Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder

An American Academy of Sleep Medicine Clinical Practice Guideline

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 and Periodic Limb Movement Disorder in adult and pediatric patients.[1] This paper reflects the current recommendations of the AASM.

Restless legs syndrome (RLS) is a sleep-related movement disorder characterized by an urge to move one 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 more than twice per 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 women, 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 (PSG) as brief (0.5-10 second), 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 (EEG) arousal but are invariably associated with elevations in heart rate and blood pressure.[10]

Periodic limb movement disorder (PLMD) is diagnosed when PLMS are 1) frequent (>15/hr in adults and >5/hr 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 (REM) 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 are only partially understood, though both brain iron deficiency and genetics likely play a role.[11, 12] Those with conditions associated with systemic iron deficiency (e.g. pregnancy, end-stage renal disease) have increased prevalence of RLS.[13] Magnetic resonance imaging (MRI), transcranial doppler, and cerebrospinal fluid (CSF) 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 20 genetic polymorphisms have been associated with the disorder using genome wide association studies.[12]

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 clinical practice guidelines to include only two 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 one or more of the following: earlier symptom onset than prior to dopaminergic treatment (e.g. 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 FDA approval did not demonstrate this complication. Similarly, because augmentation is most common and most aggressive at higher dopaminergic medication doses, and in clinical settings the common response to emerging augmentation is to increase the dose of these medications, augmentation severity often has a non-linear 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 (IRLS), [18] including the self-assessed sIRLS, [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. The IRLS scale remains a requirement for FDA approval.

This guideline, with the accompanying systematic review, 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 (COI), per the AASM's COI policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's COI 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, focusing on patient-oriented, clinically relevant outcomes. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material of the accompanying systematic review. 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 (CST) 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 (AASM SR 2024). The TF then developed clinical practice recommendations according to the GRADE process.[20, 21] The TF assessed the following four 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 clinical practice guideline 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 clinical practice guidelines 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 GRADE 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** summarizes the recommendation for interventions in adult and pediatric populations.

TABLE 1 – Implications of Strong and Conditional Recommendations for Users of AASM Clinical Practice Guidelines

Strong Recommendation *"We recommend…"*	–	Almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.
Conditional Recommendation *"We suggest…"*	–	Most patients should receive 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.

TABLE 2 – Summary of Recommended Interventions in Adult Populations

ADULTS WITH RLS						
Intervention	**Strength of recommendation**	Presence of Improvements in Critical Outcomes meeting Clinical Significance Thresholds***			Presence of Complications meeting Clinical Significance Thresholds	
		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	N	Y	-	N
IV LMW iron dextran	Conditional for	Y	-	-	-	N
Ferrous sulfate	Conditional for	Y	-	-	-	Y
Dipyridamole	Conditional for	Y	-	-	-	N
Oxycodone	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

*Outcome was reported using an invalidated tool that could not be assessed for clinical significance.
-: outcome not reported
** Patients, who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select these medications for RLS treatment.
***CSTs can be found in the accompanying systematic review
Note: Recommendations are listed by strength and class of treatment, not in order of preference.

ADULTS WITH RLS and End Stage Renal Disease (ESRD)						
Intervention	**Strength of recommendation**	Presence of Improvements in Critical Outcomes meeting Clinical Significance Thresholds**			Presence of Complications meeting Clinical Significance Thresholds	
		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* Patients, who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select these medications for RLS treatments.
**CSTs can be found in the accompanying systematic review
Note: Recommendations are listed by strength and class of treatment, not in order of preference.

ADULTS WITH PLMD						
Intervention	**Strength of recommendation**	Presence of Improvements in Critical Outcomes meeting Clinical Significance Thresholds*				Presence of Complications meeting Clinical Significance Thresholds
		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
Note: Recommendations are listed by strength and class of treatment, not in order of preference.

PEDIATRIC POPULATION WITH RLS

Intervention	Strength of recommendation	Presence of Improvements in Critical Outcomes meeting Clinical Significance Thresholds*			Presence of Complications
		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

GOOD PRACTICE STATEMENT

The following good practice statements is based on expert consensus, and its implementation is necessary for appropriate and effective management of people with restless legs syndrome.

1. In all patients with clinically significant RLS, clinicians should regularly test serum iron studies including ferritin and iron with total iron binding capacity (transferrin saturation%). The test 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 $\leq$ 75 ng/ml or transferrin saturation < 20%, and with IV iron only if serum ferritin is between 75 ng/ml 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.[22]

2. The first step in the management of RLS should be addressing exacerbating factors, such as alcohol, caffeine, antihistaminergic, serotonergic, anti-dopaminergic medications, and untreated OSA.

3. RLS is common in pregnancy; prescribers should consider the pregnancy-specific safety profile of each treatment being considered.[23]

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, 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 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 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. Overall, the TF judged that majority of patients would use gabapentin enacarbil over no treatment with gabapentin enacarbil for RLS. Patients who are at a high risk of side effects with this class of medications may choose other treatment options.

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 improvements in disease severity and sleep quality 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. The treatment would not affect health equity. The intervention was feasible to implement. Based on the combination of these studies, extrapolation from RCT results from gabapentin enacarbil (same active ingredient as gabapentin), and the significant clinical experience of the TF with use of gabapentin, the TF judged that the majority of patients would use gabapentin over no treatment with gabapentin for RLS. 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. Overall, the TF judged that the majority of patients would use pregabalin over no treatment with pregabalin for RLS. 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 ferritin < 100 ng/ml or transferrin saturation < 20% (Strong recommendation, moderate certainty of evidence).

The TF identified 4 RCTs in which the pooled estimates demonstrated clinically significant improvements in disease severity and quality of life 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. Overall, the TF judged that the majority of patients would use IV iron ferric carboxymaltose over no treatment with IV iron ferric carboxymaltose for RLS.

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 ferritin < 100 ng/ml or transferrin saturation < 20% (Conditional recommendation, very low certainty of evidence).

The TF identified 1 observational study which demonstrated clinically significant improvements 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 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 low molecular weight 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. Overall, based on the combination of this study and extensive clinical experience of the TF with use of IV LMW iron dextran, the TF judged that the majority of patients would use IV LMW iron dextran over no treatment with IV LMW iron dextran for RLS.

Recommendation 6: In adults with RLS and a ferritin level of < 75 ng/ml or transferrin saturation < 20%, the AASM suggests the use of ferrous sulfate over no ferrous sulfate supplementation (Conditional recommendation, moderate certainty 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 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. Overall, the TF judged that the majority of patients would use ferrous sulfate over no treatment with ferrous sulfate for RLS.

Recommendation 7: 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. Overall, the TF judged that the majority of patients would use dipyridamole over no treatment with dipyridamole for RLS.

Recommendation 8: In adults with RLS, the AASM suggests the use of extended-release oxycodone over no extended-release oxycodone (Conditional recommendation, moderate certainty).
Remarks: TF recommendation might be extended to other opioids not formally studied in RCTs.

The TF identified 1 RCT, which demonstrated clinically significant improvement in 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 adverse events met clinical significance. Adverse effects included fatigue, somnolence, and dizziness. The TF acknowledged the additional risks of abuse, chemical dependence, and serious effects from overdose with long-term use, although significant clinical experience in patients treated and followed for RLS suggests that these risks are relatively low. The undesirable effect size was deemed small.

The overall certainty of evidence was moderate due to imprecision. The cost of extended-release oxycodone was considered moderate (though other formulations and other opioids vary significantly). The acceptability of the medication to key stakeholders would be varied. The extended-release oxycodone would probably reduce health equity. The intervention was feasible to implement. Overall, the TF judged that the majority of patients would use extended-release oxycodone over no treatment with extended-release oxycodone for RLS.

Recommendation 9: In adults with RLS, the AASM suggests the use of peroneal nerve stimulation over no peroneal nerve stimulation (Conditional recommendation, low certainty of evidence).

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity with small effect size. 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 low due to risk of bias and imprecision. The cost of the treatment was considered high. The treatment would probably reduce health equity. The intervention was probably feasible to implement. Overall, the TF judged that the majority of patients would use peroneal nerve stimulation over no treatment with peroneal nerve stimulation for RLS.

CONDITIONAL Recommendations Against Use

Recommendation 10: In adults with RLS, the AASM suggests against the standard use of levodopa (Conditional recommendation, very low certainty of evidence).
Remarks: Patients who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use) could select levodopa for RLS treatment.

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. Overall, the TF judged that the majority of patients would not use levodopa for treatment of RLS.

Recommendation 11: In adults with RLS, the AASM suggests against the standard use of pramipexole (Conditional recommendation, moderate certainty of evidence).
Remarks: Patients who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select pramipexole for RLS treatment.

The TF identified 17 RCTs and 7 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity, quality of life, and sleep quality with moderate effect size. All RCTs reported on the presence of adverse events leading to study withdrawal; the pooled estimate of 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. Overall, the TF judged that the majority of patients would not use pramipexole for treatment of RLS.

Recommendation 12: In adults with RLS, the AASM suggests against the standard use of transdermal rotigotine (Conditional recommendation, low certainty of evidence).

Remarks: Patients who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select transdermal rotigotine for RLS treatment.

The TF identified 8 RCTs and 3 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity, sleep quality, and quality of life with moderate effect size. All RCTs reported on the presence of adverse events leading to study withdrawal; the pooled estimates 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. Overall, the TF judged that the majority of patients would not use rotigotine for treatment of RLS.

Recommendation 13: In adults with RLS, the AASM suggests against the standard use of ropinirole (Conditional recommendation, moderate certainty of evidence).

Remarks: Patients who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select ropinirole for RLS treatment.

The TF identified 13 RCTs and 2 observational studies in which the pooled estimates demonstrated clinically significant improvement in disease severity and quality of life with a small effect size. The TF identified 8 RCTs that reported adverse events leading to study withdrawal; the pooled estimate for 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 estimates 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. Overall, the TF judged that the majority of patients would not use ropinirole for treatment of RLS.

Recommendation 14: 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. Overall, the TF judged that the majority of patients would not use bupropion for treatment of RLS.

Recommendation 15: 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 met clinical significance. Adverse effects included dizziness. The TF acknowledged additional risks not limited to hepatotoxicity and adverse hematopoetic 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. Overall, the TF judged that the majority of patients would not use carbamazepine for treatment of RLS.

Recommendation 16: 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 pre-post 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. Overall, the TF judged that the majority of patients would not use clonazepam for treatment of RLS.

Recommendation 17: In adults with RLS, the AASM suggests against the use of valerian (Conditional recommendation, 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 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. Overall, the TF judged that the majority of patients would not use valerian for treatment of RLS.

Recommendation 18: 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. Overall, the TF judged that the majority of patients would not use valproic acid for treatment of RLS.

STRONG Recommendations Against Use

Recommendation 19: 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 improvement in disease severity, quality of life, 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 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. Overall, the TF judged that the majority of patients would not use cabergoline for treatment of RLS.

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 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 materials.

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 subjects in each arm or an observational study with at least 5 subjects. 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 20: 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).

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 large effect size. These studies reported on the presence of adverse events leading to study withdrawal; the pooled estimate of 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. Overall, the TF judged that the majority of patients would use gabapentin over no treatment with gabapentin for RLS in the setting of ESRD.

Recommendation 21: 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. Overall, the TF judged that the majority of patients would use IV iron sucrose over no treatment with IV iron sucrose for RLS in the setting of ESRD.

Recommendation 22: 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. Overall, the TF judged that the majority of patients would use vitamin C over no treatment with vitamin C for RLS in the setting of ESRD.

CONDITIONAL Recommendations Against Use

Recommendation 23: In adults with RLS and ESRD, the AASM suggests against the standard use of levodopa (Conditional recommendation, low certainty of evidence).
Remarks: Patients, who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select levodopa for RLS treatment.

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. Overall, the TF judged that the majority of patients would not use levodopa for treatment of RLS in the setting of ESRD.

Recommendation 24: In adults with RLS and ESRD, the AASM suggests against the standard use of rotigotine (Conditional recommendation, very low certainty of evidence).
Remarks: Patients, who place a higher value on the reduction of restless legs symptoms in the short term and a lower value on adverse effects (particularly augmentation with long-term use), could select rotigotine for RLS treatment.

The TF identified 1 RCT, which demonstrated clinically significant improvement in disease severity, quality of life, and sleep quality 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. Overall, the TF judged that the majority of patients would not use rotigotine for treatment of RLS in the setting of ESRD.

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 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 subjects in each arm or an observational study with at least 5 subjects. 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 25: 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 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. Overall, the TF judged that the majority of patients would not use triazolam for treatment of PLMD.

Recommendation 26: 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 and 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. Overall, the TF judged that the majority of patients would not use valproic acid for treatment of PLMD.

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 subjects in each arm or an observational study with at least 5 subjects. 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 27: In children with RLS and a ferritin level of < 50 ng/ml, the AASM suggests the use of ferrous sulfate over no ferrous sulfate (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 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. Overall, the TF judged that the majority of pediatric patients would use ferrous sulfate over no treatment with ferrous sulfate for RLS.

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, 24, 25] RLS can cause significant morbidity and reduction in quality of life, 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, 26, 27] 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. [28]

Published concerns about dopaminergic augmentation of RLS symptoms from levodopa date back to the mid-1990s.[28] Heightened awareness of augmentation with long-term dopamine agonist use emerged in the early 2000s as their clinical use became widespread. [28-32] Furthermore, the occurrence of impulse control disorders in patients with RLS treated with dopamine agonists also raised concerns about long-term use of these agents. [33-35] 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 three major RLS organizations.[16] However, changes to clinical practice have been slow to reflect this shift away from dopamine agonists, as national data from 2017-18 demonstrated that 60% of medication-treated RLS patients were still prescribed dopamine agonists, often at doses exceeding FDA recommendations for RLS.[17] Although this Clinical Practice Guideline (CPG) may appear to many providers to represent a paradigm shift away from the use of dopamine agonists, it is in fact just one 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 and in clinical experience. 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. [33, 34] 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, clinical experience and a published RCT suggest that treatments such as gabapentin enacarbil can be less effective after prior long-term dopaminergic treatment. [36] Thus, this CPG suggests against the use of dopamine agonists or levodopa as standard treatments in adults with RLS. Nevertheless, their prescribing may be indicated in the context of short-term use in circumstances in which movement is restricted (e.g., plane travel), as well as with poor tolerability or lack of efficacy of other RLS therapies. In these special circumstances, dopaminergic medication prescribing should be accompanied by a monitoring of augmentation and impulse control disorders. Doses that exceed maximum FDA recommendations for RLS will accelerate these risks.

This CPG also has moved the triad of alpha-2-delta ligands (gabapentin, gabapentin enacarbil, and pregabalin) into the strongly recommended category based on the combination of multiple high-quality clinical trials and overwhelming clinical experience of their efficacy for RLS. This is now consistent with published consensus papers from 2016 and 2021. [15, 16]Nevertheless, this class of medications does have adverse effects which may influence the clinical decisions of prescribers and patients alike. In the clinical trials that met inclusion criteria, pregabalin, but not gabapentin or gabapentin enacarbil, was determined to have adverse effects leading to study withdrawal which exceeded our clinical significance threshold. Prominent adverse effects of the alpha-2-delta ligands in these clinical trials were dizziness and somnolence. Furthermore, adverse effects not assessed in these clinical trials are present. In those with opioid use disorder, there is increasing evidence that alpha-2-delta ligands are misused.[37] In such cases, the side effects of respiratory suppression and sedation from these two types of medications can be enhanced. For this reason, evaluation of risk factors for misuse is recommended prior to initiating alpha-2-delta ligands. There is also evidence that alpha-2-delta ligands can produce severe exacerbations of COPD, and thus this risk should be considered when prescribing these agents to those with RLS and COPD.[38]

Intravenous 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 alike. Routine screening of iron indices is an essential component of RLS patient care (optimal iron indices are different for people with RLS than the general adult population, with recommendation of both ferritin >100 ng/ml and transferrin saturation >20%).
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 co-morbidity to obtain this treatment. IV low molecular weight (LMW) iron dextran receives a conditional recommendation for its use. There was only one observational study using validated measures of RLS severity, but extensive clinical experience of its effectiveness as one of the most commonly utilized forms of iron in clinical practice for RLS supports the findings of this study. Conversely, high quality studies of IV iron sucrose in RLS failed to show a clinically significant benefit over placebo, and this 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 and dextran.[39] Nevertheless, one 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 along with IV LMW iron dextran for RLS in the setting of ESRD. At the time of this publication, there have not been significant trials of other high-dose formulations such as ferumoxytol and ferric derisomaltose, but these formulations are commonly used in clinical practice along with ferric carboxymaltose and iron dextran.

Oral iron supplementation with ferrous sulfate is suggested with a conditional recommendation based on limited RCT data but extensive clinical experience. Oral iron is poorly absorbed in those with ferritin > 50-75 ng/mL, unlike IV iron which does not rely on gastrointestinal absorption. [22] 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 intended 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 the 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. This risk is compounded by other central 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 individuals suggests that these risks are relatively low. [40-43] Similarly, retrospective and prospective observational studies demonstrate only small dose increases in a minority of RLS patients followed over extended periods (2 to 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 subjects, 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. [40-42] 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. [43] Therefore, selection of a particular opioid can be tailored to the individual patient based on side effect profile, pharmacokinetics, and other factors. It should be noted that two 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 largely 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. [44, 45] This medication has been long used for anti-platelet therapy in stroke and peripheral vascular disease, but there is biologic rationale as to why this medicine may work for RLS.

Peroneal nerve stimulation is a new non-invasive, non-pharmacological treatment, and it also receives a conditional recommendation from initial success in a short-term sham-controlled study and a longer observational extension. The wearable device is placed below the knees and provides stimulation to the peroneal nerve with tonic activation of innervated muscles. This can send afferent signals back to the brain to reduce RLS dysesthesias in a similar way to ambulation. [46] Though 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 adult special populations with RLS, high quality evidence was only available for patients with ESRD, with conditional recommendations for gabapentin, IV iron sucrose, and vitamin C, the latter with significantly less clinical experience and direct mechanism of action for RLS outside of anti-inflammatory properties. 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. [47] Despite the large body of evidence on symptoms and consequences of RLS in pediatrics, [48] 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 quality of life, sleep, and academic performance is necessary to assess treatment efficacy and identify necessary adjustments.

Periodic limb movement disorder (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. [49] 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 two 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. [50, 51]

This CPG used the rigorous GRADE methodology for meta-analysis, systematic review and recommendations. [20] Because of the common use of off-label treatments in RLS, there was at times a discrepancy between extensive clinical experience and absence of randomized clinical trials that posed some challenges in this CPG development process. Also, 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 non-validated 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 one 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 systems, interact with iron and dopamine to produce the symptoms of RLS. [44, 45, 52-58]

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 a downgrading of dopamine agonists in this CPG. This updated recommendation represents a substantial change in first-line treatment for RLS, as dopamine agonists constitute the majority of the FDA-approved medications for RLS. Since dopamine agonists remain commonly prescribed treatments 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. This trial approach has been used for treatment-resistant depression (see STAR*D studies) and 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 first-line 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, that 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 and LMW iron dextran in this CPG, further randomized testing of newer agents including ferumoxytol and ferric derisomaltose are 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 one RCT that used a non-validated metric which showed promising results.[59]

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. RLS is associated with cardiovascular disease in adults and attention deficit hyperactivity disorder in children. Determining whether or not long-term treatments which lessen RLS severity and improve sleep also decrease prevalent or incident cardiovascular disease in adults or behavioral outcomes in children has relevance both at the clinical and population levels. In addition, 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. Similarly, RLS is often comorbid with mood and anxiety disorders and pain syndromes, which present challenges to treatment. The most common treatments for mood and anxiety disorders (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. Additionally, RLS is prevalent in people with Parkinson 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.[60] 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 intravenous iron infusion and other pharmacological and non-pharmacological interventions.

Over the past few decades, there have been great strides made 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.

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