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SPECIAL ARTICLES

Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine clinical practice guideline

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Introduction: This guideline establishes clinical practice recommendations for treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) in adults and pediatric patients.

Methods: The American Academy of Sleep Medicine (AASM) commissioned a task force of experts in sleep medicine to develop recommendations and assign strengths based on a systematic review of the literature and an assessment of the evidence using the grading of recommendations assessment, development, and evaluation methodology. The task force provided a summary of the relevant literature and the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations that support the recommendations. The AASM Board of Directors approved the final recommendations.

Good Practice Statement: The following good practice statement is based on expert consensus, and its implementation is necessary for the appropriate and effective management of patients with RLS:

1. In all patients with clinically significant RLS, clinicians should regularly test serum iron studies including ferritin and transferrin saturation (calculated from iron and total iron binding capacity). Testing should ideally be administered in the morning avoiding all iron-containing supplements and foods at least 24 hours prior to blood draw. Analysis of iron studies greatly influences the decision to use oral or intravenous (IV) iron treatment. Consensus guidelines, which have not been empirically tested, suggest that supplementation of iron in adults with RLS should be instituted with oral or IV iron if serum ferritin ≤ 75 ng/mL or transferrin saturation < 20%, and only with IV iron if serum ferritin is between 75 and 100 ng/mL. In children, supplementation of iron should be instituted for serum ferritin < 50 ng/mL with oral or IV formulations. These iron supplementation guidelines are different than for the general population.
2. The first step in the management of RLS should be addressing exacerbating factors, such as alcohol, caffeine, antihistaminergic, serotonergic, antidopaminergic medications, and untreated obstructive sleep apnea.
3. RLS is common in pregnancy; prescribers should consider the pregnancy-specific safety profile of each treatment being considered.

Recommendations: The following recommendations are intended as a guide for clinicians in choosing a specific treatment for RLS and PLMD in adults and children. Each recommendation statement is assigned a strength ("strong" or "conditional"). A "strong" recommendation (ie, "We recommend … ") is one that clinicians should follow under most circumstances. The recommendations listed below are ranked in the order of strength of recommendations and grouped by class of treatments within each PICO (Patient, Intervention, Comparator, Outcome) question. Some recommendations include remarks that provide additional context to guide clinicians with implementation of this recommendation.

Adults with RLS:

1. In adults with RLS, the AASM recommends the use of gabapentin enacarbil over no gabapentin enacarbil (strong recommendation, moderate certainty of evidence)
2. In adults with RLS, the AASM recommends the use of gabapentin over no gabapentin (strong recommendation, moderate certainty of evidence).
3. In adults with RLS, the AASM recommends the use of pregabalin over no pregabalin (strong recommendation, moderate certainty of evidence).
4. In adults with RLS, the AASM recommends the use of IV ferric carboxymaltose over no IV ferric carboxymaltose in patients with appropriate iron status (see good practice statement for iron parameters) (strong recommendation, moderate certainty of evidence).
5. In adults with RLS, the AASM suggests the use of IV low molecular weight iron dextran over no IV low molecular weight iron dextran in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, very low certainty of evidence).
6. In adults with RLS, the AASM suggests the use of IV ferumoxytol over no IV ferumoxytol in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, very low certainty of evidence).

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7. In adults with RLS, the AASM suggests the use of ferrous sulfate over no ferrous sulfate in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, moderate certainty of evidence)
8. In adults with RLS, the AASM suggests the use of dipyridamole over no dipyridamole (conditional recommendation, low certainty of evidence).
9. In adults with RLS, the AASM suggests the use of extended-release oxycodone and other opioids over no opioids (conditional recommendation, moderate certainty of evidence).
10. In adults with RLS, the AASM suggests the use of bilateral high-frequency peroneal nerve stimulation over no peroneal nerve stimulation (conditional recommendation, moderate certainty of evidence).
11. In adults with RLS, the AASM suggests against the standard use of levodopa (conditional recommendation, very low certainty of evidence).
Remarks: levodopa may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).
12. In adults with RLS, the AASM suggests against the standard use of pramipexole (conditional recommendation, moderate certainty of evidence).
Remarks: pramipexole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).
13. In adults with RLS, the AASM suggests against the standard use of transdermal rotigotine (conditional recommendation, low certainty of evidence).
Remarks: transdermal rotigotine may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).
14. In adults with RLS, the AASM suggests against the standard use of ropinirole (conditional recommendation, moderate certainty of evidence).
Remarks: ropinirole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).
15. In adults with RLS, the AASM suggests against the use of bupropion for the treatment of RLS (conditional recommendation, moderate certainty of evidence).
16. In adults with RLS, the AASM suggests against the use of carbamazepine (conditional recommendation, low certainty of evidence).
17. In adults with RLS, the AASM suggests against the use of clonazepam (conditional recommendation, very low certainty of evidence).
18. In adults with RLS, the AASM suggests against the use of valerian (conditional recommendation, very low certainty of evidence).
19. In adults with RLS, the AASM suggests against the use of valproic acid (conditional recommendation, low certainty of evidence).
20. In adults with RLS, the AASM recommends against the use of cabergoline (strong recommendation, moderate certainty of evidence).

Special adult populations with RLS:

21. In adults with RLS and end-stage renal disease (ESRD), the AASM suggests the use of gabapentin over no gabapentin (conditional recommendation, very low certainty of evidence).
22. In adults with RLS and ESRD, the AASM suggests the use of IV iron sucrose over no IV iron sucrose in patients with ferritin < 200 ng/mL and transferrin saturation < 20% (conditional recommendation, moderate certainty of evidence).
23. In adults with RLS and ESRD, the AASM suggests the use of vitamin C over no vitamin C (conditional recommendation, low certainty of evidence).
24. In adults with RLS and ESRD, the AASM suggests against the standard use of levodopa (conditional recommendation, low certainty of evidence).
Remarks: levodopa may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).
25. In adults with RLS and ESRD, the AASM suggests against the standard use of rotigotine (conditional recommendation, very low certainty of evidence).
Remarks: rotigotine may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

Adults with PLMD:

26. In adults with PLMD, the AASM suggests against the use of triazolam (conditional recommendation, very low certainty of evidence).
27. In adults with PLMD, the AASM suggests against the use of valproic acid (conditional recommendation, very low certainty of evidence).

Children with RLS:

28. In children with RLS, the AASM suggests the use of ferrous sulfate over no ferrous sulfate in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, very low certainty of evidence).

Keywords: restless legs syndrome, periodic limb movement disorder, Willis-Ekbom disease, sleep-related movement disorders
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INTRODUCTION

This clinical practice guideline (CPG) updates the 2012 American Academy of Sleep Medicine (AASM) practice parameter and provides practice recommendations for the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) in adult and pediatric patients.[1] This paper reflects the current recommendations of the AASM.

RLS is a sleep-related movement disorder characterized by an urge to move 1 or both legs (and sometimes the arms) when immobile (often associated with dysesthesias in the affected extremities), which is relieved by movement and is most prominent in the evening or at night.[2] RLS severity ranges from isolated occurrences during episodes of prolonged sitting or inactivity, to daily, near around-the-clock discomfort and movement. Neuropathy, akathisia, spasticity, positional discomfort, joint discomfort, and nocturnal leg cramps are among the conditions that can present with symptoms resembling RLS in adults,[2] and growing pains, legs cramps, and behavioral issues are mimics in children.[3] A careful clinical history is imperative as there is no objective test to aid in making an RLS diagnosis. Clinically significant RLS, defined as occurring at

least twice a week and associated with at least moderate distress, is present in 2–3% of adults and 0.5–1% of children.[2,4] In children, diagnosing RLS can be challenging as they can have difficulty describing their symptoms. In adults, RLS is roughly 50% more prevalent in females, some of which is related to pregnancy, and is also more common in those of northern European heritage. RLS can make extended immobility nearly impossible at night, leading to insomnia as the primary morbidity, with difficulty falling or staying asleep present in roughly 90% of people with RLS.[5]

Once asleep, people with RLS often exhibit periodic limb movements during sleep (PLMS) which are detected on polysomnography as brief (0.5–10 seconds), recurrent flexion movements of the lower extremities that occur roughly every 15–30 seconds. PLMS in people with RLS occur particularly during the first 4 hours of the sleep period,[6,7] and have a high night-to-night variability in both adults and children.[8,9] These movements can be associated with electroencephalogram arousal but are invariably associated with elevations in heart rate and blood pressure.[10]

PLMD is diagnosed when PLMS are (1) frequent (> 15 events/h in adults and > 5 events/h in children); (2) there is coexisting clinically significant sleep disturbance and/or daytime dysfunction that is not better explained by another concurrent sleep, medical, neurological, or mental disorder; and (3) there is an absence of sleep disorders that are associated with high rates of PLMS including RLS, untreated obstructive sleep apnea, rapid eye movement sleep behavior disorder, and narcolepsy.[7] For PLMD, the implication is that the PLMS directly cause nighttime and/or daytime symptoms of the disorder and that reductions in PLMS will result in symptomatic improvement.

The underlying pathophysiology of RLS and PLMD is only partially understood, although both brain iron deficiency and genetics likely play a role.[11,12] Those with conditions associated with systemic iron deficiency (eg, pregnancy, end-stage renal disease [ESRD]) have increased prevalence of RLS.[13] Magnetic resonance imaging, transcranial doppler, and cerebrospinal fluid analysis demonstrate reduced brain iron indices in people with RLS.[14] RLS is also strongly heritable, and roughly half of people with RLS have a first-degree relative with the disorder. At least 164 genetic polymorphisms have been associated with the disorder using genome wide association studies.

In the 2012 AASM CPG on RLS treatment, the dopamine agonists (pramipexole and ropinirole) were considered STANDARD treatments.[1] Levodopa with a dopa decarboxylase inhibitor, opioids, gabapentin enacarbil, and cabergoline (with caveats) were considered GUIDELINE level recommendations. Several treatments were considered at an OPTIONAL level of recommendation. Since that publication, the AASM has modified its CPGs to include only 2 levels: either STRONG or CONDITIONAL recommendation, either for or against a specific treatment.

Numerous clinical trials and longitudinal observational studies have been published in the last 10 years, providing greater clarification about specific RLS treatments, which are reflected in recent RLS treatment guidelines published by other organizations.[15] Specifically, the long-term risk of augmentation (iatrogenic worsening of RLS symptoms) with dopamine agonists is now clearer, and this CPG has placed special emphasis on augmentation as a critical outcome, with a corresponding reassessment of the relative risks and benefits for this class of medications.[16,17]

Augmentation clinically describes a gradual worsening of RLS symptom intensity and duration, which occurs over months to years of exposure to dopaminergic agents. Augmentation manifests as 1 or more of the following: earlier symptom onset than prior to dopaminergic treatment (eg, from nighttime to daytime), reduced latency to symptom onset with sedentary activities, and/or extension to other areas of the body. Because augmentation of RLS symptoms generally emerges with use of dopamine agonists over time, the short-term duration of the initial pivotal clinical trials of dopamine agonists for Food and Drug Administration (FDA) approval did not demonstrate this complication. In addition, augmentation is most common and aggressive at higher dopaminergic medication doses, and in clinical settings, the common response to emerging augmentation is to increase the dose of these medications. Thus, augmentation often has a nonlinear intensification of severity.

There have also been additional large clinical trials of pregabalin and ferric carboxymaltose, leading to revisions of their status. As in the 2012 CPG,[1] the most important clinical trial endpoint remains the international restless legs syndrome severity scale,[18] including the self-administered International RLS Severity Scale,[19] which is a disease-specific measure that assesses severity of RLS symptoms, their frequency and daily duration, as well as the effects on sleep, daytime function, and mood. Use of the international restless legs syndrome severity scale remains a requirement for FDA approval.

This guideline, with the accompanying systematic review,[20] provides a comprehensive update of the available evidence and a synthesis of clinical practice recommendations for the treatment of RLS and PLMD in adults and children. It is intended to optimize patient-centric care by broadly informing clinicians who care for patients with RLS and PLMD.

METHODS

The AASM commissioned a task force (TF) of sleep medicine clinicians with expertise in the treatment of adults and children with RLS or PLMD. The TF was required to disclose all potential conflicts of interest, per the AASM's conflicts of interest policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's conflicts of interest policy, TF members with a level 1 conflict were not allowed to participate. TF members with a level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

The TF conducted a systematic review of the published scientific literature, prioritizing patient-oriented, clinically relevant outcomes identified through the TF expertise and stakeholder surveys. These surveys included input from relevant professional organizations and patient advocacy groups. The key terms, search limits, and inclusion/exclusion criteria specified by

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the TF are detailed in the supplemental material of the accompanying systematic review.[20] The review's purpose was to determine whether the interventions provided clinically significant improvements in relevant outcomes relative to no treatment. The TF set a clinical significance threshold for each outcome to determine whether the mean differences between treatment and control or before and after treatment in the outcomes assessed were clinically significant.[20] The TF then developed clinical practice recommendations according to the grading of recommendations assessment, development, and evaluation process.[21,22] The TF assessed the following 4 components to determine the direction and strength of a recommendation: (1) certainty of evidence, (2) balance of beneficial and harmful effects, (3) patient values and preferences, and (4) resource use. Details of these assessments can be found in the accompanying systematic review. Taking these major factors into consideration, each recommendation statement was assigned a strength ("strong" or "conditional"). Additional information is provided in the form of "remarks" immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations and to guide clinicians in the implementation of the recommendations in daily practice.

This CPG reflects the evidence and state of knowledge at the time of the last literature search, September 2023. Scoping literature searches are performed annually on all published AASM CPGs to review new evidence. Based on this review, updates may be made if there are significant changes in areas such as the available interventions, outcomes of interest (or values placed on outcomes), or evidence regarding the existing benefits and harms. The ultimate judgment regarding the suitability of any specific recommendation requires the clinician to use clinical knowledge and experience, and strongly consider the individual patient's values and preferences to determine the best course of action.

RECOMMENDATIONS

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the grading of recommendations assessment, development, and evaluation process. The implications of the strength of recommendations for guideline users are summarized in **Table 1**. Remarks are provided to guide clinicians in the implementation of these recommendations. **Table 2**, **Table 3**, **Table 4**, and **Table 5** summarize the recommendation for interventions in adult and pediatric populations.

GOOD PRACTICE STATEMENT

The following good practice statement is based on expert consensus, and its implementation is necessary for appropriate and effective management of people with RLS:

1. In all patients with clinically significant RLS, clinicians should regularly test serum iron studies including ferritin and transferrin saturation (calculated from iron and total iron binding capacity). Testing should ideally be administered in the morning avoiding all iron-containing supplements and foods at least 24 hours prior to blood draw. Analysis of iron studies greatly influences the decision to use oral or intravenous (IV) iron treatment. Consensus guidelines, which have not been empirically tested, suggest that supplementation of iron in adults with RLS should be instituted with oral or IV iron if serum ferritin ≤ 75 ng/mL or transferrin saturation < 20%, and only with IV iron if serum ferritin is between 75 and 100 ng/mL. In children, supplementation of iron should be instituted for serum ferritin < 50 ng/mL with oral or IV formulations. These iron supplementation guidelines are different than for the general population.[23]
2. The first step in the management of RLS should be addressing exacerbating factors, such as alcohol, caffeine, antihistaminergic, serotonergic, antidopaminergic medications, and untreated obstructive sleep apnea.
3. RLS is common in pregnancy; prescribers should consider the pregnancy-specific safety profile of each treatment being considered.[24]

ADULTS WITH RLS

Recommendations for specific interventions for the treatment of adults with RLS are presented below. Remarks are provided to guide clinicians in the implementation of these recommendations. A study was included in the analysis if it was original research on the treatment of RLS in adults addressing an outcome of interest. For all interventions the TF assessed effectiveness for the treatment of RLS in adults based on improvements in disease severity, quality of life (QOL), sleep quality, and adverse effects. The recommendations listed below are ranked in the order of strength of recommendations and grouped by class of treatments within each PICO (Patient, Intervention, Comparator, Outcome) question.

STRONG recommendations for use

Recommendation 1: In adults with RLS, the AASM recommends the use of gabapentin enacarbil over no gabapentin enacarbil (strong recommendation, moderate certainty of evidence)

The TF identified 8 randomized controlled trials (RCTs) and 3 observational studies in which the pooled estimates demonstrated clinically significant improvements in disease severity, sleep quality, and QOL with a moderate effect size. All 8 RCTs reported on the presence of adverse events leading to study withdrawal; the pooled estimate for the adverse events did not meet clinical significance. Adverse effects included somnolence and dizziness. The undesirable effect size was deemed small.

The overall certainty of evidence was moderate due to imprecision. Since the cost of the medication is considered high, treatment would probably reduce health equity, but direct evidence is lacking. The intervention was feasible to implement. Patients who are at a high risk of side effects with this class of medications may choose other treatment options.

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Table 1—Implications of strong and conditional recommendations for users of AASM clinical practice guidelines.

User	Strong Recommendations: "We Recommend … "	Conditional Recommendations: "We Suggest … "
Clinicians	Almost all patients should be offered the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.	Most patients should be offered the suggested course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with their values and preferences.
Patients	Almost all patients should be offered the recommended course of action, although a small proportion of patients would not choose it.	Most patients should be offered the suggested course of action, although some may not choose it. Different choices may be appropriate for different patients. The patient should work with their clinician to determine if the suggested course of action is clinically appropriate and consistent with their values and preferences.
Policy makers	The recommended course of action can be adopted as policy for most situations. Adherence to the recommended course of action could be used as a quality criterion or performance indicator.	The ultimate judgment regarding the suitability of the suggested course of action must be made by the clinician and patient together, based on what is best for the patient. This decision-making flexibility should be accounted for when establishing policies.

Table 2—Summary of recommended interventions in adult populations (grouped by strength of recommendation and listed within class of medications): adults with RLS.

Intervention	Strength of Recommendation	Presence of Improvements in Critical Outcomes Meeting CST***			Presence of Complications Meeting CST	
		Disease Severity	Sleep Quality	Quality of Life	Augmentation of RLS Symptoms	Adverse Effects Leading to Study Withdrawal
Gabapentin	Strong for	Y	N	N	—	N
Gabapentin enacarbil	Strong for	Y	Y	Y	—	N
Pregabalin	Strong for	Y	Y	N	—	Y
IV ferric carboxymaltose	Strong for	Y	Y	Y	—	N
IV LMW iron dextran	Conditional for	Y	—	—	—	N
IV ferumoxytol	Conditional for	Y	—	—	—	N
Ferrous sulfate	Conditional for	Y	—	—	—	Y
Dipyridamole	Conditional for	Y	—	—	—	N
Oxycodone ER and other opioids	Conditional for	Y	N	—	—	Y
Peroneal nerve stimulation	Conditional for	Y	—	—	—	N
Levodopa**	Conditional against	N	N	N	Y	N
Pramipexole**	Conditional against	Y	Y	Y	Y	N
Transdermal rotigotine**	Conditional against	Y	Y	Y	Y	Y
Ropinirole**	Conditional against	Y	N	Y	Y	N
Bupropion	Conditional against	N	—	—	—	N
Carbamazepine	Conditional against	N	—	—	—	Y
Clonazepam	Conditional against	—	—	—	—	N
Valerian	Conditional against	N	N	—	—	Y
Valproic acid	Conditional against	N*	—	—	—	N
Cabergoline	Strong against	Y	—	Y	Y	Y

—Outcome not reported. *Outcome was reported using a nonvalidated tool that could not be assessed for clinical significance. **These medications may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation). ***CSTs can be found in the accompanying systematic review. CST = clinical significance threshold, ER = extended release, IV = intravenous, LMW = low molecular weight, N = no, RLS = restless legs syndrome, Y = yes.

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Table 3—Summary of recommended interventions in adult populations (grouped by strength of recommendation and listed within class of medications): adults with RLS and ESRD.

Intervention	Strength of Recommendation	Presence of Improvements in Critical Outcomes Meeting CST**			Presence of Complications Meeting CST	
		Disease Severity	Sleep Quality	Quality of Life	Augmentation of RLS Symptoms	Adverse Effects Leading to Study Withdrawal
Gabapentin	Conditional for	Y	Y	—	—	Y
IV iron sucrose	Conditional for	Y	—	—	—	N
Vitamin C	Conditional for	Y	—	—	—	—
Levodopa*	Conditional against	N	Y	—	Y	N
Transdermal rotigotine*	Conditional against	Y	—	N	Y	Y

—Outcome not reported. *These medications may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation). **CSTs can be found in the accompanying systematic review. CST = clinical significance threshold, ESRD = end-stage renal disease, IV = intravenous, N = no, RLS = restless legs syndrome, Y = yes.

Table 4—Summary of recommended interventions in adult populations (grouped by strength of recommendation and listed within class of medications): adults with PLMD.

Intervention	Strength of Recommendation	Presence of Improvements in Critical Outcomes Meeting CST*				Presence of Complications Meeting CST
		Sleep Quality	Excessive Daytime Sleepiness	Quality of Life	Work/School Performance Attendance	Adverse Effects Leading to Study Withdrawal
Triazolam	Conditional against	—	Y	—	—	N
Valproic acid	Conditional against	—	—	—	—	Y

—Outcome not reported. *CSTs can be found in the accompanying systematic review. CST = clinical significance threshold, N = no, PLMD = periodic limb movement disorder, Y = yes.

Table 5—Summary of recommended interventions in adult populations (grouped by strength of recommendation and listed within class of medications): pediatric population with RLS.

Intervention	Strength of Recommendation	Presence of Improvements in Critical Outcomes Meeting CST*			Presence of Complications Meeting CST
		Sleep Quality	Quality of Life	Work/School Performance Attendance	Adverse Effects Leading to Study Withdrawal
Ferrous sulfate	Conditional for	Y	—	—	N

—Outcome not reported. *CSTs can be found in the accompanying systematic review. CST = clinical significance threshold, N = no, RLS = restless legs syndrome, Y = yes.

Recommendation 2: In adults with RLS, the AASM recommends the use of gabapentin over no gabapentin (strong recommendation, moderate certainty of evidence)

The TF identified 2 RCTs and 4 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity with a moderate effect size. The TF identified 2 RCTs that reported on the presence of adverse effects leading to study withdrawal; the pooled estimate for the adverse events did not meet clinical significance. Adverse effects included somnolence and dizziness. The undesirable effect size was deemed small.

The overall certainty of evidence was moderate due to imprecision. The cost of the medication was considered negligible.

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The treatment would not affect health equity. The intervention was feasible to implement. Patients who are at a high risk of side effects with this class of medications may choose other treatment options.

Recommendation 3: In adults with RLS, the AASM recommends the use of pregabalin over no pregabalin (strong recommendation, moderate certainty of evidence)

The TF identified 3 RCTs in which the pooled estimates demonstrated clinically significant improvements in disease severity and sleep quality with a moderate effect size. Three studies reported on the presence of adverse events leading to study withdrawal; the pooled estimate for the adverse events met clinical significance. Adverse effects included somnolence and dizziness. The undesirable effect size was deemed small.

The overall certainty of evidence was moderate due to imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity. The intervention was feasible to implement. Patients who are at a high risk of side effects with this class of medications may choose other treatment options.

Recommendation 4: In adults with RLS, the AASM recommends the use of IV ferric carboxymaltose over no IV ferric carboxymaltose in patients with appropriate iron status (see good practice statement for iron parameters) (strong recommendation, moderate certainty of evidence)

The TF identified 5 RCTs in which the pooled estimates demonstrated clinically significant improvements in disease severity, sleep quality, and QOL with a moderate effect size. The TF identified 4 RCTs that reported on the presence of adverse events leading to study withdrawal; the pooled estimate for the adverse events did not meet clinical significance. Adverse effects included risk for hypophosphatemia and dizziness. The undesirable effect size was deemed small.

The overall certainty of evidence was moderate due to imprecision. The cost of the intervention was considered moderate. The treatment would probably reduce health equity. The intervention was probably feasible to implement.

CONDITIONAL recommendations for use

Recommendation 5: In adults with RLS, the AASM suggests the use of IV low molecular weight (LMW) iron dextran over no IV LMW iron dextran in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, very low certainty of evidence)

The TF identified 1 observational study which demonstrated clinically significant improvement in disease severity with a small effect size. The TF identified 3 observational studies that reported on the presence of adverse events leading to study withdrawal; the pooled estimate for the adverse events leading to study withdrawal did not meet clinical significance. The undesirable effect size was deemed small. An older formulation of iron dextran (high molecular weight), which is no longer available, was associated with adverse effects including risk for anaphylaxis, but LMW iron dextran has not demonstrated this risk in published literature.

The overall certainty of evidence was very low due to observational study. The cost of the intervention was considered moderate. The treatment would probably reduce health equity. The intervention was probably feasible to implement.

Recommendation 6: In adults with RLS, the AASM suggests the use of IV ferumoxytol over no IV ferumoxytol in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, very low certainty of evidence)

The TF identified 1 RCT study, which compared IV iron to another treatment and used prepost data as there was no placebo arm, demonstrated clinically significant improvement in disease severity with a small effect size. The study reported on the presence of adverse events leading to study withdrawal, not meeting clinical significance. The undesirable effect size was deemed trivial.

The overall certainty of evidence was very low due to imprecision and risk of bias. The cost of the intervention was considered moderate. The treatment would probably reduce health equity. The intervention was probably feasible to implement.

Recommendation 7: In adults with RLS the AASM suggests the use of ferrous sulfate over no ferrous sulfate in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, moderate certainty of evidence)

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity with large effect size. The TF identified 2 RCTs that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events met clinical significance. The undesirable effect size was deemed small.

The overall certainty of evidence was moderate due to imprecision. The cost of the intervention was considered negligible. The treatment would not affect health equity, The intervention was feasible to implement.

Recommendation 8: In adults with RLS, the AASM suggests the use of dipyridamole over no dipyridamole (conditional recommendation, low certainty of evidence)

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity with moderate effect size. This RCT reported on the presence of adverse events leading to study withdrawal, not meeting clinical significance. Adverse effects reported in this study included dizziness. The undesirable effect size was deemed small.

The overall certainty of evidence was low due to imprecision and risk of bias. The cost of the medication was considered negligible. The treatment would not affect health equity. The intervention was feasible to implement.

Recommendation 9: In adults with RLS, the AASM suggests the use of extended-release oxycodone and other opioids over no opioids (conditional recommendation, moderate certainty)

The TF identified 1 RCT, with extended-release oxycodone, which demonstrated clinically significant improvement in

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disease severity in patients with refractory RLS, with moderate effect size. The TF identified 2 RCTs (one of which reported on immediate-release and the other on extended-release oxycodone) that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events met clinical significance. Adverse effects included fatigue, somnolence, and dizziness. The undesirable effect size was deemed moderate. The TF acknowledged the additional risks of abuse, chemical dependence, and overdose which may vary based on formulation and patient characteristics. Based on a class effect, the TF judged the evidence for the benefits and risks to be applicable to other mu-opioid agonists.

The overall certainty of evidence for extended-release oxycodone was moderate due to imprecision. The cost of opioids varies depending on formulation. The acceptability of the medication to key stakeholders would be varied. Opioids would probably reduce health equity. The intervention was feasible to implement.

Recommendation 10: In adults with RLS, the AASM suggests the use of bilateral high-frequency peroneal nerve stimulation over no peroneal nerve stimulation (conditional recommendation, moderate certainty of evidence)

The TF identified 2 RCTs, which demonstrated clinically significant improvement in disease severity with small effect size in patients, many of whom had refractory RLS and were maintained on other treatments. The RCT reported on the presence of adverse events leading to study withdrawal, not meeting clinical significance. Adverse effects included uncomfortable sensations during stimulation and skin irritation. The undesirable effect size was deemed trivial.

The overall certainty of evidence was moderate due to risk of bias. The cost of the treatment was considered high. The treatment would probably reduce health equity. The intervention was probably feasible to implement.

CONDITIONAL recommendations against use

Recommendation 11: In adults with RLS, the AASM suggests against the standard use of levodopa (conditional recommendation, very low certainty of evidence)

Remarks: levodopa may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

The TF identified 1 RCT and 2 observational studies in which the pooled estimates demonstrated no clinically significant improvements in disease severity and sleep quality. The TF identified 3 RCTs and 7 observational studies that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events did not meet clinical significance. Adverse effects included a clinically significant risk of somnolence and dizziness/vertigo. The TF acknowledged the substantial risk of augmentation. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to risk of bias and imprecision. The cost of the intervention was considered negligible. The treatment would not affect health equity. The intervention was feasible to implement.

Recommendation 12: In adults with RLS, the AASM suggests against the standard use of pramipexole (conditional recommendation, moderate certainty of evidence)

Remarks: pramipexole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

The TF identified 17 RCTs and 7 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity, QOL, and sleep quality with moderate effect size. All RCTs reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events did not meet clinical significance. Adverse effects included somnolence, dizziness, and impulse control disorders. The TF identified 2 RCTs and 7 observational studies of variable duration in which the pooled estimates demonstrated clinically significant results for augmentation. The undesirable effect size was deemed moderate.

The overall certainty of evidence was moderate due to imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 13: In adults with RLS, the AASM suggests against the standard use of transdermal rotigotine (conditional recommendation, low certainty of evidence)

Remarks: transdermal rotigotine may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

The TF identified 8 RCTs and 3 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity, sleep quality, and QOL with moderate effect size. All RCTs reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events met clinical significance. Adverse effects included somnolence, dizziness, and application site reactions. The TF identified 3 observational studies of variable duration in which the pooled estimates demonstrated clinically significant results for augmentation. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to risk of bias, imprecision, and inconsistency. The cost of the medication was considered high. The treatment would probably reduce health equity, and the intervention was feasible to implement.

Recommendation 14: In adults with RLS, the AASM suggests against the standard use of ropinirole (conditional recommendation, moderate certainty of evidence)

Remarks: ropinirole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

The TF identified 13 RCTs and 2 observational studies in which the pooled estimates demonstrated clinically significant

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improvements in disease severity and QOL with a small effect size. The TF identified 8 RCTs that reported adverse events leading to study withdrawal; the pooled estimate for the adverse events did not meet clinical significance. Adverse effects included somnolence and dizziness. The TF identified 3 observational studies of variable duration in which the pooled estimate demonstrated clinically significant results for augmentation. The undesirable effect size was deemed moderate.

The overall certainty of evidence was moderate due to risk of bias and imprecision. The cost of the intervention was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 15: In adults with RLS, the AASM suggests against the use of bupropion for the treatment of RLS (conditional recommendation, moderate certainty of evidence)

The TF identified 1 RCT, which demonstrated no clinically significant improvement in disease severity. The study reported on the presence of adverse events leading to study withdrawal, not meeting clinical significance. Adverse effects included nausea and irritable mood. The undesirable effect size was deemed trivial.

The overall certainty of evidence was moderate due to imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 16: In adults with RLS, the AASM suggests against the use of carbamazepine (conditional recommendation, low certainty of evidence)

The TF identified 2 RCTs in which the pooled estimates demonstrated no clinically significant improvement in disease severity. The TF identified 2 RCTs that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events met clinical significance. Adverse effects included dizziness. The TF acknowledged additional risks not limited to hepatotoxicity and adverse hematopoietic effects. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to risk of bias and imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 17: In adults with RLS, the AASM suggests against the use of clonazepam (conditional recommendation, very low certainty of evidence)

The TF identified 1 RCT comparing clonazepam to another medication and used prepost data as there was no placebo arm. Due to insufficient evidence in critical outcomes with validated metrics, the beneficial effects were indeterminate. The TF identified 3 RCTs that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events did not meet clinical significance. Adverse effects included sedation. The TF acknowledged additional risks not limited to cognitive impairment and chemical dependence. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to risk of bias and imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 18: In adults with RLS, the AASM suggests against the use of valerian (conditional recommendation, very low certainty of evidence)

The TF identified 1 RCT, which demonstrated no clinically significant improvement in disease severity and sleep quality. The study reported on the presence of adverse events leading to study withdrawal, meeting clinical significance. Adverse effects included dizziness. The undesirable effect size was deemed small.

The overall certainty of evidence was very low due to imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 19: In adults with RLS, the AASM suggests against the use of valproic acid (conditional recommendation, low certainty of evidence)

The TF identified 1 RCT, which demonstrated no clinically significant improvement in sleep quality or disease severity. The study reported on the presence of adverse events leading to study withdrawal, not meeting clinical significance. The TF acknowledged additional risks not limited to hepatotoxicity and teratogenicity. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

STRONG recommendations against use

Recommendation 20: In adults with RLS, the AASM recommends against the use of cabergoline (strong recommendation, moderate certainty of evidence)

The TF identified 2 RCTs and 3 observational studies in which the pooled estimates demonstrated clinically significant improvements in disease severity, QOL, and sleep latency with a large effect size. The TF identified 2 RCTs that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events met clinical significance. Adverse effects included dizziness/vertigo and augmentation. The TF acknowledged the additional risk of cardiac valvulopathy. The undesirable effect size was deemed large.

The overall certainty of evidence was moderate due to imprecision. The cost of medication was considered moderate. The treatment would probably reduce health equity, and the intervention was feasible to implement.

No recommendations

The TF used "no recommendation" when there was value in the findings but thought further research and innovation for this intervention is needed. There was insufficient and inconclusive

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evidence to make recommendations for the following: acupuncture, botulinum toxin, cognitive and behavioral therapy, clonidine, IV iron sucrose, near infrared light therapy, perampanel, tramadol, transcranial magnetic stimulation, transcutaneous spinal direct current stimulation, vitamin D, and yoga. The evidence is reported in the accompanying systematic review and supplemental material.

SPECIAL ADULT POPULATIONS WITH RLS

The following are recommendations for the treatment of special adult populations with RLS. Remarks are provided to guide clinicians in the implementation of these recommendations. A study was included in the analysis if it was original research on the treatment of RLS in special populations of adults addressing an outcome of interest. The study may be an RCT with at least 4 individuals in each arm or an observational study with at least 5 individuals. For all interventions the TF assessed effectiveness for the treatment of RLS in special adult populations based on improvements in disease severity, QOL, sleep quality, and adverse effects.

CONDITIONAL recommendations for use

Recommendation 21: In adults with RLS and ESRD, the AASM suggests the use of gabapentin over no gabapentin (conditional recommendation, very low certainty of evidence)

The TF identified 1 RCT and 2 observational studies in which the pooled estimates demonstrated clinically significant improvements in disease severity and sleep quality with large effect size. These studies reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events met clinical significance. Adverse effects included sedation. The undesirable effect size was deemed small.

The overall certainty of evidence was very low due to risk of bias and imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 22: In adults with RLS and ESRD, the AASM suggests the use of IV iron sucrose over no IV iron sucrose in patients with ferritin < 200 ng/mL and transferrin saturation < 20% (conditional recommendation, moderate certainty of evidence)

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity with a moderate effect size. The TF identified 1 RCT that reported on the presence of adverse events leading to study withdrawal; adverse events leading to study withdrawal did not meet clinical significance. The undesirable effect size was deemed trivial.

The overall certainty of evidence was moderate due to imprecision. The cost of the intervention was considered moderate. The treatment would probably reduce health equity. The intervention was probably feasible to implement.

Recommendation 23: In adults with RLS and ESRD, the AASM suggests the use of vitamin C over no vitamin C (conditional recommendation, low certainty of evidence)

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity with moderate effect size. The study did not report on adverse events leading to study withdrawal. The undesirable effect size was deemed trivial.

The overall certainty of evidence was low due to imprecision and indirectness. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

CONDITIONAL recommendations against use

Recommendation 24: In adults with RLS and ESRD, the AASM suggests against the standard use of levodopa (conditional recommendation, low certainty of evidence)

Remarks: levodopa may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

The TF identified 1 RCT and 2 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity and sleep quality with small effect size. The TF identified 1 RCT and 3 observational studies that reported on the presence of adverse events leading to study withdrawal; the pooled estimate of adverse events did not meet clinical significance. The TF acknowledged the substantial risk of augmentation. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to imprecision. The cost of the intervention was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 25: In adults with RLS and ESRD, the AASM suggests against the standard use of rotigotine (conditional recommendation, very low certainty of evidence)

Remarks: rotigotine may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity only, with moderate effect size. The study reported on the presence of adverse events leading to study withdrawal, meeting clinical significance. The TF acknowledged the risk of augmentation with long-term use. The undesirable effect size was deemed moderate.

The overall certainty of evidence was low due to imprecision. The cost of the medication was considered high. The treatment would probably reduce health equity, and the intervention was feasible to implement.

No recommendations

The TF used 'no recommendation' when there was value in the findings but thought further research and innovation for this intervention is needed. There was insufficient and inconclusive

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evidence to make recommendations for the following: vitamin E and combination of vitamin C + vitamin E.

The evidence is reported in the accompanying systematic review and supplemental materials.

ADULTS WITH PLMD

The following are recommendations for the treatment of adults with PLMD. Remarks are provided to guide clinicians in the implementation of these recommendations. A study was included in the analysis if it was original research on the treatment of PLMD in adults addressing an outcome of interest. The study may be an RCT with at least 4 individuals in each arm or an observational study with at least 5 individuals. For all interventions, the TF assessed effectiveness for the treatment of adults with PLMD based on improvements in daytime sleepiness, QOL, sleep quality, work/school performance, and adverse effects.

CONDITIONAL recommendations against use

Recommendation 26: In adults with PLMD, the AASM suggests against the use of triazolam (conditional recommendation, very low certainty of evidence)

The TF identified 1 RCT that showed clinically significant improvement in excessive daytime sleepiness with a small effect size. Two RCTs reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events did not meet clinical significance. The undesirable effect size was deemed small.

The overall certainty of evidence was very low due to imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

Recommendation 27: In adults with PLMD, the AASM suggests against the use of valproic acid (conditional recommendation, very low certainty of evidence)

The TF identified 1 observational study that reported a decrease in PLM frequency, but it did not report any validated measures in critical outcomes, so the beneficial effects were indeterminate. The study reported on the presence of adverse events leading to study withdrawal, meeting clinical significance. The TF acknowledged additional risks not limited to hepatotoxicity and teratogenicity. The undesirable effect size was deemed moderate.

The overall certainty of evidence was very low due to risk of bias and imprecision. The cost of the medication was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

PEDIATRIC POPULATIONS WITH RLS

The following are recommendations for the treatment of children with RLS. Remarks are provided to guide clinicians in the implementation of these recommendations. A study was included in the analysis if it was original research on the treatment of RLS in children addressing an outcome of interest. The study may be an RCT with at least 4 individuals in each arm or an observational study with at least 5 individuals. For all interventions the TF assessed effectiveness for the treatment of children with RLS based on improvements in disease severity, QOL, sleep quality, and adverse effects.

CONDITIONAL recommendations for use

Recommendation 28: In children with RLS, the AASM suggests the use of ferrous sulfate over no ferrous sulfate in patients with appropriate iron status (see good practice statement for iron parameters) (conditional recommendation, very low certainty of evidence)

The TF identified 2 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity with small effect size. The studies reported on the presence of adverse events leading to study withdrawal; the pooled estimate of the adverse events did not meet clinical significance. The undesirable effect size was deemed trivial.

The overall certainty of evidence was very low due to risk of bias and imprecision. The cost of the intervention was considered negligible. The treatment would not affect health equity, and the intervention was feasible to implement.

SPECIAL PEDIATRIC POPULATIONS WITH RLS

No evidence found.

PEDIATRIC POPULATIONS WITH PLMD

No evidence found.

DISCUSSION

Over the past 30 years, national specialty and general practice guidelines have consistently recommended medical treatment of clinically significant RLS in adults.[1,25,26] RLS can cause significant morbidity and reduction in QOL, in part due to the discomfort from the symptoms themselves. More disabling is the disruption of sleep caused by the need to move the legs or get out of bed to walk at night to relieve RLS symptoms.[5,27,28] As the initial FDA-approved treatments for RLS in adults, dopamine agonists were rapidly adopted as first-line therapy by specialists and general practitioners alike for this often ignored and untreated sensorimotor disorder.[29]

Published concerns about dopaminergic augmentation of RLS symptoms from levodopa date back to the mid-1990s.[29] Heightened awareness of augmentation with long-term dopamine agonist use emerged in the early 2000s as their clinical use became widespread.[29–33] Furthermore, the occurrence of impulse control disorders in patients with RLS treated with dopamine agonists also raised concerns about long-term use of

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these agents.[34–36] Nevertheless, expert recommendations for RLS in adults did not change until 2016, at which point alpha-2-delta ligand medications were promoted to first-line pharmacotherapy as an alternative to dopamine agonists by the consensus of 3 major RLS organizations.[16] However, changes to clinical practice have been slow to reflect this shift away from dopamine agonists, as national data from 2017–2018 demonstrated that 60% of medication-treated RLS patients were still prescribed dopamine agonists, often at doses exceeding FDA recommendations for RLS.[17] Although this CPG may appear to many providers to represent a paradigm shift away from the use of dopamine agonists, it is in fact just 1 more step in a continued evolution in this process over a series of published clinical guidelines.[1,15]

RLS is often a chronic and lifelong disease, and treatment should thus primarily be aimed at effectiveness over the lifespan. There is no argument that dopamine agonists have demonstrated short-term efficacy in clinical trials. However, augmentation of RLS due to dopaminergic agents is anathema to the fundamentals of chronic management—that the treatment itself can cause a gradual worsening of the condition, often to a severity not observed in the natural history of the disease. Moreover, tapering and discontinuation of a dopamine agonist can be incredibly challenging due to the severe rebound RLS symptoms.[34,35] Finally, it is unclear whether the increased RLS severity caused by augmentation is reversible, as the extended temporal distribution of symptoms may persist long after dopaminergic discontinuation. In fact, a published RCT suggests that treatment with gabapentin enacarbil can be less effective after prior long-term dopaminergic treatment.[37] Thus, in balancing the risks of augmentation against the clinical benefits of dopamine agonists or levodopa, this CPG suggests against their use as standard treatments in adults with RLS. Nevertheless, their prescribing may be indicated for individual patients based on the patient and their preference. For example, dopamine agonists or levodopa may be considered in the context of short-term use in circumstances in which movement is restricted (eg, plane travel), as well as with poor tolerability or lack of efficacy of other RLS therapies. In these circumstances, dopaminergic medication prescribing should be accompanied by regular monitoring of augmentation and impulse control disorders. Doses that exceed maximum FDA recommendations for RLS will accelerate these risks.

The suggestion that dopaminergic agents should only be used in the limited circumstances described above should not lead providers to abruptly discontinue them in patients currently using these medications, as dramatic rebound RLS can occur. The patient and clinician should discuss a long-term plan, generally including the addition of a new treatment and gradual taper off the dopaminergic agent, while monitoring for rebound symptoms related to RLS and mood as the dopaminergic system begins to acclimate to the reduced exogenous dopaminergic input.[15,38]

This CPG also has moved the triad of alpha-2-delta ligands (gabapentin, gabapentin enacarbil, and pregabalin) into the strongly recommended category based on multiple high-quality clinical trials of their efficacy for RLS. This is now consistent with published consensus papers from 2016 and 2021.[15,16] This class of medications can have adverse effects, including dizziness and somnolence, which may influence shared decision-making for prescribers and patients. It should be noted that in those with opioid use disorder, there is increasing evidence that alpha-2-delta ligands are misused.[39] For this reason, evaluation of risk factors for misuse is recommended prior to initiating alpha-2-delta ligands. In addition, the side effects of respiratory depression and sedation from these 2 types of medications can be enhanced when they are combined in cases of untreated obstructive sleep apnea. There is also evidence from 1 study in non-RLS adults that alpha-2-delta ligands are associated with increased risk of severe exacerbation of chronic obstructive pulmonary disease.[40]

IV ferric carboxymaltose receives a strong recommendation for adults in this CPG, which is a significant addition from 2012, with multiple recent RCTs supporting its use. Brain-iron deficiency has emerged as a leading concept in the pathophysiology of RLS, but awareness of the importance of serum iron assessment and supplementation is still lacking among clinicians and third-party payers. Routine screening of iron indices is an essential component of RLS patient care (supplementation indices are different for people with RLS than the general adult population, see Good Practice Statement above).

Further, people with RLS need regular and affordable access to iron infusion, not only at specialized RLS centers. Currently, this treatment is not reimbursed by payers specifically for RLS, and most patients require a comorbidity to obtain this treatment. Although the properties of IV LMW iron dextran and ferumoxytol are similar to IV ferric carboxymaltose, they only receive conditional recommendations for their use as there was only 1 observational study using validated measures of RLS severity for each formulation. Conversely, high quality studies of IV iron sucrose in RLS failed to show a clinically significant benefit over placebo, which may be supported by the pharmacology of these fast-release, low-dose formulations lacking the necessary H-ferritin binding and macrophage iron uptake that enables penetrance of iron into the central nervous system that is seen in the slow-release, higher dose formulations such as carboxymaltose, ferumoxytol, and dextran.[41] Nevertheless, 1 RCT using IV iron sucrose did show efficacy in adults with RLS and ESRD with a transferrin saturation < 20%. This form of IV iron is conditionally recommended.

Oral iron supplementation with ferrous sulfate is suggested with a conditional recommendation based on limited RCT data. Oral iron is poorly absorbed in those with ferritin > 50–75 ng/mL, unlike IV iron which does not rely on gastrointestinal absorption.[23] Use of ferrous sulfate and other forms of oral iron, unlike that of IV iron, may also be limited by side effects such as constipation.

Extended-release oxycodone and, with reasonable extension, other formulations of low-dose opioids, not formally assessed in high-quality studies, are given a conditional recommendation for moderate to severe cases of RLS. Low-dose opioids are often necessary to treat dopamine agonist-related augmentation of RLS symptoms, can facilitate taper and discontinuation of the dopamine agonist, and then usually remain the primary treatment for RLS symptoms. Caution should be used with opioids as central sleep apnea and respiratory depression can emerge with increased morphine equivalent dosing in most opioids with the exception of buprenorphine, which has a reduced risk of respiratory depression.[42–44] This risk is compounded by other central

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nervous system inhibitory drugs that may increase respiratory depression including sedative hypnotics, muscle relaxants, and alpha-2-delta ligands, which may already be part of a treatment regimen for an individual with RLS when opioids are considered.

While there is a risk of abuse and/or overdose with opioids, the evidence regarding long-term use of low-dose opioids for the treatment of RLS in appropriately screened adults suggests that these risks are relatively low in these patients.[45–48] Similarly, retrospective and prospective observational studies generally demonstrate only small dose increases in RLS patients followed over extended periods (2–10 years) of opioid treatment. Although the one large, randomized trial of opioids for RLS, using validated RLS severity measures, was with extended-release oxycodone in refractory individuals, the TF notes that the benefit of opioids for RLS is likely a class effect since observational studies have demonstrated efficacy of other opioids for treatment of RLS, particularly methadone.[45–47] Indeed, a recent large national registry study demonstrated that many different opioids are used with efficacy to treat RLS, with methadone being the most common.[48] Therefore, selection of a particular opioid can be tailored to the adult patient based on side effect profile, pharmacokinetics, and other factors. It should be noted that 2 oral long-acting opioids commonly used to treat RLS, methadone and buprenorphine, are also used as long-term maintenance therapy in opioid use disorder, further supporting a lower risk profile compared to other opioids.

Dipyridamole receives a conditional recommendation based on a short-term RCT published in 2021. Brain-iron deficiency may lead to a hypoadenosinergic state, and dipyridamole increases extracellular adenosine and activation of striatal adenosine receptors.[49,50] This medication has been long used for antiplatelet therapy in stroke and peripheral vascular disease, but there is biologic rationale as to why this medicine may work for RLS in adults.

Bilateral high-frequency peroneal nerve stimulation is a new noninvasive nonpharmacological treatment, and it also receives a conditional recommendation from initial success in 2 short-term sham-controlled studies and a longer observational extension. The wearable device is placed below the knees and provides stimulation to the peroneal nerve with resulting tonic activation of innervated muscles.[51] Although there was limited real-world use at the time of the CPG, it represents an alternative approach to pharmacological agents and the potential adverse systemic effects that come with them.

In special populations of adults with RLS, high quality evidence was only available for patients with ESRD, with conditional recommendations for gabapentin, IV iron sucrose, and vitamin C. There are conditional recommendations against levodopa and rotigotine for similar reasons to the standard adult population, specifically, augmentation with long-term use.

There is very little published literature on pediatric RLS treatment, but as in adults, the evidence points to the use of oral iron supplementation in cases of iron deficiency as a low-risk, accessible treatment that may address an underlying cause of the condition. Important considerations for treatment with oral iron in children include identification of potential side effects that could lead to discontinuation of therapy, most commonly constipation.[52] Despite the large body of evidence on symptoms and consequences of RLS in pediatrics,[53] there was previously insufficient evidence on the effectiveness of any therapy or on the balance between benefit and harms of therapies of RLS in children. The TF did not find evidence to support treating children with RLS with other medications commonly used in adults. Regularly monitoring RLS symptoms and the effect on the child's QOL, sleep, and academic performance is necessary to assess treatment efficacy and identify necessary adjustments.

PLMD is a controversial diagnosis in adults, and some studies call into question the *causality* of periodic limb movements during sleep (PLMS) with sleep disturbance or daytime sleepiness.[54] The small number of higher-quality treatment studies were limited to the 1990s to early 2000s, leading to conditional recommendations against the use of triazolam and valproic acid, as their potential side effects outweighed any demonstrable clinical benefit. The literature is devoid of treatment studies for PLMD within the past 2 decades. The value of independent treatment of PLMS in the context of RLS is now of unclear significance, with the current focus being treatment of the symptoms of RLS rather than the sleep-related limb movements. PLMS are also associated with aging and with a variety of medical and neurological conditions, and the indication for treatment in these contexts remains uncertain.[55,56]

This CPG used the rigorous grading of recommendations assessment, development, and evaluation methodology for meta-analysis, systematic review and recommendations.[21] The requirement to define minimum clinical important difference thresholds for trial metrics was a struggle, both for tools routinely used in clinical trials and even more so for nonvalidated measurement scales often used in older studies. However, the TF is confident that these new guidelines most closely reflect the current best evidence-based recommendations and that most clinicians should feel comfortable using this CPG as a basis for clinical management of RLS.

Finally, with the conditional recommendation against the dopamine agonists in adults with RLS, gabapentin enacarbil is the only FDA-approved drug for RLS recommended by this CPG. All but 1 strongly recommended treatment for RLS in this CPG are off-label and repurposed from other conditions. Moving forward, the need for interest among clinicians and researchers to develop treatments specifically for RLS could not be more apparent.

Future directions

Enormous progress has been made over the past 30 years in the development of efficacious treatments for RLS. However, RLS pharmacotherapy development over this period has generally derived from serendipity or modest modifications of existing agents, rather than a clear understanding of underlying syndrome pathophysiology. Up to this point, there is no single biological explanation as to what causes the idiosyncratic symptoms of RLS. Without a more complete understanding of the pathobiology of RLS, advances in RLS treatment may stall. Therefore, mechanistic research exploring the underlying biology of RLS is critical, particularly to show how other biologic systems including, but not limited to, glutamatergic, GABAergic, endogenous opioid, melanocortin, and histaminergic

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systems, interact with iron and dopamine to produce the symptoms of RLS.[49,50,57–63]

Many important clinical gaps remain in established RLS treatments. In particular, augmentation of RLS symptoms with use of dopamine agonists is a major issue that led to the downgrading of dopamine agonists in this CPG. This represents a substantial change in recommended treatment for RLS. As dopamine agonists constitute the majority of the FDA-approved medications and the most commonly prescribed agents for RLS, management of augmentation is an important challenge facing clinicians who treat RLS. Trials are needed to assess an algorithmic approach to the use of alpha-2-delta ligands, opioids, and iron (all recommended treatments in this CPG), combined with dopamine agonist taper and discontinuation, as this would provide important clinical guidance in management of augmented RLS. Furthermore, if there were predictors of augmentation, including genetic markers, iron status, or other at-risk clinical phenotypes, dopamine agonists could potentially be reestablished as recommended treatments for some patients.

Iron treatment is an important addition to this CPG. In the general population, iron administration is generally recommended for those with evidence of iron deficiency as determined by serum iron studies. In RLS, however, it is likely brain iron deficiency, particularly in specific brain regions, is involved in its pathophysiology. Therefore, there are patients with normal serum iron studies who benefit from iron administration, which is borne out by the clinical trials. Determining better approaches to evaluate brain iron deficiency and the patient populations more likely to respond to iron treatment are needed. With current evidence pointing to the efficacy of slower-release, high-dose formulations of IV iron, including ferric carboxymaltose, ferumoxytol, and LMW iron dextran in this CPG, further randomized testing of these and newer agents including ferric derisomaltose is needed to assess the differences in effectiveness and adverse effects among formulations that are somewhat used interchangeably at present in RLS. For adults with RLS and ESRD, future studies evaluating iron dextran are warranted given 1 RCT that used a nonvalidated metric showed promising results.[64]

In addition to identifying novel treatment pathways in RLS, it is important to broaden the definition of treatment success in RLS to include novel clinically relevant outcomes. First, RLS is associated with cardiovascular disease in adults and attention deficit hyperactivity disorder in children.[65,66] Determining whether long-term treatments which lessen RLS severity and improve sleep also decrease prevalent or incident cardiovascular disease in adults or behavioral outcomes in children is relevant at the clinical and population levels. Second, other forms of "secondary" RLS such as pregnancy and ESRD have important treatment limitations (potential teratogenesis and poor drug excretion, respectively) and specific trials in these populations are warranted. Third, RLS is often comorbid with mood, anxiety, and pain disorders, which present challenges to treatment because the most common treatments—serotonergic reuptake inhibitors—often worsen RLS. In addition, the use of opioids in pain syndromes more commonly leads to loss of efficacy than is seen in RLS alone. Fourth, RLS is prevalent in people with Parkinson's disease whose pathologic hallmark is loss of dopamine-producing neurons. Use of levodopa is an essential treatment in people with Parkinson Disease, and whether dopaminergic stimulation in this population is associated with the clinically important augmentation observed in other RLS populations, remains to be determined.[67] It will be important to develop a better understanding of RLS in these conditions to allow for appropriate treatment plans.

There is still a significant gap in the treatment of RLS in children. Many medications used to treat RLS in adults have not been studied in children or may not be suitable due to potential side effects and lack of safety data. The TF emphasizes the need for rigorous, high-level evidence studies that address treatment options for RLS in children. The inclusion in this CPG of oral iron supplementation in the form of ferrous sulfate for children is a step forward from prior guidelines and a move in the right direction to provide treatment options for pediatric RLS. The TF did not identify studies assessing the benefits of lifestyle modifications and behavioral interventions for children with RLS. Nevertheless, the TF recognizes the well-established importance of healthy sleep routines for the overall health in children. Areas for future research include long-term treatment efficacy and safety of IV iron infusion and other pharmacological and nonpharmacological interventions.

Over the past few decades, the medical field has made great strides in the understanding, evaluation, and treatment of RLS. Some of these advances are reflected in this CPG. Nonetheless, there still remains much work to be done at the basic science, translational, and clinical levels to further improve the lives of people with RLS.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
CPG, clinical practice guideline
ESRD, end-stage renal disease
FDA, Food and Drug Administration
IV, intravenous
LMW, low molecular weight
PLMD, periodic limb movement disorder
QOL, quality of life
RCT, randomized controlled trials
RLS, restless legs syndrome
TF, task force

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DISCLOSURE STATEMENT

The development of this paper was funded by the American Academy of Sleep Medicine (AASM).

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- Dr. Falck-Ytter is a paid consultant for the AASM and an affiliated member of the United States Grading of Recommendations Assessment, Development and Evaluation Network and the Evidence Foundation.
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- Dr. DelRosso is the Treasurer of the International RLS Study Group (2022–present) and Secretary of the World Sleep Society's Executive Committee (July 2023–present).

No other task force members have relevant conflicts of interest to disclose.

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