to play a role and striatal dopamine receptors appear to be down regulated. Decreased adenosine and increased glutamate may be contributing factors.^{6,7} RLS may be precipitated by systemic iron deficiency, the use of certain medications, pregnancy, chronic renal failure, and peripheral neuropathy among other disorders, but secondary causes are not identified in most patients.

The management of RLS has evolved over the years but remains problematic in many patients due to only moderate efficacy of most therapeutic agents, as well as medication side effects and complications. Multiple evidence-based practice parameters have been published, including a 2025 Clinical Practice Guideline from the American Academy of Sleep Medicine.⁸ The Scientific and Medical Advisory Board (SMAB) of the non-profit RLS Foundation has published three previous iterations of a practical algorithm for RLS management in 2004,⁹ 2013¹⁰ and 2021.¹¹ The reasons behind the need for such algorithms have been explained in detail in the previous papers. In summary, the rigorous methodology

of practice parameters emphasizes short term, controlled trials but de-emphasizes long term follow-up studies and expert experience. While they provide evidence-based conclusions of the degree of efficacy of individual therapeutic modalities, they rarely provide a pathway for the inexperienced clinician to decide in what order to use different agents, how to practically implement therapy, and how to monitor progress. Because of the high prevalence of RLS, most patients will not have the opportunity to see a specialist in the disorder and thus primary care physicians, neurologists and general sleep specialists need to be familiar with the intricacies of management.

Although only five years have passed since publication of the last RLS Foundation algorithm update, the Foundation Board of Directors felt that sufficient changes had occurred in approaches to RLS management for a fresh version to be developed and published. These changes include new insights into the role of intravenous iron therapy, advances in understanding the serious consequences of unidentified augmentation from dopamine agonists, consensus approaches to the management of established augmentation, new data on the long term use of opioids for RLS, experience in the use of buprenorphine as an opioid agent for RLS management, the approval of peroneal nerve stimulation as an adjunctive therapeutic modality, and changes in the approach to RLS in special circumstances such as childhood and pregnancy. This algorithm is intended to complement and extend the 2025 AASM clinical practice guideline and not to supersede or replace it. Reasons for the occasional areas where the recommendations of this algorithm differ from those in the practice parameter are discussed in the relevant sections. Because periodic limb movement disorder is a condition separate from RLS, it falls outside the scope of this algorithm. It is acknowledged that the recommendations provide a predominantly USA perspective and

that differences in the availability of medications, physician preferences, and regulation of medical practice may require adaptation in other countries, similar to those noted in a recent international evaluation of the 2025 AASM guidelines.¹²

Methods

The SMAB of the RLS Foundation is a group of scientists and physicians with extensive expertise in RLS research and clinical management appointed by the Foundation Board of Directors who serve without remuneration. A task force of nine members of the SMAB was selected to develop the current algorithm and met remotely eleven times between February and November 2025. Many members of the task force had participated in the development of the prior SMAB algorithms and four had served on the group who developed the 2025 American Academy of Sleep Medicine RLS Clinical Practice Guidelines.⁸ The algorithm was then approved by the SMAB as a whole. The process was supported financially and logistically by the Board of Directors, executive director and staff of the Foundation, but they provided no input or oversight into the conclusions.

A search of the literature was conducted through PubMed for all articles on RLS management between January 2020 (the year before the publication of the last algorithm) and January 2025. From 243 articles identified, a subset of 75 papers was selected based on the criteria of controlled trials, case series with at least ten subjects, meta-analyses, systematic review papers and practice parameters developed by medical organizations. An additional 17 relevant papers were identified by task force members. All these papers were read by members of the task force. Although a rigorous rating scale was not used, most weight was given to randomized controlled trials followed by case series, especially those with follow-up information of more than one year. Review papers and practice parameters

provided background information. The algorithm was developed by informal consensus decision making, taking into account the medical literature and the extensive clinical experience of task force participants with disagreements resolved by discussion resulting in recommendations deemed acceptable to all members. Most recommendations were based on a combination of data from published studies and consensus-based expert opinion. Areas with a paucity of published data are mentioned in the text. Any algorithm is current only on the date of publication and we confidently expect new advances to modify treatment approaches in the future. Although every effort has been made to establish the accuracy of information provided, it is incumbent on individual practitioners to check specific details of medications they prescribe, including indications, dosages and potential side effects. Of note, the US Food and Drug Administration has approved pramipexole, ropinirole, rotigotine, gabapentin enacarbil and peroneal nerve stimulation for RLS management. All other agents discussed are considered off-label for management of the disorder in the United States.

Box 1 provides a roadmap to the topics covered in this paper and **Figure 1** is a flow diagram outlining the algorithm in broad terms with references to each relevant section of the paper.

Box 1

Roadmap to the Algorithm

Diagnosis and Assessment of Response to Treatment

General Therapeutic Considerations

- Iron Therapy
- Exacerbating Conditions and Medications

Intermittent RLS

Chronic Persistent RLS

Management of Dopaminergic Augmentation

Pediatrics and Special Circumstances

- Childhood
- Pregnancy
- Lactation
- Perioperative Period
- End Stage Renal Disease

Alternative, Investigative and Potential Future Therapies

Diagnosis and Assessment of Response to Therapy

RLS is diagnosed by history. The essential symptom is the intense and uncontrollable urge to move the legs, usually but not always associated with limb discomfort. It is important to establish that the urge to move comes on at rest and is temporally relieved by movement, most commonly walking. Symptoms are worst during the evening or at night, often resulting in disabling insomnia.³ Other areas of the body, including the arms and trunk, may occasionally also experience restlessness. Associated involuntary jerking of the legs known as periodic limb movements of sleep (PLMS) are present in about 80% of patients with RLS.¹³ and similar involuntary movements may accompany the sensation of restlessness while awake. Most of the distress and disability from RLS comes from the sensory and motor symptoms while awake and the PLMS are generally of lesser importance in the disturbance

of the patient's rest. In addition, PLMS are nonspecific in that they may accompany multiple other sleep disorders and occur very frequently in asymptomatic older persons. The separate entity of periodic limb movement *disorder* can only be diagnosed following polysomnography after excluding RLS and other secondary causes of PLMS. In contrast, it is *not* necessary to confirm the presence of PLMS on a polysomnogram in adults in order to make a diagnosis of RLS. RLS needs to be differentiated from other causes of leg discomfort at night,¹⁴ including nocturnal leg cramps, positional discomfort relieved by changing position in bed, tingling or burning sensations due to peripheral neuropathy, arthralgias and akathisia. In cases of diagnostic uncertainty, a neurologic examination of the legs may provide helpful information, especially if a peripheral neuropathy is suspected.

RLS is challenging to diagnose in childhood, and careful attention should be paid to the child's own words in describing symptoms. A strong family history in first-degree relatives may be helpful in questionable cases. In children, the presence of PLMS on polysomnography (≥ 5 /hour) may provide supportive diagnostic information. A relationship between RLS, periodic limb movements of sleep, and attention-deficit/hyperactivity disorder has been proposed.

The response to any treatment is best assessed clinically through a narrative history. Patients should be asked to compare the frequency, duration, timing and severity of RLS before and after initiation of therapy. For example, a patient might describe severely distressing RLS occurring every day, starting when sitting down at 7:00 p.m., delaying sleep onset by an hour, waking the patient twice during the night and preventing re-initiation of sleep for an hour at a time. After starting a specific therapy, the symptoms might be reduced to only twice a week, no longer occurring in the evening, delaying sleep onset by

only 10 minutes, and waking the patient during the night at most once with milder symptoms, allowing a return to sleep within 10 minutes. For clinicians who prefer a more quantitative approach, the International RLS Study Group Severity Scale (IRLS) scale is a 10-question, 40-point questionnaire that can be used to compare symptoms before or after treatment (available free for clinicians at [ePROVIDE™ - Online Support for Clinical Outcome Assessments](#)). A value of less than 10 is generally considered to indicate mild RLS, 11-20 moderate, 21-30 severe and 31-40 very severe. An alternative option is the Clinical Global Impressions of Change (CGIC), a 7-point scale ranging from substantial worsening through substantial improvement of symptoms that has been shown to correlate with IRLS scores.¹⁵

General Therapeutic Considerations

Iron Therapy

RLS has been known to be associated with iron deficiency for 75 years, and it is thought that the relationship is explained by decreased iron in the brain, probably in the basal ganglia. The goal of iron therapy in RLS is therefore to increase intracerebral iron. Ultrasound and specialized MRI scans of the substantia nigra^{16,17} have been used experimentally to estimate iron content in RLS patients but these techniques are not generally used clinically. Thus, serum measurements of systemic iron stores are used as surrogate markers for iron in the brain although there is poor correlation between these markers and cerebral iron content. Most patients with RLS will have systemic iron markers within normal limits but may still benefit from iron therapy. Serum ferritin, the most easily assessed sensitive marker of systemic iron status, is also an acute phase reactant and so can increase in acute and chronic inflammatory and neoplastic conditions. In addition, serum ferritin values are dependent on the commercial assay used by each laboratory with some considerable variations.^{18,19} For

the sake of simplicity, the Beckman or equivalent assay values are used in this document, but **Table 1** shows the equivalent values using the Roche assay. Healthcare providers should be aware of these variations and, where possible, ascertain which assay their laboratory utilizes.

All patients with RLS should have fasting serum measurements of ferritin, iron, and total iron-binding capacity with calculated percentage transferrin saturation (TSAT).²⁰ Patients should discontinue any oral iron formulations 48 hours before obtaining serum iron measurements because oral iron supplements affect plasma hepcidin levels and iron absorption for that time.²¹ A complete blood count should be performed if serum ferritin or TSAT is abnormal or if there is a clinical suspicion of any other hematologic condition.

Oral iron therapy

Oral iron is poorly absorbed from the gastrointestinal system. Absorption decreases with increasing levels of serum ferritin with minimal absorption once serum ferritin concentration is $\geq 75 \mu\text{g/l}$ (to convert to pmol/l , multiply by 2.247). Absorption also decreases after each dose of oral iron for about 48 hours as discussed above. Therefore, oral iron should be administered no more frequently than once a day and preferably once every other day.²⁰ There is evidence from non-human primates that iron is preferentially transported into the brain at night²² and thus a nighttime dose of iron is considered potentially more effective than a morning dose. Ideally, iron should be taken at least two hours after eating or ingesting calcium, magnesium, or caffeine. However, gastrointestinal side effects are common, and should they develop, iron can be taken with food. Any formulation of oral iron containing 65 mg elemental iron is acceptable. Absorption may be increased by adding 100 to 200 mg of vitamin C with each dose.

Oral iron therapy should be considered for all RLS patients with serum ferritin $\leq 75 \mu\text{g/l}$ and TSAT $< 45\%$. In patients with acute or chronic inflammatory conditions, when serum ferritin may be spuriously raised, a better measure of systemic iron deficiency may be a TSAT $< 20\%$. Oral iron should not be administered empirically, because it may result in hepatic iron overload in patients with undiagnosed hemochromatosis. Should the baseline TSAT be $\geq 45\%$ on more than one occasion, genetic testing for hemochromatosis is recommended. For patients with serum ferritin concentrations below the lower limit of normal for age and gender, a search for a cause for iron deficiency should be instituted. Frequent etiologies include menorrhagia, upper or lower gastrointestinal pathology, vegan diet, frequent blood donations, and the use of proton pump inhibitors or histamine H2 receptor antagonists which may inhibit iron absorption.²³ Serum ferritin should be rechecked after three months of oral iron therapy. If RLS symptoms continue to be bothersome, intravenous iron therapy should be considered.

Intravenous iron therapy

Indications for intravenous iron therapy are summarized in **Box 2**. Intravenous iron should be considered for any patient with chronic persistent RLS with serum ferritin in the range of 75 to 300 $\mu\text{g/l}$ and percentage saturation less than 45%. Oral iron is not adequately absorbed in this range of ferritin values. For patients with serum ferritin $< 75 \mu\text{g/l}$ and TSAT $< 45\%$, intravenous iron is indicated for moderate or severe chronic persistent RLS if oral iron cannot be adequately absorbed due to gastrointestinal disease or prior bariatric surgery, oral iron has not been tolerated because of side effects, RLS has not improved after three months of oral iron therapy, or the RLS is severe enough that a rapid response is desired.

The serum ferritin range within which intravenous iron is recommended has been changed since the 2021 iteration of this algorithm¹¹ and a 2018 clinical practice guideline²⁴ where intravenous iron was only recommended if initial baseline serum ferritin levels were < 100 µg/l. This new recommendation differs from that of the 2025 AASM clinical practice guideline,⁸ which was based on literature published up to September 2023. The reason for this change is that studies are now available suggesting that RLS in patients with serum ferritin concentration in the range of 100 to 300 µg/l responds equally well to intravenous iron compared to those with concentration less than 100 µg/l, and that the risk of hepatic iron overload appears to be extremely low even within the higher concentration range.^{25,26} Additionally, the 2021 algorithm did recommend administration of repeat doses of intravenous iron in the 100 to 300 µg/l serum ferritin concentration range if an initial dose had been successful, but RLS had recurred. As with any new recommendation based on evolving evidence, reassessments may be needed as more studies become available in the future. Intravenous iron should not be administered without consultation with a hematologist if a complete blood count shows abnormalities other than those that could be ascribed to iron deficiency anemia and especially if there is a suspicion of a hematologic malignancy. It should be emphasized that intravenous iron should not be given if the TSAT is greater than 45% to avoid the possibility of hepatic iron overload.

Box 2 Indications for Intravenous Iron Therapy

Chronic persistent RLS with TSAT < 45%

AND

Serum ferritin concentration 75-300 µg/l

Serum ferritin concentration <75µg/l

AND one or more of

- Inability to absorb oral iron due to GI disease or prior surgery
- Inability to tolerate oral iron due to side effects
- RLS has not improved after three months of oral iron therapy
- Due to severity of RLS, a rapid response is desired

Intravenous preparations in which the iron-carbohydrate moiety dissociates slowly after absorption should be used, as these allow fewer doses to be administered with greater penetration into the brain. There are four major preparations that meet that criterion: ferric carboxymaltose, low-molecular weight iron dextran, ferumoxytol, and ferric derisomaltose. Placebo controlled studies showing efficacy have only been performed for ferric carboxymaltose²⁷ but open label studies of iron dextran^{28,29} and a study comparing ferumoxytol to oral iron³⁰ suggest benefit from these agents. Considerations such as price, availability, ease of administration and side effects may determine the choice of preparation. In particular, ferric carboxymaltose can result in hypophosphatemia in approximately 40 to 70% of adults³¹ and 18-20% of children.^{32,33} This is usually asymptomatic unless patients receive repeated infusions for iron deficiency anemia or have extremely low serum ferritin levels, usually from ongoing chronic GI or uterine blood loss, in which cases asthenia, muscle weakness, and osteomalacia with fractures may occur. The risk of severe allergic reactions, including anaphylaxis, for any intravenous iron preparation is about 1:200,000 but nevertheless intravenous iron should be administered in a location where resuscitation is possible, preferably in an infusion center. Most side effects, when present, are due to minor

infusion reactions, such as facial flushing, manageable by briefly pausing the infusion and then slowing the infusion rate.³⁴ Premedication with antihistamines should not be used, as side effects from these drugs can mimic infusion reactions and exacerbate RLS. **Table 2** shows the doses, methods of administration, advantages, and disadvantages of each preparation.

Intravenous iron is usually highly successful in alleviating RLS symptoms in patients with definite systemic iron deficiency (serum ferritin less than the upper limit of normal for age and gender). In patients with ferritin concentration in the normal serum range, intravenous iron infusions are successful in improving RLS in 37 to 59% of patients.²⁴ The clinical response to treatment is not always immediate and may be delayed for up to 6 to 8 weeks. In patients with severe RLS causing considerable distress and sleeplessness, a joint decision should be made between the patient and the healthcare provider whether to introduce or modify pharmacologic therapy in parallel to the administration of intravenous iron rather than waiting to determine if iron therapy alone alleviates the symptoms. While this may result in immediate relief to patients, it may complicate the judgment of whether or not the intravenous iron infusion has been successful. There is no specific goal for an optimal serum ferritin concentration and it is not generally necessary to retest serum ferritin or iron concentrations after an infusion (as they almost always increase), unless symptoms recur in a patient who had initial improvement and a subsequent infusion is being considered. An exception may be patients with very low serum ferritin concentration or percentage saturation < 20% who have not responded to intravenous iron to determine whether a supplementary dose might be indicated.

If initial infusions of IV iron have been successful in relieving RLS symptoms, repeat infusions can be considered if RLS recurs greater than 3 months after the initial treatment. Repeat iron studies must demonstrate serum ferritin concentration ≤ 300 $\mu\text{g/l}$ and TSAT $< 45\%$. Should serum ferritin concentration have fallen to below 75 $\mu\text{g/l}$, oral iron therapy could be considered as an alternative. For patients who have received ferric carboxymaltose, measuring serum phosphate concentration can be considered before repeat infusions. Should values be low, it would be reasonable to defer further infusions or to use an alternative form of IV iron.

Potential Exacerbating Factors

Alcohol intake may precipitate episodes of RLS in some patients. Heavy exercise or excessive immobility on a particular day may result in a later exacerbation of RLS.

Concomitantly occurring sleep disorders should be considered and treated in all patients with RLS. Untreated obstructive sleep apnea may exacerbate RLS, presumably by causing frequent nocturnal arousals, and continuous positive airway pressure (CPAP) treatment may be helpful.³⁵ Insomnia in patients with RLS may be multifactorial with behavioral factors, anxiety, or depression requiring concurrent treatment.

All antidepressants, except bupropion, may exacerbate RLS.³⁶ If antidepressants are considered medically necessary, these medications may be continued and RLS can be managed with other interventions. Sedating antihistamines (including those found in non-prescription medications) may also worsen RLS and should be avoided when clinically possible. Because of their anti-dopaminergic effects, neuroleptic agents and dopamine blocking antiemetics such as metoclopramide should be avoided if possible.

Intermittent RLS

Intermittent RLS is defined as RLS troublesome enough to require treatment but occurring on average less than two days a week. **(Box 3)**

Nonpharmacologic Approaches

Not all RLS requires management with medication. During an episode of RLS, relief can sometimes be achieved by movement such as walking, leg massages, or warm or alternating temperature showers or baths. In contrast to other forms of insomnia, mental alerting techniques such as concentrating on computer games may be helpful in relieving or blocking symptoms. A trial of reducing or avoiding alcohol can be attempted to see if this reduces the frequency of RLS episodes. Consistent aerobic exercise may reduce RLS, reported to be especially beneficial when undertaken in the morning.³⁷ As discussed earlier, attention should always be paid to iron status and considering the effects of potentially exacerbating conditions and medications.

Pharmacological Approaches

Medications can be used intermittently to prevent RLS that is known to occur in predictable circumstances such as plane flights, long car journeys, or audience situations such as concerts. They can also be used to treat RLS when it occurs unpredictably, either as a single episode or for several nights in a row.

A half or single tablet of carbidopa/levodopa 25/100 mg can be taken 30 minutes before activities known to precipitate RLS or as soon as an episode of RLS unpredictably starts. During an episode continuing for several nights with RLS waking the patient after sleep onset, a single tablet of the controlled release form of carbidopa/ levodopa 25/100 mg can

be used before bed. For maximum effectiveness, levodopa should not be taken together with high-protein food. *However, it must be strongly emphasized that levodopa should never be used more than three times a week because of the very high frequency of augmentation (drug-induced exacerbation of RLS discussed in more detail later under Dopamine Agonists) when it is taken more often.*

Dopamine agonists, such as pramipexole or ropinirole, can also be used intermittently but need to be taken two hours before the onset of symptoms. Therefore, their use is generally restricted to predictable sedentary situations known from experience to precipitate RLS.

Alternatives to dopaminergic medication for intermittent RLS are low potency opioids. Codeine in doses of 30 to 90 mg or tramadol in doses of 50 to 100 mg are often effective. As with levodopa, tramadol should not be used more frequently than three times a week, as regular use may also worsen RLS.

Box 3 Management of Intermittent RLS**Nonpharmacological Approaches**

- Walking, massages, warm or alternating temperature baths or showers, mental alerting techniques for acute episodes
- Trial of avoiding alcohol
- Regular aerobic exercise but avoiding sudden increases in exercise
- Checking and addressing iron status
- Considering potentially exacerbating conditions and medications

Pharmacological Approaches

- Intermittent carbidopa/levodopa*
- Intermittent dopamine agonists*
- Intermittent low potency opioids such as codeine or tramadol*

**Never more frequently than three times a week*

Chronic Persistent RLS**First-line therapies**

Chronic persistent RLS is defined as RLS that is troublesome enough to require daily treatment, usually occurring on average at least twice a week and resulting in moderate or severe distress. First-line treatments for chronic persistent RLS are iron therapy and gabapentinoids.

Iron Therapy

See earlier under the General Considerations section.

Gabapentinoids

Gabapentinoids (alpha-2-delta agonists) are the initial drugs of choice for most patients with chronic persistent RLS after management of iron status. At therapeutic doses, they are effective in approximately 70% of patients.^{38,39}

This drug category includes gabapentin, gabapentin enacarbil, and pregabalin. Gabapentin and pregabalin can be administered once or twice a day in the evening or before bed, depending on the timing of symptoms. It is not necessary to administer these agents three times a day if RLS is not problematic earlier. Because of nonlinear saturable kinetics, gabapentin has inconsistent absorption after oral administration in doses greater than 600 mg with the result that multiple smaller doses may be required to achieve the same serum concentration.⁴⁰ Gabapentin enacarbil is a prodrug of gabapentin converted to gabapentin after absorption, resulting in slow release of gabapentin with more constant serum concentrations, thus requiring only a single dose at 5:00 p.m. Pregabalin has more linear pharmacokinetics than gabapentin with better correlation of dose to serum concentration.⁴⁰

Gabapentinoids are excreted through the kidneys and therefore doses should be modified in patients with renal dysfunction. Doses should also be lower initially in older people. The dose of gabapentin and pregabalin can be increased every few days until a symptomatic response is achieved. Most patients will require doses of gabapentin in the range of 900 to 1,800 mg daily, although doses of 3,600 mg are occasionally required. The usual effective

pregabalin dose is 300 mg daily with a range of 150 to 600 mg. Gabapentin enacarbil is usually effective at 600 mg daily but occasionally doses of 1,200 to 1,800 mg are needed. It should be emphasized that the dose of gabapentin enacarbil may differ from equally effective doses of gabapentin. **Table 3** provides more detailed information regarding initial and maximum recommended dosages.

There are certain situations in which clinicians should be cautious in the prescription of gabapentinoids. In these situations, joint decision making between patients and their healthcare providers is advised, balancing the relative risks and benefits of gabapentinoids versus other classes of medication. The drugs carry a low risk of new onset or worsening mood disturbance.⁴¹ Especially in patients with a history of severe depression with suicidal ideation, careful monitoring of mood is essential. About 20% of patients taking gabapentinoids may experience clinically significant weight gain,⁴² and thus patients should be checked regularly for symptoms of increasing appetite or body mass. A history of opioid use disorder may increase the risk of abuse of gabapentinoids and the drugs should be used only with caution in this population.⁴³ Especially in older people and those with underlying neurologic or orthopedic disorders affecting gait, gabapentinoids can cause unsteadiness with increased risk of falls. The drugs should be used with caution in patients in respiratory failure or in combination with opioids, requiring monitoring of respiratory function, especially during sleep. Other side effects sometimes noted are a sense of mental fogging, dizziness, daytime sleepiness, and occasionally fluid retention with lower extremity edema. In contrast, patients with comorbidities of chronic pain, psychophysiologic insomnia, or anxiety may obtain additional benefit from gabapentinoids.

Two out of three retrospective insurance database studies of chronic pain patients treated with gabapentinoids suggested an association with incident dementia;^{44,45} one did not.⁴⁶ These studies rely on unconfirmed diagnoses, cannot exclude confounding factors such as the effects of chronic pain on sleep and cognition, and do not indicate causation. Additionally, a controlled study of patients with minimal or mild cognitive impairment did not show an increased decline in cognitive status in those subsequently treated with gabapentin.⁴⁷

Other Therapies

Indications for Other Therapies

Indications for other therapies for chronic persistent RLS are listed in **Box 4**. These therapies include low-dose-opioids, dopamine agonists, peroneal nerve stimulation, and dipyridamole. These are each discussed, followed by an approach to the choice of an appropriate agent.

Box 4 Indications for Other Therapies

Chronic Persistent RLS

Unresponsive to iron therapy (IV) or criteria for iron replacement not met

and one of the following:

- Gabapentinoid therapy was ineffective at tolerable doses
- Gabapentinoid therapy resulted in intolerable side effects

- By joint decision making, patient and provider have decided that gabapentinoids should not be used

Low-Dose Opioids

A large placebo-controlled trial of extended-release oxycodone,⁴⁸ case series using methadone^{49,50}, a large prospective registry,⁵¹ and clinical experience all attest to the efficacy of low-dose opioid therapy in the management of RLS. In low-total daily doses and with appropriate precautions, opioids can be used safely in most patients with largely manageable side effects and low risk of the development of tolerance or dependence.^{51,52}

Relative doses of different opioids can best be compared in terms of morphine milligram equivalents (MME). The baseline median total daily MME in the National RLS Opioid Registry was 30 mg (equivalent to 20 mg oxycodone, 30 mg hydrocodone and 6.4 mg methadone), and this remained largely unchanged after 5 years of use. Only 13% of patients increased their dose > 25 MME (6% >50 MME) over five years of follow-up, confirming that the risk of significant dose escalation is low.⁵³ Opioid side effects include constipation (usually controlled by changes in diet or use of stool softeners), nausea (sometimes needing serotonin blocking agents such as ondansetron), insomnia, testosterone deficiency resulting in sweating and sexual dysfunction, adrenal insufficiency, itch, cognitive dysfunction, and gait unsteadiness with a risk of falls, especially at night. While some patients experience drowsiness, especially with longer-acting agents, others describe greater daytime alertness because of the improvement in sleep duration. Some patients may also find opioids alerting and have difficulty falling asleep. Opioids may induce central sleep apnea and, particularly in patients on higher doses, may worsen obstructive sleep apnea. Therefore, alertness to the

possibility of sleep-disordered breathing and careful monitoring of patients with known sleep apnea are necessary when opioids are used. Opioids should be prescribed cautiously when used together with benzodiazepines, gabapentinoids, or other sedating agents. When the daily dose exceeds 50 MME, patients should be offered a prescription for naloxone nasal spray to be used in the event of an intentional or inadvertent overdose.

Prescribers must familiarize themselves with federal and state regulations regarding opioid prescription. Use of an opioid contract is recommended so the patient clearly understands that prescriptions will only be refilled at the appropriate time, that opioids should only be prescribed by a single provider, that patients agree not change their dose without discussion with their provider, and that they will not share the medication with anyone else.⁵² Once they are on a stable dose, patients on opioids should be seen back regularly for reassessment of response and side effects as required by local rules and patient circumstances, but at least yearly. The practice of monthly face-to-face visits for no other purpose than to receive each prescription is discouraged. The Opioid Risk Tool is an instrument which can be used to predict those patients who may need more intensive monitoring.⁵⁴ Depending on specific patient circumstances and regulatory requirements, urine drug screens may be considered. However, the interpretation of urine drug screens is complex, and anomalous results should be discussed with laboratory personnel before concluding that misuse might have occurred. In particular, it should be noted that buprenorphine and methadone may not be detected on routine urine drug screens without a specific order. It is recognized that there may sometimes be barriers to the prescription of opioids, depending on factors such as institutional rules, state regulations, and pharmacy

access. Providers may need to collaborate with sleep medicine specialists or pain clinics that provide longitudinal care in order to ensure that their patients receive appropriate therapy.

The different opioids that may be used with dosages, advantages, and disadvantages are summarized in **Table 4**. The medications have not been compared with each other in controlled trials. The choice of an opioid depends on several factors, including the provider's familiarity with specific drugs, their ease of use, potential side effects, and their cost and availability in different regions and insurance markets. It is also important to consider whether short-acting or long-acting medications would be most appropriate for specific patients, based most importantly on the timing and duration of RLS symptoms. Short-acting agents may have fewer daytime side effects but may necessitate multiple doses if symptoms are present throughout the night or during the day with the attendant risk of interdose emergence of restless legs. If one opioid is ineffective or poorly tolerated, trials of other opioid agents should be undertaken. With the availability of other opioids, tramadol should generally be avoided for the treatment of chronic persistent RLS as, distinct from the other opioids, its chronic use may result in worsening symptoms (similar to dopamine "augmentation") with the need for increasing doses of the drug.⁵⁵

Because most providers are less familiar with the use of buprenorphine compared to other opioids, further details are provided regarding the medication and its administration in RLS, based largely on clinical experience and pharmacologic considerations. Buprenorphine is a partial opioid-receptor agonist with relative antagonist features clinically and dosages cannot be accurately converted to MME. Buprenorphine has a ceiling effect limiting significant respiratory depression and thus reducing the risk of catastrophic overdose or poisoning. It is administered as a buccal film, sublingual film or tablet, or transdermal

patch. For patients who have not previously used opioids, treatment can be started with a nightly 75 µg buccal film (which may be expensive), one-eighth or one-sixteenth of a 2 mg sublingual film (the lowest strength available, so the film needs to be cut with scissors), or a transdermal patch at 5 µg/hour. The dose can be increased every 2 to 5 nights. If a buccal film of ≥ 0.5 mg or a transdermal patch of ≥ 20 µg/hour is required, patients should be converted to the cheaper sublingual film. Patients should refrain from food or drink 15 minutes before application of buccal or sublingual films and should brush their teeth not sooner than an hour after the film has dissolved. Despite buprenorphine having a long half-life, some patients require more than one dose per day. For patients who are converting from a different opioid, the initial opioid should be discontinued for 24 hours before the first dose of buprenorphine is given. For such patients, commencing with a sublingual film of 0.5 mg is appropriate, and this can be increased every 1 to 2 nights. Conversion from methadone is complex and generally requires the expertise of a physician experienced in this area.

Dopamine Agonists

Despite extensive controlled trials demonstrating their short-term efficacy, dopamine agonists are no longer considered first-line agents for the management of RLS and a recent clinical practice guideline paper from the American Academy of Sleep Medicine gave a conditional recommendation *against* their use in most circumstances.⁸ This is predominantly because with chronic use, dopamine agonists very frequently cause a paradoxical worsening of RLS, known as augmentation. This is characterized by symptoms developing earlier in the day after an evening dose of medication, symptoms spreading to other parts of the body, especially the arms, and a shorter duration of action with symptoms breaking through

during the night. Often the first symptom is a need to increase the dose which results in worsening augmentation. Augmentation and not disease progression should be considered the cause in every patient in whom RLS symptoms have worsened while using a dopamine agonist. Augmentation occurs in 42 to 70% of patients treated with dopamine agonists over 8 to 10 years, equivalent to a rate of 5 to 7% per year.^{49,57-59} The risk of augmentation may be reduced by keeping the total daily doses of agonists low. It is essential to identify the phenomenon early by educating patients about the symptoms of augmentation and inquiring about them at every follow-up visit. **Box 5** provides several screening questions which can be used to identify augmentation. Severe augmentation is profoundly distressing to patients, often resulting in extreme insomnia and mood disturbances. It is very difficult to treat, sometimes requiring experts experienced in this area. Augmentation must be detected early and the medication weaned and, if at all possible, discontinued, substituting other agents. Under no circumstances should the symptoms of augmentation be treated by increasing the dopamine agonist dose as this inevitably worsens the augmentation.

Box 5 Augmentation with Dopaminergic Medication *

Any worsening of RLS symptoms while on a stable dose of a dopaminergic medication must be considered to be due to augmentation unless proven to be due to other factors

1. Do RLS symptoms appear earlier than when the drug was first started?
2. Are higher doses of the drug now needed, or do you need to take the medicine earlier to control the RLS symptoms, compared to the original effective dose?
3. Has the intensity of symptoms worsened since starting the medication?
4. Have symptoms spread to other parts of the body (e.g. the arms) since starting the medication?

* Adapted with permission from Garcia-Borreguero D, Silber MH, Winkelman JW et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-Foundation. *Sleep Med.* 2016;;21:1-11.⁶⁰

Table 5 describes the three dopamine agonists FDA-approved for treatment of RLS: pramipexole, ropinirole, and the rotigotine patch. Pramipexole is usually given once a day two hours before bed, but an additional dose can be given in the late afternoon or early evening if necessary. The initial dose should be 0.125 mg, increasing by 0.125 mg every two to three days until relief is obtained or a maximum daily dose of 0.5 mg is reached. The equivalent initial dose for ropinirole is 0.5 mg administered 1.5 hours before bed with the maximum total daily dose being 2 mg. The rotigotine patch provides sustained release of a dopamine agonist over 24 hours and is most useful for symptoms occurring during the day as well as the night, being applied once daily in an initial strength of 1 mg and a maximum strength of 3 mg. These maximum doses are considerably lower than when the medications are used for Parkinson disease but should be strictly adhered to in order to reduce the risk of augmentation.

In addition to augmentation, dopamine agonists can cause impulse control disorder (ICD) (e.g. compulsive shopping, pathologic gambling, and hypersexual behaviors) in 6 to 17% of patients, with the risk possibly being dose-dependent. Symptoms commence an average of 9 months after introduction of the drug⁶¹ and therefore, it is necessary to remind patients about this possibility at every visit. The impulse control urges usually dissipate rapidly if the drug is withdrawn or sometimes if the dose is reduced. Practitioners should be aware that

there have been several medical malpractice lawsuits regarding failure to warn patients or recognize symptoms of ICDs when prescribing dopamine agonists, including for RLS. Other minor side effects of dopamine agonists are uncommon with the low doses used, but may include nausea, lightheadedness due to orthostatic hypotension, leg edema, and insomnia. Daytime sleepiness is uncommon unless the medication is also taken during the day, but sleep attacks with little premonitory warning have occasionally been reported. The rotigotine patch may cause skin reactions which can be minimized by daily changes of the application site. It should be noted that older ergoline-derived dopamine agonists, such as cabergoline and bromocriptine, should not be used because of the risk of producing systemic fibrosis. Levodopa should never be used for chronic RLS because of the very high risk of augmentation.

Dipyridamole

Dipyridamole, an equilibrative nucleoside transporter (ENT) blocker may reduce RLS by increasing extracellular adenosine. There is limited evidence in support of its use in the form of a small, short duration, single-center controlled trial.⁶² Clinical experience, based mainly on treating patients unresponsive to other agents, suggests that some patients may benefit from its use, although the effect often dissipates after a few months. Use may be limited by side effects, including abdominal distention, insomnia and dizziness. As dipyridamole has antiplatelet effects, caution should be exercised in patients on anticoagulants and other antiplatelet agents. Hypotension can occur in patients using antihypertensive medications. The recommended dosage is 100 mg to 300 mg once a day in the evening.

Bilateral High Frequency Peroneal Nerve Stimulation

This technique consists of bilateral external high frequency stimulation of the peroneal nerves over the neck of the fibula below the knees for 30 minutes at a time. Its use is supported by the results of a large multi-center, controlled trial of patients who had failed at least one drug used to treat RLS.⁶³ The mechanism of action is thought to involve stimulation of afferent nerve fibers resulting in tonic contractions of the anterior tibialis muscles mimicking voluntary leg movements. The 4-week trial suggested improvement in 45% of participants using the device with this increasing to 73% in a 24-week open label extension study.⁶⁴

The device is currently FDA approved for moderate to severe RLS in patients who have failed at least one medication. Prescriptions, insurance processing, patient education and follow-up are currently managed by the single company that supplies the device. Clinical experience suggests that the technique is helpful as adjunctive therapy to medications and may allow the dose of drugs, especially opioids, to be reduced, a finding confirmed by one study.⁶⁵ It is very unusual for peroneal nerve stimulation to allow medications to be completely withdrawn. The role of the device in medication-naïve patients needs further study.

Patients can apply the device for 30 minutes at a time up to four times a day. It seems most useful if applied before bed, on waking with RLS during the night, or in situations that a patient knows provoke RLS, such as a period of prolonged sitting in the afternoon. The effect seems to persist for several hours after the device is turned off. The device is generally well tolerated with administration site irritation being the most common side effect. The availability of this treatment is still limited outside the U.S.A.

Choice of Other Agents

Before considering the use of agents other than iron and gabapentinoids, it is appropriate to recheck that there are no exacerbating factors for RLS that can be appropriately modified, such as serotonergic antidepressant use or sleep disordered breathing. A trial of peroneal nerve stimulation can be considered if the technique is available and affordable.

Dipyridamole can also be considered, taking into account potential side effects and limited proof of efficacy.

If these measures are ineffective or considered inappropriate, options include low-dose opioids and dopamine agonists. Which of these classes of medication should be tried initially should be decided by shared decision making between the patient and the healthcare provider after the patient has been fully educated about the risks and benefits of each class. Patient preference is paramount, although providers should feel comfortable sharing their personal experiences and suggestions. Although the 2025 AASM clinical practice guidelines gave a conditional recommendation against the use of dopamine agonists in most circumstances, this was qualified by statement that “nevertheless, their prescribing may be indicated for individual patients based on the patient and their preference” in the context of circumstances such as “poor tolerability or lack of efficacy of other RLS therapies”⁸. The recommendations in this algorithm do not significantly diverge from the AASM statements and expand upon the precautions needed to safely prescribe these agents.

Factors that should be considered include the very high risk of augmentation over time with dopamine agonists (up to 70%) and the often extreme difficulty in managing this complication once it becomes established. Although at least 30% of patients do not seem to develop augmentation over eight to ten years.^{49,57-59}, it is not currently possible to predict in

advance which patients will follow this more benign course, and it is possible that these patients may eventually also develop this complication. The risks of ICDs should also be carefully considered. These considerations have led some experts to advocate that the use of dopamine agonists should be restricted to situations where low-dose opioids have failed to control RLS or resulted in unacceptable side effects. Opioid therapy is very often effective and generally well-tolerated with only 3% of patients needing a significant increase in dose over five years of use for RLS.⁶⁶ While low-dose opioids do not cause augmentation, many patients are concerned about these medications and the stigma associated with their use, despite opioid use disorder being very uncommon with low-dose therapy for RLS. There are often onerous regulatory constraints, lack of availability at pharmacies, and side effects that may be troublesome, such as nausea and constipation.

For each class of agent, it is essential to follow the recommendations in **Boxes 6 and 7**.

Box 6

Conditions for the Use of Low Dose Opioids

- Patients must be educated about potential side effects, the risks of dependence, and the need to secure the medication supply, and providers must be familiar with side effects and potential drug interactions.

- Patients must be prepared to sign an opioid use contract as determined by local requirements
- Patients and providers must understand other regulatory requirements, such as the need for regular follow-up visits, urine drug screens, and assessment of state pharmacy databases
- Doses should be adjusted to provide effective control of symptoms but should rarely exceed the recommended limits in **Table 4**.

Box 7

Conditions for the Use of Dopamine Agonists

- Patients must be educated about augmentation and ICD, must agree never to increase the dose by themselves, and to report immediately if RLS symptoms worsen or ICD develop
- Doses must be kept as low as possible, *never* exceeding the maximum daily limits (pramipexole 0.5 mg, ropinirole 2 mg, rotigotine 3 mg)
- Return visits are essential, at least every 6 months at which times the patient and any partner should be carefully questioned about worsening RLS symptoms and specific types of ICD
- If RLS symptoms worsen while on dopamine agonists, the provider must appropriately wean and, if possible, discontinue dopamine agonist therapy with substitution of other appropriate agents (or alternatively refer the patient to an RLS expert). The dose of dopamine agonist should never be increased in response to worsening RLS symptoms.

Management of Dopamine Agonist Augmentation

The management of patients who have already developed augmentation on dopamine agonists requires empathy and patience. It is important to bear in mind certain important principles. First, once any symptoms of augmentation develop, a plan should be developed to wean the patient from dopamine agonists. An increase in dose may provide short-term benefit, but the problem will only inevitably worsen with time. For the same reason, we do not recommend converting patients on immediate release dopamine agonists to long-acting dopamine agonists such as the rotigotine patch or extended release ropinirole or pramipexole.

Second, dopamine agonists should never be abruptly discontinued as this can result in profound insomnia with an increase in RLS sometimes associated with severe mood disturbances and occasionally suicidal ideation, analogous to dopamine agonist withdrawal syndrome described after withdrawal of agonists in patients with Parkinson's disease. Instead, dopamine agonists should be weaned slowly, usually after the introduction of an alternative class of agents. If patients have not failed gabapentinoids in the past, these drugs can be tried, but are not always effective^{67,68} and most patients will require low-dose opioids. Some patients may prefer to attempt dopamine agonist withdrawal without the addition of another agent, but this requires very careful monitoring.

Third, the rate of reduction of dopamine agonists is dependent on patient preference and the degree of withdrawal symptoms that develop. Some patients prefer a slow process over several weeks to many months while others prefer a relatively rapid withdrawal process over days to weeks.^{67,68} Irrespective of the speed, the process of weaning can be very unpleasant for patients who should be warned about temporary worsening of restless legs and mood

disturbances, especially around the time they eventually discontinue the agonist. An increase in the dose of gabapentinoid or low dose opioid may be needed as the process unfolds. Despite maximum coverage with gabapentinoids or low-dose opioids, many patients will have a significant but limited period of resurgence of their RLS symptoms each time the dose of the dopamine agonist is reduced and particularly when the dopamine agonist is finally discontinued, and some may choose to remain on a minimal dose of the agonist together with a drug from another class. Once the patient has discontinued the dopamine agonist and restless legs symptoms have stabilized, it may be possible to reduce the dose of the alternative agent or occasionally discontinue it.

Fourth, dopamine agonists should never be reintroduced after a drug holiday. While the patient may obtain temporary relief, augmentation inevitably redevelops, often with a shorter latency than initially.

Box 8 provides a practical approach to augmentation management.

Box 8 Management of Dopamine Agonist Augmentation

- Reassess systemic iron stores and administer intravenous iron if indicated
- Introduce an agent of another class (most often low-dose opioids, but gabapentinoids can be tried if they have not been previously used unsuccessfully).
- Once a dose within the therapeutic range of the alternative agent has been reached (see **Tables 3 and 4**), start weaning the dopamine agonist. Pramipexole should be reduced in steps of 0.25 mg, ropinirole in steps of 1 mg, and the rotigotine patch in steps of 1 mg. The size of the reductions may need to be reduced as lower doses are

reached. Anticipate temporary rebound of RLS symptoms at each dose reduction.

The *rate* of reduction depends on patient preference and tolerance. This should never be less than once every 3 days and can be as long as once per month. The rate can be varied during weaning depending on patient tolerance. The dose of the low-dose opioid or gabapentinoid may need to be increased to cover symptoms of dopamine agonist withdrawal. Despite maximum coverage, many patients experience a recurrence of RLS when the dopamine agonist is fully discontinued, and some may choose to remain on a minimal dose of the agonist.

- Once the patient has successfully discontinued the dopamine agonist, consider whether the dose of low dose opioid or gabapentinoid can be reduced.

Pediatrics and Special Circumstances

Childhood (Box 9)

Nonpharmacologic approaches are especially important for the management of RLS in childhood. All patients should establish consistent bedtime routines, limiting evening screen time and caffeine intake, participate in regular physical activity and stretching, and use calming strategies such as warm baths or leg massage.

Iron deficiency is associated with RLS in children, with the cause varying by age. In infants (6–12 months), risks arise from exclusive breastfeeding without iron-rich supplements or early introduction of cow's milk. Among preschool-aged children (1–4 years), inadequate dietary intake or excessive cow's milk consumption are common causes. In school-aged children (5–12 years), poor nutrition or gastrointestinal conditions are contributing factors. Adolescents, particularly females, are at increased risk due to rapid growth, dietary restrictions, heavy menstrual bleeding, or high levels of physical activity. As a result of these

factors, serum ferritin concentration is often lower in children than adults and was less than 50 µg/L in 83% of children with RLS in one study.⁶⁹

In children with RLS, serum ferritin concentration should always be measured and iron supplementation should be considered if the serum ferritin concentration is below 50 µg/L.⁸ This figure is based on the distribution of serum ferritin levels in children with RLS and lack of data regarding the safety and efficacy of iron therapy with higher levels of serum ferritin in this age group. Administration of iron at serum ferritin levels ≥ 50 µg/L could be considered on an individual basis for older adolescents. Oral ferrous sulfate 3 mg/kg in either tablet or liquid form should be administered once daily or once every other day before bed. Constipation and abdominal discomfort are possible adverse effects. Liquid iron preparations can cause staining of teeth. Serum ferritin concentration should be checked in three months to ensure that the level has risen above 50 µg/L.⁷⁰ If oral iron therapy is not tolerated or is not accompanied by a satisfactory rise in serum ferritin concentration, consideration can be given to intravenous administration of iron. Most data are available for ferric carboxymaltose which can be administered as 15 mg/kg with a maximum dose of 750 mg.⁷¹ The same considerations regarding transient hypophosphatemia apply in children as in adults (see under Iron Therapy). If ferric carboxymaltose is unavailable, iron sucrose, given as 5 mg/kg to a maximum of 200 mg infused over two hours, has been reported effective in a case series.⁷² Alternatively, low molecular weight iron dextran has been safely and effectively used in children with iron deficiency anemia in doses of 100-1,000 mg, based on a weight-related formula⁷³ although there are no data regarding its uses in childhood RLS. Potential side effects of intravenous administration of iron include subcutaneous extravasation with brownish skin discoloration, abdominal discomfort, and minor infusion reactions, such as facial flushing. Repeated infusions may be necessary, especially in younger

children, those with comorbidities, or persistent low ferritin levels after initial IV treatment.⁷⁴ Symptom improvement is commonly seen within 8 weeks post-infusion, with serum ferritin levels typically increasing above 100 µg/L.⁷⁵

There are no large, controlled trials of pharmacologic agents in childhood and no drugs approved by the FDA for RLS treatment in children. The following recommendations are therefore based on anecdotal experience and case series.^{76,77} As in adults, first line drug therapy should be the gabapentinoids. Gabapentin (5-10 mg/kg) and pregabalin (2-3 mg/kg) can be used if iron is not needed or is ineffective. Clonazepam (0.1-1 mg) may be helpful if comorbid parasomnias are present, noting sedation and paradoxical hyperactivity as possible adverse effects. Clonidine, an alpha 2-adrenergic agonist, can be considered in children (0.05-0.2 mg) who also have an anxiety disorder or attention-deficit/ hyperactivity disorder. Its use may be limited by adverse effects including sedation, irritability, depression, and hypotension.

Box 9 Management of RLS in Childhood

- Non-pharmacologic approaches, including a consistent bedtime routine, avoidance of sleep deprivation, elimination of caffeine, warm baths, and leg massages should be tried.
- The mainstay of RLS treatment in children is iron replacement. Serum ferritin concentration should be measured; iron supplementation should be prescribed if levels are < 50 µg/L. If oral iron is ineffective in 3 months or poorly tolerated, intravenous iron with ferric carboxymaltose, iron sucrose, or low-molecular weight iron dextran should be considered.
- As in adults, first-line drug therapy if needed in children should be gabapentinoids

- Other drugs that can be considered include clonazepam (if comorbid parasomnias) or clonidine (if comorbid anxiety or attention deficit / hyperactivity disorder) but potential side effects should be carefully considered

Pregnancy (Box 10)

RLS can present for the first time, worsen in intensity, or progress from intermittent to persistent symptoms in pregnancy with one study suggesting 26% of pregnant women experience the condition.⁷⁸ Symptoms usually remit around delivery but some women will experience a recurrence of RLS later in life. Management approaches outlined here are based on a 2015 consensus practice guideline⁷⁹ and more recent advances.

Non-pharmacological approaches may be helpful, including warm or alternating temperature showers or baths, daytime compression stockings, aerobic low intensity and leg stretching exercises, muscle relaxation training⁸⁰⁻⁸², and Vitamin D supplementation, if stores are low.⁸³ Optimization of iron status is fundamental to RLS management in pregnancy. Criteria for oral or intravenous iron therapy are the same for pregnant and non-pregnant adults. There is one study of the use of intravenous iron for RLS during the third trimester,⁸⁴ and extensive studies of IV iron for iron deficiency anemia during the second and third trimesters, demonstrating safety and efficacy with multiple formulations, including low molecular weight iron dextran and ferric carboxymaltose.^{85,86} Because of a lack of data related to safety, intravenous iron should not be given during the first trimester.

Medications may be considered in the second and third trimesters for severe RLS unresponsive to behavioral therapies or iron administration. Recommendations are based primarily on expert opinion in the absence of systematic studies. The risk-benefit ratio of

each drug should be openly discussed with patients, allowing joint decision making about introduction and continuation of pharmacological agents. It is often helpful to engage the input of the patient's obstetrician or a maternal fetal medicine specialist. When appropriate, doses should be kept low and intermittent therapy considered.

Studies of gabapentin have shown increased risk of neonatal ICU admission and, in some studies, increased preterm births and neonates small for gestational age, with one study suggesting an increased risk of cardiac fetal anomalies with repeated dosing.⁸⁷ A single study of pregabalin⁸⁸ found no definitive evidence for adverse consequences to the fetus or neonate. Carbidopa/levodopa may be helpful for intermittent RLS in pregnancy but should not be used more than three times a week because of the high frequency of augmentation. Limited human studies of carbidopa/levodopa have not suggested risk to the fetus.

There may be a slight risk of certain congenital abnormalities with the use of opioids in the first trimester.⁸⁹ Neonates born to mothers on opioids need careful monitoring for respiratory depression and signs of opioid or benzodiazepine withdrawal.

Box 10 Management of RLS in Pregnancy

- Non-pharmacological therapies are preferred, including warm or alternating temperature showers or baths, relaxation techniques, aerobic low-intensity exercise, muscle stretches, compression stockings, and, if stores are low, vitamin D supplementation
- Iron therapy is safe and should be offered as in non-pregnant adults, including intravenous iron in the second and third trimesters, as indicated

- The use of medications for severe RLS in the second and third trimesters should be based on joint decision making, balancing benefits and risks. Doses should be kept low, and intermittent therapy considered. Gabapentinoids, oxycodone, methadone, buprenorphine and intermittent carbidopa-levodopa can be considered.

Lactation

Recommendations are based primarily on expert opinion in the absence of systematic studies. Intravenous iron-carbohydrate complexes have very low expected transfer into breast milk and no adverse infant outcomes have been reported, although data is limited. Therefore, when the patient qualifies for intravenous iron therapy, breastfeeding need not be interrupted.

If medications are needed during lactation, gabapentin should be considered. There are no documented cases of harm to the infant although gabapentin can be found in breast milk. If this is ineffective, opioids can be used, but the infant should be monitored for sedation, poor feeding, respiratory depression and lack of weight gain. Dopamine agonists and levodopa should not be used as dopamine suppresses lactation.

End-Stage Renal Disease

RLS is common in patients with end-stage renal disease (ESRD), especially in the setting of chronic dialysis. The use of erythropoietin may be beneficial, and patients should have low iron stores replenished. Non-pharmacological approaches that might be helpful include the use of exercise, massage, vitamin C and E supplementation and possible use of dialysate 1-

1.5 degrees C cooler than the usual standard.⁹⁰ RLS often improves or resolves after successful kidney transplantation.

Recommendations for pharmacologic therapy are based predominantly on expert opinion and drug metabolic and excretion characteristics. Gabapentin or pregabalin can be used but because these drugs are excreted by the kidney, low doses should be prescribed initially and side effects, including sedation and unsteadiness, carefully monitored. One approach is to give these medications the night after dialysis. The only opioids used to treat RLS whose metabolism is not significantly impacted by renal failure are methadone and buprenorphine. Most other opioids or their active metabolites are excreted by the kidneys and thus should only be used with extreme caution.⁹¹ If dopamine agonists are selected, ropinirole or rotigotine should be used as they undergo extensive metabolism in the liver to inactive products whereas pramipexole is excreted unchanged by the kidneys.

Perioperative Management (Box 11)

General measures for the care of RLS in the perioperative period should include keeping immobilization to a minimum and encouraging early ambulation. Restraints should not be used and care should be taken to differentiate the movements of severe RLS from signs of delirium. Attention should be given to preventing sleep deprivation in the postoperative period. Medications that can exacerbate restless legs symptoms should be avoided, including antihistamines and dopamine antagonists such as metoclopramide, prochlorperazine, and neuroleptic drugs.⁹² Ondansetron can be safely used for post-operative nausea. If surgery has resulted in significant blood loss, blood transfusions or

intravenous iron replacement should be considered if restless legs symptoms have worsened, although this has not been systematically studied.

Whenever possible, maintenance RLS treatment should be continued in the perioperative period, maintaining the same dosages and timing of medications. For patients using pramipexole or ropinirole who cannot take oral agents postoperatively, the rotigotine patch should be substituted.⁹³ Recommendations regarding opioids are predominantly based on data from patients taking opioids for chronic pain. For patients on opioid therapy for RLS, a higher dose may be needed to control postoperative pain as chronic use may result in the development of tolerance for analgesia. If buprenorphine has been prescribed for RLS, this can be continued, and it is considered safe to add conventional opioids such as oxycodone or fentanyl for acute pain relief.⁹⁴ A similar approach can be followed for those on low-dose methadone maintenance therapy. For patients who are not using opioids for RLS, the use of opioid analgesics carries the risk of precipitating RLS rebound on their withdrawal. Therefore, they should be used in the lowest dose and for as short a time as possible compatible with adequate pain relief and, if higher doses are needed, the medication should be withdrawn slowly rather than abruptly.

Box 11 Perioperative Management of RLS

- Whenever possible, continue maintenance RLS therapy at the same dose and timing
- Avoid sleep deprivation, keep immobilization to a minimum, and encourage early ambulation
- Do not use restraints and differentiate severe RLS from postoperative delirium
- Avoid medications that can exacerbate RLS including antihistamines and dopamine antagonist anti-emetics and neuroleptics

- Address significant postoperative blood loss by blood transfusions or intravenous iron should RLS worsen
- For patients on oral dopamine agonists, convert to the rotigotine patch if oral intake is not permitted
- For patients on buprenorphine or methadone, continue the same dose and add conventional opioids for pain control. For patients on oxycodone, hydrocodone or morphine, temporarily increase the dose for analgesia if necessary
- For patients not on chronic opioid therapy, use postoperative opioids in as low a dose and for as short a time as possible compatible with adequate pain relief and withdraw higher dose opioids slowly

Alternative, Investigative and Potential Future Approaches

Conventional therapies for RLS based on strong scientific evidence are not always effective or well-tolerated. This section discusses alternative and potential future therapies, but it should be recognized that the current evidence for their effectiveness is generally based on anecdote, small controlled trials, or open-label studies with the risk of placebo effects, a phenomenon well recognized in RLS.

Mechanical Devices

Vibration and pneumatic compression applied to the legs have been studied although the evidence for benefit is low.⁹⁵ However, the devices do not cause any known harm and some patients may find them helpful.

Central Nervous System Neuromodulation

Non-invasive techniques, such as transcutaneous electrical spinal cord stimulation,⁹⁶ transcranial magnetic stimulation⁹⁷ or non-invasive vagal nerve stimulation⁹⁸ have shown some promise but further well-designed studies are needed. Implanted spinal cord electrodes for the treatment of chronic pain have been reported to relieve concomitant RLS.⁹⁹ Similarly, deep brain stimulation in Parkinson disease or essential tremor^{100,101} has also been reported to be beneficial. Extensive further studies will be needed before determining whether these invasive techniques have a role in the management of primary RLS.

Cannabis

Case series¹⁰² and anecdotal experience suggest the possibility of some benefits from cannabis, but optimal formulation, dosage, and mode of administration is uncertain, and no adequate controlled trials have demonstrated efficacy. Anecdotal experience from some patients suggest that inhaled cannabis (1-3 inhalations) may provide rapid but short-lived relief of symptoms. Use of cannabis should be balanced with the understanding that the drug interacts with multiple other medications used to treat RLS, including dopamine agonists and gabapentinoids, potentially increasing adverse effects. Inhaled cannabis may be harmful to patients with asthma or chronic obstructive pulmonary disease. Long-term complications of cannabis have been inadequately studied and, despite the drug being legal in many jurisdictions, as of December 2025 it remains illegal under federal law in the United States.

Minerals, Vitamins and Supplements

The use of iron supplementation has been discussed in detail earlier. In order to help delineate which patients are most likely to benefit from iron replacement, further research is needed to explore non-invasive imaging techniques for measuring iron in the basal ganglia, such as transcranial sonography and MRI scans.

Some patients report benefit from the use of magnesium. Some evidence of support for this contention comes from an open label study (including objective measurements of periodic limb movements of wakefulness) suggesting benefit with 200 mg magnesium citrate daily.¹⁰³ A single controlled trial suggested benefit of vitamin C and vitamin E in RLS patients with end-stage renal failure¹⁰⁴ and a meta-analysis noted lower Vitamin D levels in pregnant women with RLS.⁸³ Apart from these studies, there is no support for the use of vitamin supplements.

There is no evidence or experience to suggest that melatonin is helpful for RLS.

Medications

The development of novel medications for the management of RLS should be a research priority. Identification of potentially effective new drugs will require more basic science studies investigating the pathophysiology of the disorder. As an example, a recent genome-wide association meta-analysis suggested that investigating glutamate receptor antagonists and drugs influencing the cholecystokin-B receptor might be fruitful future approaches.¹⁰⁵

Studies to better understand the dopamine agonist augmentation phenomenon might result in the ability to identify patients at low risk from this complication.

Older studies suggested the possible effectiveness of carbamazepine. Perampanel, a glutamate AMPA receptor antagonist¹⁰⁶ and lamotrigine¹⁰⁷ have shown encouraging results in small pilot open label studies. Larger controlled studies of newer anticonvulsant drugs should be undertaken.

Other drugs recently tried include calcitonin gene-related peptide (CGRP) monoclonal antibodies, that showed promise in a small group of patients being treated for migraine.¹⁰⁸ A small, single-site, proof of concept controlled trial of the dual orexin receptor antagonist suvorexant showed improvement in insomnia indices as well as in secondary outcomes related to restless legs syndrome.¹⁰⁹ Further studies of clonidine, long used in pediatric RLS, might help better delineate its role.

Conclusion

The treatment of RLS has advanced with increased emphasis on iron and gabapentinoids as first-line agents and improved understanding of the use of low-dose opioids as alternative drugs. The risks of dopamine agonists and the strict conditions under which they may be used are better understood. Neuromodulation with peroneal nerve stimulation is a new option. Despite these advances and newer options, current treatments are imperfect. Basic and clinical research into future novel approaches is essential to aid those suffering from this distressing disorder. We have no doubt that future advances will again necessitate revisions of this algorithm.

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Table 1. Equivalent Serum Ferritin Concentrations.^a

Beckman or Equivalent Method	Roche Method
75 µg/l	121 µg/l
100 µg/l	158 µg/l
300 µg/l	457 µg/l

^a Data from *J Clin Sleep Med.* ¹⁸

Table 2. Intravenous Iron Preparations

	Administration	Advantages	Disadvantages
Ferric carboxymaltose	2 doses of 750 mg each one week apart or one dose of 1,000 mg over 15 min	Most supporting data from clinical trials	High cost. Results in hypophosphatemia in 40-70% of adults (18-20% of children), but generally not clinically significant unless repeated doses administered for anemia from chronic ongoing GI or uterine blood loss
Low molecular weight iron dextran	25 mg test dose and 975 mg in 1,000 ml normal saline over one hour	Low cost	Longer time of administration
Ferumoxytol	2 doses of 510 mg each one week apart or one dose of 1,020 mg over 20-30 min	Intermediate cost	May interfere with interpretation of MRI contrast studies for 3

			months after administration
Ferric derisomaltose	One dose of 1,000 mg over 15 min		High cost. No published studies on use in RLS; rare hypophosphatemia ($< 10\%$)

Table 3

Comparison of Gabapentinoids used to treat RLS

	Gabapentin^a	Pregabalin^a	Gabapentin Enacarbil^a
Time to maximum blood level	2-3 hrs	1.5 hours fasting; 3 hours with food	7-9 hrs
Elimination half-life	5-7 hrs	6 hrs	Relatively stable plasma levels over 18-24 hrs (elimination half-life 6 hrs)
Metabolism and excretion	Renal	Renal	Intestinal metabolism; renal excretion
Initial daily dose (≤ 65 years) ^b	300 mg	75 mg	600 mg
Initial daily dose (> 65 years)^b	100 mg	50 mg	300 mg
Usual Effective Dose^b	900-1,800 mg in divided doses	300 mg	600 mg
Maximum daily dose^b	3,600 mg	600 mg	1,800 mg ^c

- a. As of March 2026, gabapentin and pregabalin are available as generics in the U.S. but not gabapentin enacarbil
- b. Doses should be adjusted for renal dysfunction
- c. Value differs from FDA approved maximum of 600 mg

Table 4 Use of Opioids in RLS^a

	Starting Dose	Usual Effective Daily Dose	MME Ratio	Advantages	Disadvantages
Oxycodone IR	5-10 mg	10-30 mg	1.5:1	Short-acting	May require multiple doses
Oxycodone ER	9-10 mg	10-30 mg	1.5:1	Intermediate-acting	May produce daytime sedation
Hydrocodone IR	10-15 mg	15-45 mg	1:1	Short-acting	May require multiple doses
Morphine CR	10-15 mg	15-45 mg	1:1	Intermediate-acting	May produce daytime sedation
Methadone	2.5-5 mg	5-20 mg	4.7:1	Long-acting; less tolerance or euphoria	Prolonged QTc at higher doses; may produce daytime sedation

Buprenorphine (sublingual or buccal film)	0.075-0.5 mg (75- 500 µg)	0.5-6 mg	Not calculable	Long-acting; less tolerance, euphoria, or respiratory depression; Schedule III, so refills and 90-day supplies allowable	Buccal film expensive; more complex for patients to use; may produce daytime sedation; risk of dental/gum problems
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- a. No opioids are FDA approved for treatment of RLS

Table 5 Dopamine Agonists for the Treatment of RLS

	Pramipexole^a	Ropinirole^a	Rotigotine patch^a
Time to maximum blood level	2 hrs	1-1.5 hrs	15-18 hrs
Elimination half-life	8-12 hrs (increases with decreasing glomerular filtration rate and age)	6 hrs	Stable plasma levels over 24 hrs. (Elimination half -life biphasic: 3 and 6 hrs)
Metabolism and excretion	Renal	Hepatic metabolism; renal excretion	Hepatic metabolism; renal excretion
Initial daily dose	0.125 mg	0.5 mg	1 mg
Maximum daily dose	0.5 mg	2 mg	3 mg

a. As of March 2026, pramipexole and ropinirole are available as generics in the U.S. but not rotigotine.

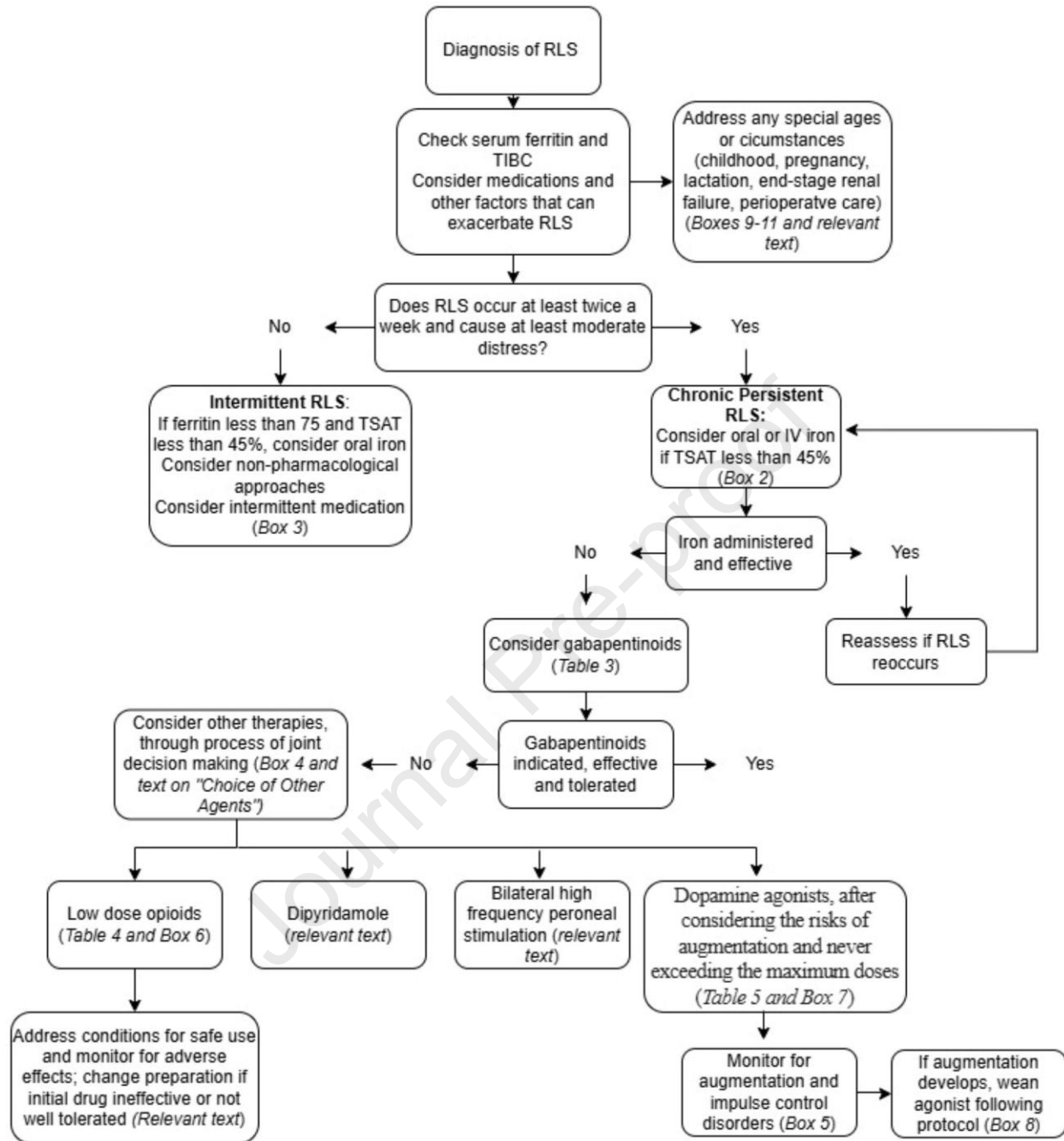
Figure Legend

Figure:

Flow Diagram Summarizing Recommendations of the Algorithm

RLS, restless legs syndrome; TIBC, total iron binding capacity; TSAT, transferin saturation

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