Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder

An American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment

INTRODUCTION

This systematic review provides supporting evidence for the accompanying clinical practice guideline [insert ref] on the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) in adults and children. This systematic review is an update to the previously published American Academy of Sleep Medicine (AASM) guideline on the treatment of RLS and PLMD in 2012.[1]

RLS is characterized by an uncomfortable urge to move, often associated with dysesthesias in the affected extremity, which occurs when at rest, predominantly in the evening and/or at night and is relieved temporarily with movement.[2] It often results in difficulty falling and/or staying asleep. Those with RLS may have frequent periodic limb movements during sleep but, by definition, cannot have PLMD; the diagnosis of RLS and PLMD are mutually exclusive. PLMD consists of periodic limb movements during sleep with resulting sleep disruption and/or daytime dysfunction, all occurring in the absence of RLS.[3]

The aims of the present systematic review are to assess (1) the efficacy of pharmacologic and nonpharmacologic interventions for the treatment of RLS and PLMD in both adults and children as well as in special populations such as chronic kidney disease/end-stage renal disease, (2) to evaluate the potential for adverse effects of these interventions, and (3) to identify gaps in the treatment research literature and offer recommendations for optimizing quality and uniformity of future investigations.

RLS is a disorder with both variable chronicity (from time limited to chronic) and severity (from occasional and mild to daily and severe). Roughly 2-3% of adults in the US and Europe have clinically important symptoms occurring at least twice per week with at least moderate distress. For these sufferers, the need for chronic RLS medical therapy is common. While our understanding of the efficacy of medical treatments for RLS as well as its pathophysiology have increased substantially in the past two to three decades, RLS treatment is currently perhaps most challenged by a delay in the change of clinical practice as this new information has emerged. This systematic review and its accompanying clinical practice guideline aim to align clinical practice and current evidence on the medical treatment of RLS and PLMD.

The development of new medications for the treatment of RLS has been slowed by our limited understanding of its pathophysiology. Despite this, several evidence-based treatments with distinct mechanisms of action exist, with demonstrated efficacy and unique side effect profiles. The alpha-2 delta ligands, gabapentin, gabapentin enacarbil and pregabalin, have efficacy in treating RLS, putatively through a mechanism of decreased glutamate release. [4] Brain iron deficiency, specifically in the striatum, appears central in the pathogenesis of RLS, having been demonstrated in imaging and post-mortem studies, potentially explaining the efficacy of iron administration. [5, 6] On the other hand, excess striatal dopamine appears to be secondary to brain iron deficiency.[7, 8] Despite dopamine being in excess in RLS, all dopaminergic agents are very effective, at least initially, in treating RLS symptoms. Over time, however, dopaminergic medications are commonly associated with a paradoxical worsening of RLS, a phenomenon termed augmentation. [9] This exposes a pathophysiology-treatment mismatch as the approach of using dopaminergic

medications to treat RLS was popularized during a time when the prevailing thought was that RLS was caused by a reduction of dopamine.[10]

Our understanding of RLS pathophysiology has been aided by its clinical responsiveness to low-dose opioids. This clinical observation made over 30 years ago has guided research which demonstrates reductions in the endogenous opioid, βendorphin, in post-mortem brain of RLS patients, perhaps validating the use of opioids to treat RLS.[11, 12]Other treatment options include peroneal nerve stimulation and dipyridamole. The diverse pharmacology of agents effective in treating RLS reflects the complexity of RLS pathophysiology, which despite much work, still needs clarification. Thus, it is likely and needed that other treatments for RLS which target novel biologic pathways could emerge.

RLS affects approximately 2% of children.[13] The identification of pediatric RLS poses specific challenges as children do not always present with the typical symptoms of leg discomfort or "urge" to move the legs. Instead, they express symptoms with their own words or actions (rubbing or scratching their legs), often leading to delays in diagnosis and treatment.[13] Studies assessing treatment options in children are scarce, and treatment usually consists of lifestyle modifications, iron supplementation, and possibly off-label medications.

PLMS, commonly seen in adults with RLS, may present differently in young children as isolated or non-periodic limb movements but when present, PLMS in children have shown, similarly to adults, high night-to-night variability, contributing to challenges in their identification and quantification. [14]

PLMD is a diagnosis of exclusion which requires that specific other sleep disorders (narcolepsy, untreated OSA, RBD, or RLS) cannot be present, and that medical/neurological/psychiatric disorders cannot better explain the periodic limb movements of sleep or nocturnal sleep disruption or daytime dysfunction. Given the necessity of this extensive clinical evaluation, which is often not performed in clinical practice or in research studies, the true prevalence of PLMD remains uncertain. Beyond this, there are few, if any, high quality randomized clinical trials for PLMD treatment and only a small portion of the systematic review will discuss treatment of PLMD.

This systematic review provides supporting evidence for the accompanying clinical practice guideline for the treatment of RLS and PLMD in adults and children. It provides details on outcomes and adverse effects related to different treatments which the Task Force reviewed in order to develop the proposed guidelines, but that were not included in the guideline proper. Treatment and adverse event outcomes were considered and categorized as critical or important. Critical outcomes included disease severity, quality of life, sleep quality, augmentation, and unwanted side effects leading to study withdrawal. Important outcomes included PLM frequency, sleep latency, and wake after sleep onset. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to determine guidelines based upon assessment of four components: certainty of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described in more detail below.

METHODS

Expert Task Force

The AASM commissioned a task force (TF) comprised of board-certified sleep medicine specialists with proficiency in the treatment of adults and children with RLS and PLMD to develop this systematic review. 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 this paper. 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 COI are listed in the Disclosures section.

PICO Questions and Clinical Significance Thresholds

PICO (**P**atient, **I**ntervention, **C**omparison, and **O**utcomes) questions were developed to assess the efficacy of interventions based on a review of the existing AASM practice parameters on the treatment of RLS and PLMD, and a review of systematic reviews, meta-analyses, and guidelines published since 2012. The AASM Board of Directors (BOD) approved the final list of PICO questions presented in **Table 1** before the literature searches were conducted. Through consensus, the TF then developed a list of patient-oriented, clinically relevant outcomes to determine the efficacy of the interventions. The TF rated the relative importance of each outcome to determine which outcomes were critical versus important for decision-making. A summary of these outcomes by PICO is presented in **Table 2**.

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. Standardized mean differences were used when the TF concluded that the interpretation of effect sizes would be more meaningful. The CST was defined as the minimum level of improvement in the outcome of interest that would be considered clinically important to clinicians and patients. CSTs were determined based on a TF literature review of commonly used thresholds. When no clearly established threshold values could be determined, the TF used their clinical judgment and experience to establish a CST based on consensus. A summary of the CSTs for the clinical outcome measures is presented in **Table 3**.

When considering RLS severity, priority was given to the International RLS Study Group Severity scale (IRLS) scores. The IRLS scale is the most frequently used scale to assess severity of RLS and treatment effects.

Table 1 - PICO Questions

1	**Population:** Adults with RLS **Intervention:** Pharmacological and non-pharmacological treatments **Comparison:** Placebo or no treatment **Outcomes:** Disease severity, sleep quality, quality of life (QOL), sleep latency, wake after sleep onset (WASO), PLM frequency, adverse effects
2	**Population:** Adults with RLS and ESRD **Intervention:** Pharmacological and non-pharmacological treatments **Comparison:** Placebo or no treatment **Outcomes:** Disease severity, sleep quality, quality of life (QOL), sleep latency, wake after sleep onset (WASO), PLM frequency, adverse effects
3	**Population:** Adults with PLMD **Intervention:** Pharmacological and non-pharmacological treatments **Comparison:** Placebo or no treatment **Outcomes:** Sleep quality, quality of life (QOL), excessive daytime sleepiness, wake after sleep onset (WASO), PLM frequency, adverse effects, work/school performance

4	**Population:** Children with RLS **Intervention:** Pharmacological and non-pharmacological treatments **Comparison:** Placebo or no treatment **Outcomes:** Disease severity, sleep quality, quality of life (QOL), PLM frequency, adverse effects, work/school performance, resolution of ADHD symptoms
5	**Population:** Special population of children with RLS **Intervention:** Pharmacological and non-pharmacological treatments **Comparison:** Placebo or no treatment **Outcomes:** Disease severity, sleep quality, quality of life (QOL), fatigue, PLM frequency, adverse effects, resolution of ADHD symptoms
6	**Population:** Children with PLMD **Intervention:** Various pharmacological and non-pharmacological treatments **Comparison:** Placebo or no treatment **Outcomes:** Sleep quality, quality of life (QOL), excessive daytime sleepiness, PLM frequency, adverse effects, work/school performance, resolution of ADHD symptoms

Table 2 –Outcomes by PICO Question

Outcomes	PICO Question #					
	1	2	3	4	5	6
Excessive Sleepiness			√			√*
Disease Severity	√	√		√	√*	
Quality of Life	√	√	√	√	√	√
Sleep quality	√	√	√	√	√	√
Sleep Latency	√*	√*				
WASO	√*	√*	√*			
Fatigue					√*	
Work/School Performance			√	√*		√
Resolution of ADHD Symptoms				√*	√*	√*
PLM Frequency	√*	√*	√*	√*	√*	√*
Adverse Effects	√	√	√	√	√	√

*Outcomes considered important but not critical for decision-making.

Table 3 – Summary of Clinical Significance Thresholds for Outcome Measures

Outcome Measure[1]	Clinical Significance Threshold*†
Excessive sleepiness	---
ESS	-2 points [Insert Antic 2009, Craig 2012]
Quality of Life	---
RLS QOL (Abetz)	+5 points
RLS QOL (Kohnen)	-2.5 points
RLS QLI	+5 points [Insert Atkinson, MJ 2004]
Sleep quality	---
PSQI	-3 points [Insert Buysee 2011]
MOS	SMD = 0.2
Disease severity	---
*IRLS	-3 points
RLS-6	SMD = 0.2
CGI-I	15% responders

CGI-S PGI-I JHRLSS ASRS	0.5 points 15% responders +1 point -3 points
Sleep latency (PSG)	-10 minutes
WASO (PSG)	-10 minutes
Fatigue FSS SF-36 vitality	--- -0.25 points +5 points
PLM Frequency PLMI	--- ---
School/work performance WPAI GPA Attendance	--- --- -1 point -30%
Adverse effects Adverse events leading to study withdrawal Specific adverse events	--- 50/1000 patients 50/1000 patients
Resolution of ADHD symptoms	---

*References used to inform task force consensus

† The clinical significance thresholds are for comparison of pre- versus post-treatment effects as well as between intervention and control.

*TF gave higher value to the IRLS scale for disease severity

ESS – Epworth Sleepiness Scale; RLS – Restless Legs Syndrome; RLS QOL – RLS Quality of Life; RLS QLI – RLS Quality of Life Instrument; PSQI – Pittsburgh Sleep Quality Index; MOS – Medical Outcomes Sleep Scale; SMD = standardized mean difference; IRLS – International Restless Legs Syndrome Study Group Rating Scale; RLS-6 – Restless Legs Syndrome-6 Scale; CGI-I – Clinical Global Impressions-Improvement Scale; CGI-S – Clinical Global Impressions-Severity Scale; PGI-I – Patient Global Impression of Improvement Scale; JHRLSS – Johns Hopkins Restless Legs Severity Scale; ASRS – Adult ADHD [Attention Deficit Hyperactivity Disorder] Self-Report Scale; PSG – polysomnography; WASO – wake after sleep onset; FSS – Fatigue Severity Scale; SF-36 – 36-Item Short Form Health Survey questionnaire; PLM – periodic limb movement; PLMI – periodic limb movement index; WPAI – Work Productivity and Activity Impairment questionnaire; GPA – grade point average; TF – task force.

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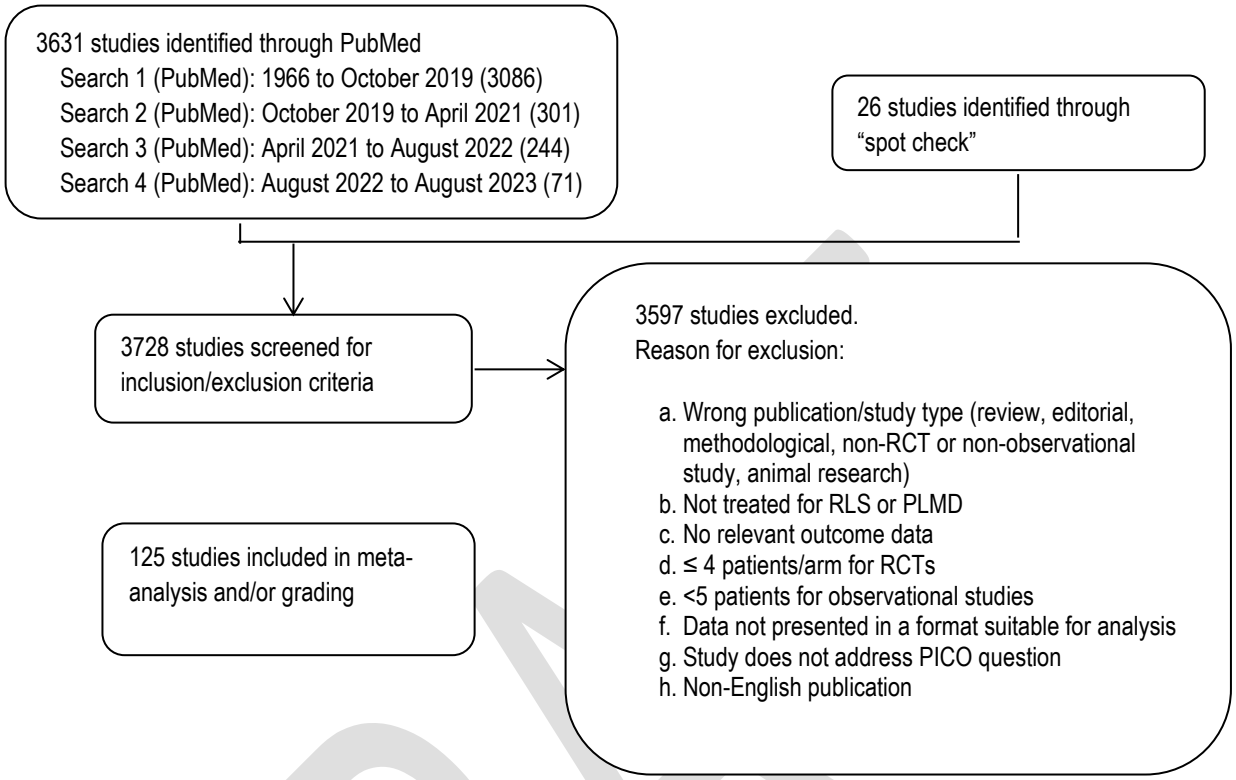
Literature Searches, Evidence Review, and Data Extraction

The TF performed an extensive review of the scientific literature to retrieve articles that addressed the PICO questions. Literature searches were performed by the TF to address each PICO question using the PubMed database (see **Figure 1**). The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material.

The initial literature search in PubMed was performed in October 2019. Additional searches were performed in April 2021, August 2022, and August 2023 to update the evidence during completion of the draft. These searches identified a total of 3,728 articles. Lastly, the TF reviewed previously published guidelines, systematic reviews, and meta-analyses to spot check for references that may have been missed during the prior searches. The TF identified 26 additional articles that were screened for inclusion/exclusion in the guideline.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material. All studies were reviewed based on inclusion/exclusion criteria by two TF members. Any discrepancies between the reviewers were discussed and resolved by the two reviewers or a third TF member. A total of 125 studies were determined to be suitable for meta-analysis and/or grading.

Figure 1 – Evidence Base Flow Diagram



Statistical methods, meta-analysis, and interpretation of clinical significance

Meta-analysis was performed on outcomes of interest, when possible, for each PICO question (see **Table 1**). Comparisons of interventions to controls and/or assessment of efficacy before and after treatment of RLS or PLMD were performed. The analyses were performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. Post-treatment data from each arm were used for meta-analysis of RCTs when change values were not reported and baseline values between the two study groups were statistically similar. Pre-and posttreatment data were used for meta-analyses of observational studies. The pooled results for each continuous outcome measure were usually expressed as the mean difference between the intervention and control for RCTs or pre-treatment versus posttreatment for observational studies; however, for some outcomes where individual component scales were pooled, a standardized mean difference (SMD) or effect size was determined. The pooled results for dichotomous outcome measures were expressed as the risk ratio or risk difference between the intervention and comparator or pre- versus posttreatment. The relative risk data were converted to an absolute risk estimate expressed as the number of events/1000 patients treated. All analyses were performed using a random effects model with results displayed as a forest plot. Interpretation of clinical significance for the outcomes of interest was conducted by comparing the mean difference in effect size, or the risk difference for dichotomous outcomes, of each treatment approach to the CST (see **Table 3**).

GRADE Assessment for Developing Recommendations

The assessment of evidence quality was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. [Insert Guyatt, 2011; Morgenthaler 2016] The TF assessed the following four components to determine the direction and strength of a recommendation: certainty of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below.

1. Certainty of evidence: Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval crosses the CST and/or sample size < 100 participants), inconsistency ($I^2 \geq 50\%$), indirectness (study population vs target patient population), and risk of publication bias, the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical patients with RLS or PLMD would see. The quality of the evidence was based on outcomes that the TF deemed critical for decision making; important outcomes are not considered when determining the overall certainty of evidence.

2. Benefits vs. Harms: Based on the meta-analysis of adverse effects reported within the accepted literature and on the clinical expertise of the TF, the TF determined whether the beneficial outcomes of using each intervention outweighed any harms.

3. Patient values and preferences: Based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences, the TF determined if patient values and preferences would be generally consistent across most patients, and if patients would use the intervention based on the relative harms and benefits identified.

4. Resource use: Based on the clinical expertise of the TF members, the TF determined whether the accessibility and costs associated with each treatment approach compared favorably to those associated with alternative treatments. Information on costs to both patients and the health care system, impact on health equity, acceptability and feasibility to implement the treatments were considered.

A summary of each GRADE domain is provided after the detailed evidence review.

Public Comment and Final Approval

A draft of the guideline and systematic review was made available for public comment for a four-week period on the AASM website. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the comments. The revised guideline and systematic review were submitted to the AASM BOD for subsequent approval.

The AASM expects this systematic review to have an impact on professional behavior, patient outcomes, and possibly health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

RESULTS

The aims of the current literature reviews and data analyses were focused on addressing 6 questions to assess the efficacy of various interventions to treat RLS and PLMD. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. All figures and a summary of the study characteristics can be found in the supplemental materials. All values of the critical outcomes results are reported

in the following text. For important outcomes results, values are only reported if the results met the clinical significance threshold. Each evidence summary is accompanied by a discussion of the certainty of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the recommendations provided in the accompanying clinical practice guideline. [insert ref] The interventions below are listed in alphabetical order.

The following interventions are those for which recommendations were made in the accompanying clinical practice guideline.

PICO 1: Adults with RLS

Gabapentin enacarbil

A total of 8 RCTs [15-22] and 2 observational studies[23, 24] investigated the use of gabapentin enacarbil in adults with RLS to improve one or more of the following outcomes: disease severity, QOL, sleep quality, sleep latency, WASO, PLM frequency, and unwanted side effects. Participants in the RCTs had a mean age of 50 years (56% female) and were diagnosed with moderate to severe RLS. Participants received dosages of gabapentin enacarbil from 600mg - 2400mg. Three of the trials used a crossover design, with patients serving as their own controls, and the remaining five trials had separate placebo control groups. The observational studies were before-and-after treatment design investigating participants with moderate-to-severe RLS, receiving dosages of 300mg - 1500mg. Meta-analyses were performed to assess the efficacy of gabapentin enacarbil as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S1** through **Figure S19**. A summary of findings table is provided in the supplemental material, **Table S1**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of gabapentin enacarbil to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of gabapentin enacarbil to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 7 RCTs[15, 17, 18, 20-22, 25] including a total of 1511 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -4.93 points (95% CI: -6.85 to -3.02 points) as measured by the IRLS (see supplemental material, **Figure S1**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the IRLS was also evaluated using a meta-analysis of 2 observational studies.[23, 24] of 148 participants. The duration of patient follow-up after treatment ranged from 8 to 52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -12.64 points (95% CI: -24.53 to -0.76 points) as measured by the IRLS (see supplemental material, **Figure S2**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the CGI-I was evaluated using a meta-analysis of 7 RCTs.[16-22] in 1632 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 34% (95% CI: 24 to 45%) as measured by the CGI-I (see supplemental material, **Figure S3**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the CGI-I was also evaluated using a meta-analysis of 2 observational studies.[23, 24] in 443 participants. The duration of patient follow-up after treatment ranged from 12 to 52 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 83% (95% CI: 76 to 90%) as measured by the CGI-I (see supplemental material, **Figure S4**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the PGI was evaluated using a meta-analysis of 5 RCTs.[12, 17-19, 25] in 1061 participants. The duration of patient follow-up after treatment ranged from 3 to 12 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 34% (95% CI: 16 to 53%) as measured by the PGI (see supplemental material, **Figure S5**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the PGI was also evaluated using a meta-analysis of 2 observational studies. [23, 24] in 440 participants. The duration of patient follow-up after treatment ranged from 12 to 52 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 83% (95% CI: 76 to 91%) as measured by the PGI (see supplemental material, **Figure S6**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the CGI-S was evaluated using an analysis of 1 RCT[15] in 78 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant decrease in disease severity of -1.20 points (95% CI: -1.67 to -0.73 points) as measured by the CGI-S (see supplemental material, **Figure S7**).

The efficacy of gabapentin enacarbil to reduce disease severity as measured by the RLS-6 was evaluated using an analysis of 1 RCT[15] in 78 participants. The duration of patient follow-up after was 2 weeks. The analysis demonstrated a clinically significant decrease in disease severity reporting a standardized mean difference of -0.45 (95% CI: -0.90 to -0.0) as measured by the RLS-6 (see supplemental material, **Figure S8**).

The certainty of evidence for disease severity ranged from very low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of gabapentin enacarbil to improve QOL was evaluated from an analysis of 1 RCT[17] that reported on the RLS QOL – Abetz scale in 221 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant improvement in QOL of 7.30 points (95% CI: 2.78 to 11.82) as measured by the RLS QOL – Abetz scale (see supplemental material, **Figure S9**). The certainty of evidence was moderate due to imprecision.

SLEEP QUALITY: The efficacy of gabapentin enacarbil to improve sleep quality was evaluated based on an analysis of 1 RCT[15] that reported on the Medical Outcomes Study Sleep (MOSS) scale in 78 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant improvement reporting a standardized mean difference of 0.59 (95% CI: 0.14 to 1.04) as measured by the MOSS scale (see supplemental material, **Figure S10**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 8 RCTs[15, 17-22, 25] reported on the total adverse events that led to study withdrawal in a total of 1729 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of adverse events leading to study

withdrawal of 2.2 (95% CI: 1.21 to 3.98) with an absolute risk of 48 events/1000 patients (95% CI: 26 to 87 events/1000 patients) with use of gabapentin enacarbil (see supplemental material, **Figure S11**).

A meta-analysis of 2 observational studies[23, 24] reported the risk of unwanted side effects and total adverse events that led to study withdrawal in 508 participants. The duration of patient follow-up after treatment ranged from 12 to 52 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.13 (95% CI: 0.10 to 0.16) with an absolute risk of 130 events/1000 patients (95% CI: 10 to 16 events/1000) with use of gabapentin enacarbil (see supplemental material, **Figure S12**).

A meta-analysis of 8 RCTs[15, 17-22, 25]reported on the incidence of somnolence in a total of 1733 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of somnolence of 3.41 (95%: 1.92 to 6.05) with an absolute risk of 176 events/1000 patients (95% CI: 66 to 366 events/1000 patients) with use of gabapentin enacarbil (see supplemental material, **Figure S13**).

An analysis of 1 observational study[24] reported on the incidence of somnolence in 182 participants. The duration of patient follow-up after treatment was 52 weeks. The analysis demonstrated a clinically significant risk difference of 0.41 (95% CI: 0.34 to 0.48) with an absolute risk of 410 events/1000 patients (95% CI: 340 to 480 events/1000) with use of gabapentin enacarbil (see supplemental material, **Figure S14**).

A meta-analysis of 8 RCTs[15, 17-22, 25]reported on the incidence of dizziness in a total of 1733 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of dizziness of 4.57 (95%: 3.07 to 6.80) with an absolute risk of 150 events/1000 patients (95% CI: 87 to 241 events/1000 patients) with use of gabapentin enacarbil (see supplemental material, **Figure S15**).

An analysis of 1 observational study[24] reported on the incidence of dizziness in 182 participants The duration of patient follow-up after treatment was 52 weeks. The analysis demonstrated a clinically significant risk difference of 0.46 (95% CI: 0.39 to 0.53) with an absolute risk of 460 events/1000 patients (95% CI: 390 to 530 events/1000) with use of gabapentin enacarbil (see supplemental material, **Figure S16**).

The certainty of evidence for unwanted side effects ranged from high to low due to risk of bias associated with observational studies and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of gabapentin enacarbil: PLM frequency, sleep latency, and WASO.

PLM FREQUENCY: The efficacy of gabapentin enacarbil to decrease PLM frequency was evaluated using a meta-analysis of 2 RCTs.[18, 22] in 330 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a decrease of -8.38 PLMs/hour (95% CI: -14.03 to -2.72 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S17**). The clinical significance threshold for this outcome was not determined as the TF could not reasonably estimate a threshold for this measure.

SLEEP LATENCY: The efficacy of gabapentin enacarbil to decrease sleep latency was evaluated using a meta-analysis of 2 RCTs[18, 22] in 330 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks.

Meta-analysis demonstrated a non-clinically significant decrease of -2.44 minutes (95% CI: -8.16 to 3.28 minutes) (see supplemental material, **Figure S18**). The certainty of evidence was moderate due to imprecision.

WASO: The efficacy of gabapentin enacarbil to decrease WASO was evaluated using a meta-analysis of 2 RCTs[18, 22] in 330 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of -28.34 minutes (95% CI: -39.91 to -16.77 minutes) with gabapentin enacarbil (see supplemental material, **Figure S19**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of gabapentin enacarbil in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S1**).

Benefits vs harms

The potential benefits of gabapentin enacarbil in adults with RLS include a clinically significant improvement in disease severity, QOL, sleep quality, and WASO. The potential harms include a clinically significant risk of somnolence and dizziness that may or may not resolve over time. Other side effects including headache, nasopharyngitis, nausea, fatigue, diarrhea, and vertigo have been reported. Based on their combined clinical experience, the TF judged that the potential benefits of gabapentin enacarbil in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for gabapentin enacarbil is $14.45 for a 300 mg tablet and $14.41 for a 600 mg tablet.[26] The TF judged these costs are large.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with gabapentin enacarbil.

Gabapentin

A total of 2 RCTs[26-28] and 4 observational studies[29-32] investigated the use of gabapentin in adults with RLS to improve one or more of the following outcomes: disease severity, QOL, sleep quality, sleep latency, WASO, PLM frequency, and side effects.. Participants in the RCTs received dosages of gabapentin starting at 300 mg or 600 mg with up-titration for symptom relief. Participants had a mean age of 56 years (69% female). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving dosages of 300 mg – 2400 mg for 1 week to 10 months. Meta-analyses were performed to assess the efficacy of gabapentin as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S20** through **Figure S35**. A summary of findings table is provided in the supplemental material, **Table S2**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of gabapentin to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of gabapentin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 RCT[27] in 44 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -8.40 points (95% CI: -12.0 to -4.8 points) as measured by the IRLS (see supplemental material, **Figure S20**).

The efficacy of gabapentin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 3 observational studies[30-32] in 33 participants. The duration of patient follow-up after treatment ranged from 2 to 10 months. The meta-analysis demonstrated a clinically significant reduction in disease severity of -9.77 points (95% CI: -12.35 to -7.2 points) as measured by the IRLS (see supplemental material, **Figure S21**).

The efficacy of gabapentin to reduce disease severity as measured by the CGI-S was evaluated using an analysis of 1 RCT[27] in 44 participants. The duration of patient follow-up after treatment was 6 weeks. The analysis demonstrated a clinically significant decrease in disease severity of -1.1 points (95% CI: -1.93 to -0.27 points) as measured by the CGI-S (see supplemental material, **Figure S22**).

The certainty of evidence for disease severity ranged from moderate to low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of gabapentin to improve QOL was evaluated from an analysis of 1 observational study[30] that reported on the RLS QLI scale in 9 participants. The duration of patient follow-up after treatment was 10 months. The analysis demonstrated a non-clinically significant improvement in QOL of 1.6 points (95% CI: -0.12 to 3.32) as measured by the RLS QLI scale (see supplemental material, **Figure S23**). The certainty of evidence was very low due to imprecision.

SLEEP QUALITY: The efficacy of gabapentin to improve sleep quality was evaluated based on an analysis of 1 RCT[27] in 44 participants that reported on the Pittsburgh Sleep Quality Index (PSQI) scale. The duration of patient follow-up after treatment was 6 weeks. The analysis demonstrated a non-clinically significant improvement in sleep quality of -2.90 points (95% CI: -4.02 to -1.78) as measured by the PSQI scale (see supplemental material, **Figure S24**).

The efficacy of gabapentin to improve sleep quality was evaluated based on an analysis of 2 observational studies[30, 32] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in 25 participants. The duration of patient follow-up after treatment ranged from 2 to 10 months. The analysis demonstrated a non-clinically significant improvement in sleep quality of -3.73 points (95% CI: -10.68 to 3.22) as measured by the PSQI scale (see supplemental material, **Figure S25**).

The certainty of evidence for sleep quality ranged from low to moderate due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: A meta-analysis of 2 RCTs[27, 28] reported on the total adverse events that led to study withdrawal. There was a total of 64 participants in the studies. The duration of patient follow-up after treatment was up to 6 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to

study withdrawal of 0.0 (95% CI: -0.04 to 0.04) with an absolute risk of 0 events/1000 patients (95% CI: -40 to 40 events/1000 patients) with use of gabapentin (see supplemental material, **Figure S26**).

A meta-analysis of 4 observational studies[29-32] reported on the total adverse events that led to study withdrawal. There were a total of 50 participants in the studies. The duration of patient follow-up after treatment ranged from 2 to 10 months. The meta-analysis demonstrated a clinically significant risk difference of 0.06 (95% CI: -0.03 to 0.15) with an absolute risk of 60 events/1000 patients (95% CI: -30 to 150 events/1000) with use of gabapentin (see supplemental material, **Figure S27)**.

A meta-analysis of 1 RCT[27] reported on the incidence of somnolence. There was a total of 48 participants in the study. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.09 (95%: -0.05 to 0.22) with an absolute risk of 90 events/1000 patients (95% CI: -50 to 220 events/1000 patients) with use of gabapentin (see supplemental material, **Figure S28**).

An meta-analysis of 3 observational studies[29-31] reported on the incidence of somnolence. There was a total of 26 participants in the studies. The duration of patient follow-up after treatment ranged from 6 to 10 months. The analysis demonstrated a clinically significant risk difference of 0.16 (95% CI: -0.01 to 0.32) with an absolute risk of 160 events/1000 patients (95% CI: -10 to 320 events/1000) with use of gabapentin (see supplemental material, **Figure S29**).

A meta-analysis of 3 observational studies[29-31] that reported on the incidence of dizziness. There was a total of 26 participants in the studies. The duration of patient follow-up after treatment ranged from 6 to 10 months. The meta-analysis demonstrated a clinically significant risk difference of 0.13 (95%: -0.09 to 0.34) with an absolute risk of 130 events/1000 patients (95% CI: -90 to 340 events/1000 patients) with use of gabapentin (see supplemental material, **Figure S30**).

Analysis of 1 RCT[27] that reported on the incidence of augmentation. There was a total of 48 participants in the study. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of 0.00 (95%: -0.08 to 0.08) with an absolute risk of 0 events/1000 patients (95% CI: -80 to 80 events/1000 patients) with use of gabapentin (see supplemental material, **Figure S31**).

The certainty of evidence for unwanted side effects ranged from very low due to risk of bias associated with observational studies and imprecision to high.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of gabapentin: PLM frequency, sleep latency, and WASO.

PLM FREQUENCY: The efficacy of gabapentin to decrease PLM frequency was evaluated using a meta-analysis of 2 RCTs. [27, 28] There was a total of 64 participants in the studies. The duration of patient follow-up after treatment was up to 6 weeks. The meta-analysis demonstrated a decrease of -9.2 PLMs/hour (95% CI: -17.0 to -1.3 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S32**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

The efficacy of gabapentin to decrease PLM frequency was evaluated using a meta-analysis of 2 observational studies.[30, 31] There was a total of 17 participants in the studies. The duration of patient follow-up after treatment was 10 months. The meta-analysis demonstrated a decrease of -17.0 PLMs/hour (95% CI: -31.8 to -2.3 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S33**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

SLEEP LATENCY: The efficacy of gabapentin to decrease sleep latency was evaluated using a meta-analysis of 2 RCTs.[27, 28] There was a total of 64 participants in the studies. The duration of patient follow-up after treatment was up to 6 weeks. Meta-analysis demonstrated a non-clinically significant decrease of -8.2 minutes (95% CI: -16.9 to 0.5 minutes) (see supplemental material, **Figure S34**).

WASO: The efficacy of gabapentin to decrease WASO was evaluated using analysis of 1 RCT.[28] There was a total of 80 patients in the study. The duration of patient follow-up after treatment was not reported. Meta-analysis demonstrated a clinically significant decrease in WASO of -60.5 minutes (95% CI: -86.7 to -34.3 minutes) with gabapentin (see supplemental material, **Figure S35**).

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of gabapentin in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S2**).

Benefits vs harms

The potential benefits of gabapentin in adults with RLS include a clinically significant reduction in disease severity and WASO. The potential harms include a clinically significant risk of somnolence and dizziness that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential benefits of gabapentin in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for gabapentin ranges from $0.03 for a 100 mg capsule to $9.20 for a 600 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with gabapentin.

Pregabalin

A total of 3 RCTs[33-35] investigated the use of pregabalin in adults with RLS to improve one or more of the following outcomes: disease severity, QOL, sleep quality, WASO, and unwanted side effects. Participants in a dose-finding RCT received 50mg – 450mg pregabalin while the remaining RCTs participants received 300mg pregabalin. Participants in the RCTs had a mean age of 54 years (62% female) and were diagnosed with moderate to severe RLS. Meta-analyses were performed to assess the efficacy of pregabalin as a treatment for adults with RLS. The

meta-analyses are provided in the supplemental material, **Figure S36** through **Figure S42**. A summary of findings table is provided in the supplemental material, **Table S3**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of pregabalin to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of pregabalin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 RCTs[33, 34] in a total of 486 participants. The duration of patient follow-up after treatment ranged from 6 to 52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -4.8 points (95% CI: -6.2 to -3.4 points) as measured by the IRLS (see supplemental material, **Figure S36**). The certainty of evidence for disease severity was high.

QOL: The efficacy of pregabalin to improve QOL was evaluated from an analysis of 1 RCT[34] that reported on the RLS-QOL Abetz scale in a total of 349 participants. The duration of patient follow-up after treatment was 52 weeks. The analysis demonstrated a non-clinically significant improvement in QOL of 4.6 points (95% CI: 2.0 to 7.2 points) as measured by the RLS-QOL Abetz scale (see supplemental material, **Figure S37**). The certainty of evidence was moderate due to imprecision.

SLEEP QUALITY: The efficacy of pregabalin to improve sleep quality was evaluated based on an analysis of 2 RCTs[33, 35]that reported on the Medical Outcomes Study Sleep (MOSS) scale in a total of 282 participants. The duration of patient follow-up after treatment ranged from 4 to 6 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of 0.4 points (95% CI: 0.1 to 0.7 points) as measured by the MOSS scale (see supplemental material, **Figure S38**). The certainty of evidence for sleep quality was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 3 RCTs[33-35] reported on the total adverse events that led to study withdrawal in a total of 585 participants. The duration of patient follow-up after treatment ranged from 4 to 52 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.12 (95% CI: -0.04 to 0.29) with an absolute risk of 120 events/1000 patients (95% CI: -40 to 290 events/1000 patients) with use of pregabalin (see supplemental material, **Figure S39**).

A meta-analysis of 3 RCTs[33-35] reported dizziness as a side effect in a total of 705 participants. The duration of patient follow-up after treatment ranged from 4 to 52 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.18 (95%: 0.12 to 0.25) with an absolute risk of 180 events/1000 patients (95% CI: 120 to 250 events/1000 patients) with use of pregabalin (see supplemental material, **Figure S40**).

A meta-analysis of 3 RCTs[33-35] also reported somnolence in a total of 646 participants. The duration of patient follow-up after treatment ranged from 4 to 52 weeks. The analysis demonstrated a clinically significant risk difference of 0.17 (95% CI: 0.10 to 0.23) with an absolute risk of 170 events/1000 patients (95% CI: 100 to 230 events/1000) with use of pregabalin (see supplemental material, **Figure S41**).
The certainty of evidence for adverse effects ranged from high to moderate due to imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of pregabalin: WASO.

WASO: The efficacy of pregabalin to decrease WASO was evaluated using a meta-analysis of 1 RCT[35] in a total of 145 participants. The duration of patient follow-up after treatment was 4 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of -27.1 minutes (95% CI: -38.7 to -15.5 minutes) with pregabalin (see supplemental material, **Figure S42**). The certainty of evidence for WASO was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of pregabalin in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S3**).

Benefits vs harms

The potential benefits of pregabalin in adults with RLS include a clinically significant improvement in disease severity, sleep quality and WASO. The potential harms include a clinically significant risk of somnolence and dizziness that may or may not resolve over time. Other side effects including weight gain, peripheral edema, fatigue, and vertigo have been reported.[36]. Based on their combined clinical experience, the TF judged that the potential benefits of pregabalin in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for pregabalin ranges from $0.08 for a 75 mg capsule to $8.25 for a 300 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with pregabalin.

Intravenous Iron (IV) Ferric Carboxymaltose

A total of 4 RCTs[37-40] investigated the use of intravenous iron (IV) ferric carboxymaltose in adults with RLS to improve one or more of the following outcomes: disease severity, QOL, sleep quality, and adverse effects. Participants in the RCTs received 500mg – 1500mg of IV ferric carboxymaltose and had a mean age of 52 years (79% female). Meta-analyses were performed to assess the efficacy of intravenous iron (IV) as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S43** through **Figure S48**. A summary of findings table is provided in the supplemental material, **Table S4**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV ferric carboxymaltose to treat adults with RLS: disease severity, QOL, sleep quality, and adverse effects.

DISEASE SEVERITY: The efficacy of IV ferric carboxymaltose to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 4 RCTs [37-40] in a total of 219 participants. The duration of patient follow-up after treatment ranged from 4 to 52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -7.0 points (95% CI: -12.1 to -1.8 points) as measured by the IRLS (see supplemental material, **Figure S43**).

The efficacy of IV ferric carboxymaltose to reduce disease severity as measured by the CGI-I was evaluated using a meta-analysis of 2 RCTs[37, 40] in a total of 53 participants. The duration of patient follow-up after treatment ranged from 4 to 24 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 30% (95% CI: 16 to 44%) as measured by the CGI-I (see supplemental material, **Figure S44**).

The efficacy of IV ferric carboxymaltose to reduce disease severity as measured by the PGI was evaluated using a meta-analysis of 1 RCT[37] in a total of 40 participants. The duration of patient follow-up after treatment was 24 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 37% (95% CI: 12 to 63%) as measured by the PGI (see supplemental material, **Figure S45**). The certainty of evidence for disease severity ranged from moderate due to imprecision to high.

The certainty of evidence for disease severity ranged from moderate to high due to imprecision.

QOL: The efficacy of IV ferric carboxymaltose to improve QOL was evaluated from an analysis of 3 RCTs[37-39] that reported on the RLS-QOL Abetz scale in a total of 136 participants. The duration of patient follow-up after treatment ranged from 6 to 52 weeks. The analysis demonstrated a clinically significant improvement in QOL of 11.1 points (95% CI: -0.3 to 22.5 points) as measured by the RLS-QOL Abetz scale (see supplemental material, **Figure S46**). The certainty of evidence was moderate due to imprecision.

SLEEP QUALITY: The efficacy of IV ferric carboxymaltose to improve sleep quality was evaluated based on an analysis of 2 RCTs[38, 39] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 93 participants. The duration of patient follow-up after treatment ranged from 6 to 52 weeks. The analysis demonstrated a non-clinically significant improvement in sleep quality of -2.5 points (95% CI: -9.4 to 4.4 points) as measured by the PSQI scale (see supplemental material, **Figure S47**). The certainty of evidence for sleep quality was very low due to imprecision and inconsistency.

ADVERSE EFFECTS: A meta-analysis of 4 RCTs[37-40] reported on the total adverse events that led to study withdrawal in a total of 248 participants. The duration of patient follow-up after treatment ranged from 4 to 52 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: -0.03 to 0.03) with an absolute risk of 0 events/1000 patients (95% CI: -30 to 30 events/1000 patients) with use of IV ferric carboxymaltose (see supplemental material, **Figure S48**). The certainty of evidence for unwanted side effects was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV ferric carboxymaltose in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S4**).

Benefits vs harms

The potential benefits of IV ferric carboxymaltose in adults with RLS include a clinically significant improvement in disease severity and QOL. The potential harms include a non-clinically significant risk of dizziness that may or may not resolve over time. Based on their combined clinical experience, the TF judged that the potential benefits of IV ferric carboxymaltose in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs for IV ferric carboxymaltose to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with IV ferric carboxymaltose.

Intravenous (IV) Iron Dextran

One observational study[41] investigated the use of intravenous (IV) iron dextran in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. Participants in the observational study received 1000 mg of IV iron dextran and had a mean age of 55 years (72% female). Analyses were performed to assess the efficacy of IV iron dextran as a treatment for adults with RLS. The analyses is provided in the supplemental material, **Figure S49** through **Figure S50**. A summary of findings table is provided in the supplemental material, **Table S5**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron dextran to treat adults with RLS: disease severity, and adverse events.

DISEASE SEVERITY: The efficacy of IV iron dextran to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 observational study[41] in a total of 23 participants. The duration of patient follow-up after treatment was 3 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -6.8 points (95% CI: -11.5 to -2.1 points) as measured by the IRLS (see supplemental material, **Figure S49**). The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: A meta-analysis of 3 observational studies[41-43] reported on the total adverse events that led to study withdrawal in a total of 59 participants. The duration of patient follow-up after treatment ranged from 2 to 60 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.03 (95% CI: -0.04 to 0.09) with use of IV iron dextran (see supplemental material, **Figure S50**). The certainty of evidence for unwanted side effects was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV iron dextran in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S5**).

Benefits vs harms

The potential benefits of IV iron dextran in adults with RLS include a clinically significant improvement in disease severity. The potential harms include a non-clinically significant risk of adverse events that lead to study withdrawal. Based on their combined clinical experience, the TF judged that the potential benefits of IV iron dextran in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs for IV iron dextran to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with IV iron dextran.

Oral Iron

A total of 2 RCTs[44, 45] investigated the use of oral iron in adults with RLS and an iron deficiency to improve one or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCTs received 325mg ferrous sulfate, once or twice daily, and had a mean age of 59 years (65% female). Meta-analyses were performed to assess the efficacy of oral iron as a treatment for adults with RLS and an iron deficiency. The meta-analyses are provided in the supplemental material, **Figure S51** through **Figure S52**. A summary of findings table is provided in the supplemental material, **Table S6**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of oral iron to treat adults with RLS and an iron deficiency: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of oral iron to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 RCT[45] in a total of 18 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -9.2 points (95% CI: -15.2 to -3.2 points) as measured by the IRLS (see supplemental material, **Figure S51**). The certainty of evidence for disease severity was moderate due to imprecision.

UNWANTED SIDE EFFECTS: A meta-analysis of 2 RCTs[44, 45] reported on the total adverse events that led to study withdrawal in a total of 46 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.10 (95% CI: -0.12 to 0.32) with an absolute risk of 100 events/1000 patients (95% CI: -120 to 320 events/1000 patients) with use of oral iron (see supplemental material, **Figure S52**). The certainty of evidence for disease severity was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of oral iron in adults with RLS and an iron deficiency was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S6**).

Benefits vs harms

The potential benefits of oral iron in adults with RLS and an iron deficiency include a clinically significant reduction in disease severity. Based on their combined clinical experience, the TF judged that the potential benefits of oral iron in adults with RLS and an iron deficiency outweigh the potential harms, despite the potential risk of abuse or overdose.

Resource use

The TF judged the costs of oral iron are negligible.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS and an iron deficiency would generally be accepting of treatment with oral iron.

Dipyridamole

A total of 1 RCT[46] and 1 observational study[47] investigated the use of dipyridamole in adults with RLS to improve one or more of the following outcomes: disease severity, sleep latency, WASO and unwanted side effects. Participants in the RCT received dosages of dipyridamole starting at 100 mg with up-titration to 300 mg if clinically necessary. Participants had a mean age of 60 years (65% female). The observational study was a before-and-after treatment design with participants serving as their own controls and receiving dosages starting at 100 mg with up-titration to 400 mg if clinically necessary. Meta-analyses were performed to assess the efficacy of dipyridamole as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S53** through **Figure S58.** A summary of findings table is provided in the supplemental material, **Table S7**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of dipyridamole to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of dipyridamole to reduce disease severity as measured by the IRLS was reported in one RCT[46] in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant reduction in disease severity of -7.6 points (95% CI: -9.1 to -6.1 points) as measured by the IRLS (see supplemental material, **Figure S53**). The certainty of evidence was moderate due to imprecision.

UNWANTED SIDE EFFECTS: One RCT[46] reported on the total adverse events that led to study withdrawal in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: -0.07 to 0.07)

with an absolute risk of 0 events/1000 patients (95% CI: -70 to 70 events/1000 patients) with use of dipyridamole (see supplemental material, **Figure S54**).

One RCT[46] reported on the incidence of dizziness in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant risk ratio of 1.5 (95% CI: 0.3 to 8.3) with an absolute risk of 35 events/1000 patients (95% CI: -52 to 521 events/1000 patients) with use of dipyridamole (see supplemental material, **Figure S55**).

One observational study[47] reported on the incidence of dizziness in a total of 15 participants. The duration of patient follow-up after treatment was 2 months. The analysis demonstrated a clinically significant risk difference of 0.13 (95% CI: --0.06 to 0.33) with an absolute risk of 130 events/1000 patients (95% CI: -60 to 330 events/1000 patients) with use of dipyridamole (see supplemental material, **Figure S56**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of dipyridamole: sleep latency and WASO.

SLEEP LATENCY: The efficacy of dipyridamole to decrease sleep latency was reported in one RCT[46] in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. Meta-analysis demonstrated a non-clinically significant decrease of -7.2 minutes (95% CI: -12.3 to -2.1 minutes) (see supplemental material, **Figure S57**). The certainty of evidence was moderate due to imprecision.

WASO: The efficacy of dipyridamole to decrease WASO was reported in one RCT[46] in a total of 56 participants. The duration of patient follow-up after treatment was 2 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of -14.5 minutes (95% CI: -28.6 to -0.4 minutes) with dipyridamole (see supplemental material, **Figure S58**). The certainty of evidence for WASO was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of dipyridamole in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S7**).

Benefits vs harms

The potential benefits of dipyridamole in adults with RLS include a clinically significant reduction in disease severity and WASO. The potential harms include a clinically significant risk of dizziness that may or may not resolve over time. Based on their combined clinical experience, the TF judged that the potential benefits of dipyridamole in adults with RLS outweigh the potential harms.

Resource use

The current unit costs for dipyridamole ranges from $1.06 for a 25 mg tablet to $1.35 for a 50 mg tablet.[26 21] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with dipyridamole.

Oxycodone

A total of 2 RCTs[48, 49] investigated the use of oxycodone in adults with RLS to improve one or more of the following outcomes: disease severity, sleep quality, sleep latency and unwanted side effects, either extended-release oxycodone-naloxone or oxycodone immediate release. Participants in the RCTs received dosages of oxycodone starting at 5 mg with up-titration to 40mg if clinically necessary. Participants had a mean age of 62 years (66% female). Meta-analyses were performed to assess the efficacy of oxycodone as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S59** through **Figure S66**. A summary of findings table is provided in the supplemental material, **Table S8**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of oxycodone to treat adults with RLS: disease severity, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of oxycodone to reduce disease severity as measured by the IRLS was evaluated in one RCT[48] in a total of 276 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant reduction in disease severity of -5.6 points (95% CI: -8.2 to -3.0 points) as measured by the IRLS (see supplemental material, **Figure S59**). The certainty of evidence for disease severity was high.

SLEEP QUALITY: The efficacy of oxycodone to improve sleep quality was evaluated in one RCT[48] that reported on the Medical Outcomes Study Sleep (MOSS) scale in a total of 276 participants. The duration of patient follow-up after treatment was 12 weeks. The results for sleep quality was 0.14 points (95% CI: -0.10 to 0.37 points) as measured by the MOSS scale which did not show a clinically significant improvement (see supplemental material, **Figure S60**). The certainty of evidence for sleep quality was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 2 RCTs[48, 49] reported on the total adverse events that led to study withdrawal in a total of 326 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.06 (95% CI: -0.00 to 0.12) with an absolute risk of 60 events/1000 patients (95% CI: -0 to 120 events/1000 patients) with use of oxycodone (see supplemental material, **Figure S61**).

One RCT[48] reported on the incidence of fatigue in a total of 304 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 2.3 (95% CI: 1.4 to

3.6) with an absolute risk of 169 events/1000 patients (95% CI: 52 to 338 events/1000 patients) with use of oxycodone (see supplemental material, **Figure S62**).

One RCT[48] reported on the incidence of somnolence in a total of 304 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 2.4 (95% CI: 1.0 to 5.5) with an absolute risk of 64 events/1000 patients (95% CI: 0 to 205 events/1000 patients) with use of oxycodone (see supplemental material, **Figure S63**).

One RCT[48] reported on the incidence of dizziness in a total of 304 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 3.3 (95% CI: 1.1 to 10.0) with an absolute risk of 60 events/1000 patients (95% CI: 3 to 234 events/1000 patients) with use of oxycodone (see supplemental material, **Figure S64**).

The certainty of evidence for unwanted side effects was moderate due to imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of oxycodone: PLM frequency and sleep latency.

PLM FREQUENCY: The efficacy of oxycodone to decrease PLM frequency was reported in one RCT[49] in a total of 11 patients. The duration of patient follow-up after treatment was 2 weeks. The meta-analysis demonstrated a decrease of -34.5 PLMs/hour (95% CI: -62.7 to -6.4 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S65**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

SLEEP LATENCY: The efficacy of oxycodone to decrease sleep latency was evaluated reported in one RCT[49] in a total of 11 patients. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a clinically significant decrease of -25.5 minutes (95% CI: -68.4 to 17.4 minutes) (see supplemental material, **Figure S66**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of oxycodone in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S8**).

Benefits vs harms

The potential benefits of oxycodone in adults with RLS include a clinically significant reduction in disease severity and sleep latency. The potential harms include a clinically significant risk of fatigue, somnolence and dizziness that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential benefits of oxycodone in adults with RLS outweigh the potential harms, despite the potential risk of abuse or overdose.

Resource use

The current unit costs for oxycodone ranges from $0.07 for a 5 mg tablet to $18.12 for a 36 mg tablet. [26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is important uncertainty or variability in how much patients value the main outcomes. The TF judged that there would be variability among adults with RLS regarding the long-term use of oxycodone. These variabilities are due to the potential risks of abuse, dependence, and death in the event of a significant overdose of oxycodone.

Peroneal nerve stimulation

One RCT[50] investigated the use of peroneal nerve stimulation in adults with RLS to improve one or more of the following outcomes: disease severity. Participants in the RCT utilized a self-administered stimulation session for 30 minutes at bedtime. Participants had a mean age of 56 years (54% female). Meta-analyses were performed to assess the efficacy of peroneal nerve stimulation as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S67** and **Figure S68**. A summary of findings table is provided in the supplemental material, **Table S9**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of peroneal nerve stimulation to treat adults with RLS: disease severity.

DISEASE SEVERITY: The efficacy of peroneal nerve stimulation to reduce disease severity as measured by the IRLS was reported 1 RCT[50] in a total of 72 participants. The duration of patient follow-up after treatment was 2 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -3.4 points (95% CI: -6.0 to -0.8 points) as measured by the IRLS (see supplemental material, **Figure S67**).

The efficacy of peroneal nerve stimulation to reduce disease severity as measured by the CGI-I was evaluated using a meta-analysis of 1 RCT[50] in a total of 72 participants. The duration of patient follow-up after treatment was 2 weeks. The meta-analysis demonstrated a clinically significant improvement in the number of participants whose symptoms responded to treatment of 48% (95% CI: 26 to 70%) as measured by the CGI-I (see supplemental material, **Figure S68**).

The certainty of evidence for disease severity was low due to risk of bias (lack of adequate blinding and allocation concealment) and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of peroneal nerve stimulation in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias and imprecision. (see supplemental material, **Table S9**).

Benefits vs harms

The potential benefits of peroneal nerve stimulation in adults with RLS include a clinically significant reduction in disease severity. Side effects including uncomfortable sensations, skin irritation, muscle fatigue, upper respiratory infection, GI distress, and flu have been reported. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential benefits of neuromuscular stimulation in adults with RLS outweigh the potential harms.

Resource use

The current unit cost for the peroneal nerve stimulation device is $7500.[26] The TF judged these costs are high.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with peroneal nerve stimulation.

Levodopa

A total of 3 RCTs[51-53] and 7 observational studies[54-60] investigated the use of levodopa in adults with RLS to improve one or more of the following outcomes: disease severity, QOL, sleep quality, WASO, and unwanted side effects. Participants in the RCTs received 100 mg to 200 mg of levodopa (with peripheral decarboxylase inhibitor carbidopa or benserazide). Participants had a mean age of 55 years (51% female). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving 100 mg to 500 mg of levodopa (with peripheral decarboxylase inhibitor carbidopa or benserazide). Meta-analyses were performed to assess the efficacy of levodopa as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S69** through **Figure S76**. A summary of findings table is provided in the supplemental material, **Table S10**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of levodopa to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of levodopa to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies.[55, 58] in a total of 81 participants. The duration of patient follow-up after treatment ranged from 3 days to 4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -4.7 points (95% CI: -7.0 to -2.4 points) as measured by the IRLS (see supplemental material, **Figure S69**).

The efficacy of levodopa to reduce disease severity as measured by the CGI-S was reported in one RCT[53] in a total of 34 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a non-clinically significant improvement of -0.2 (95% CI: -0.8 to 0.4) as measured by the CGI-S (see supplemental material, **Figure S70**).

The certainty of evidence for disease severity ranged from very low to low due to risk of bias associated with observational studies and imprecision.

QOL: The efficacy of levodopa to improve QOL was evaluated from an analysis of one observational study[58] that reported on the RLS-QLI scale in a total of 18 participants. The duration of patient follow-up after treatment was 3 days. The analysis demonstrated a non-clinically significant improvement in QOL of 0.1 points (95% CI: -0.7 to 0.9 points) as measured by the RLS-QLI scale (see supplemental material, **Figure S71**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

SLEEP QUALITY: The efficacy of levodopa to improve sleep quality was evaluated based on an analysis of one observational study[58] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 18 participants. The duration of patient follow-up after treatment was 3 days. The analysis demonstrated a clinically significant improvement in sleep quality of -3.2 points (95% CI: -6.3 to -0.1) as measured by the PSQI scale (see supplemental material, **Figure S72**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: A meta-analysis of 3 RCTs[51-53] reported on the total adverse events that led to study withdrawal in a total of 138 participants. The duration of patient follow-up after treatment ranged from 4 weeks to 18 months. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of -0.02 (95% CI: -0.08 to 0.04) with an absolute risk of -20 events/1000 patients (95% CI: -80 to 40 events/1000 patients) with use of levodopa (see supplemental material, **Figure S73**).

A meta-analysis of 2 RCTs[51, 52] reported on the incidence of augmentation in a total of 104 participants. The duration of patient follow-up after treatment ranged from 4 weeks to 18 months. The meta-analysis demonstrated a clinically significant risk difference of 0.11 (95%: -0.03 to 0.25) with an absolute risk of 115 events/1000 patients (95% CI: 29 to 202 events/1000 patients) with use of levodopa (see supplemental material, **Figure S74**).

A meta-analysis of 7 observational studies[54-60] reported on the incidence of augmentation in a total of 416 participants. The duration of patient follow-up after treatment ranged from 3 days to 12 months. The meta-analysis demonstrated a clinically significant risk difference of 0.39 (95%: 0.17 to 0.61) with an absolute risk of 310 events/1000 patients (95% CI: 266 to 355 events/1000 patients) with use of levodopa (see supplemental material, **Figure S75**).

A meta-analysis of 2 observational studies[55, 59] reported on the incidence of dizziness/vertigo in a total of 246 participants. The duration of patient follow-up after treatment ranged from 4 to 30 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.11 (95%: 0.00 to 0.22) with an absolute risk of 110 events/1000 patients (95% CI: 0 to 220 events/1000 patients) with use of levodopa (see supplemental material, **Figure S76**).

One observational study[52] reported on the incidence of somnolence in a total of 40 participants. The duration of patient follow-up after treatment was 18 months. The meta-analysis demonstrated a clinically significant risk difference of 0.05 (95%: -0.18 to 0.28) with an absolute risk of 50 events/1000 patients (95% CI: -180 to 280 events/1000 patients) with use of levodopa (see supplemental material, **Figure S77**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of levodopa in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S10**).

Benefits vs harms

The potential benefits of levodopa in adults with RLS include a clinically significant improvement in disease severity and sleep quality. The potential harms include a clinically significant risk of somnolence, dizziness/vertigo and augmentation that may or may not resolve over time. Based on their combined clinical experience, the TF judged that the potential harms of levodopa in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for levodopa was $0.10 for a 25/100 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant risk of harms, the TF judged that most with RLS would generally not be accepting treatment with levodopa.

Pramipexole

A total of 17 RCTs[33, 35, 61-75] and 7 observational studies[55, 63, 76-80] investigated the use of pramipexole in adults with RLS to improve one or more of the following outcomes: disease severity, quality of life, sleep quality and unwanted side effects. Participants in the RCTs had a mean age of 55 years (65% female) and were diagnosed with moderate to severe RLS. Most participants received dosages of pramipexole from 0.125 mg to 0.75 mg, with a single study allowing up to 1.5 mg. Five observational studies were before-and-after treatment design (including long-term follow up), with participants serving as their own controls. Two observational studies were retrospective records reviews. Meta-analyses were performed to assess the efficacy of pramipexole as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S78** through **Figure S86**. A summary of findings table is provided in the supplemental material, **Table S11**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of pramipexole to treat adults with RLS: disease severity, quality of life, sleep quality and unwanted side effects.

DISEASE SEVERITY: The efficacy of pramipexole to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 10 RCTs[34, 61-63, 65, 70, 72-75] in a total of 2,917 participants. The duration of patient follow-up after treatment ranged from 3 to 52 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -4.9 points (95% CI: -6.2 to -3.5 points) as measured by the IRLS (see supplemental material, **Figure S78**). The certainty of evidence was high.

QOL: The efficacy of pramipexole to improve QOL was evaluated from an analysis of 4 RCTs[34, 61, 70, 74] that reported on the RLS-QOL Abetz scale in a total of 1,634 participants. The duration of patient follow-up after treatment ranged from 12 to 52 weeks. The analysis demonstrated a clinically significant improvement in QOL of 5.4 points

(95% CI: 2.1 to 8.7 points) as measured by the RLS-QOL Abetz scale (see supplemental material, **Figure S79**). The certainty of evidence was moderate due to inconsistency.

SLEEP QUALITY: The efficacy of pramipexole to improve sleep quality was evaluated based on an analysis of 2 RCTs[61, 81] that reported on the Pittsburgh Sleep Quality Index (PSQI) and Medical Outcomes Study Sleep (MOSS) scale in a total of 397 participants. The duration of patient follow-up after treatment ranged from 12 to 52 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of 0.7 (95% CI: -0.1 to 1.5) as measured by the PSQI and MOSS scales (see supplemental material, **Figure S80**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 17 RCTs[33, 35, 61-75] reported on the total adverse events that led to study withdrawal in a total of 3,548 participants. The duration of patient follow-up after treatment ranged from 3 to 52 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.02 (95% CI: -0.02 to 0.06) with an absolute risk of 20 events/1000 patients (95% CI: -20 to 60 events/1000 patients) with use of pramipexole (see supplemental material, **Figure S81**).

A meta-analysis of 2 RCTs[34, 62] reported on the incidence of augmentation in a total of 825 participants. The duration of patient follow-up after treatment ranged from 26 to 52 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.09 (95%: 0.04 to 0.14) with an absolute risk of 90 events/1000 patients (95% CI: 40 to 140 events/1000 patients) with use of pramipexole (see supplemental material, **Figure S82**).

A meta-analysis of 7 observational studies[55, 63, 76-80] reported on the incidence of augmentation in a total of 640 participants. The duration of patient follow-up after treatment ranged from 4 weeks to 12 years. The meta-analysis demonstrated a clinically significant risk difference of 0.18 (95%: 0.08 to 0.27) with an absolute risk of 180 events/1000 patients (95% CI: 80 to 270 events/1000 patients) with use of pramipexole (see supplemental material, **Figure S83**).

A meta-analysis of 7 RCTs[34, 62, 63, 65, 72-74] reported on the incidence of somnolence in a total of 1,998 participants. The duration of patient follow-up after treatment ranged from 6 weeks to 52 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of 0.04 (95%: 0.01 to 0.06) with an absolute risk of 40 events/1000 patients (95% CI: 10 to 60 events/1000 patients) with use of pramipexole (see supplemental material, **Figure S84**).

A meta-analysis of 6 RCTs[34, 65, 71, 72, 74, 75] reported on the incidence of dizziness in a total of 1,745 participants. The duration of patient follow-up after treatment ranged from 6 weeks to 52 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of 0.04 (95%: 0.00 to 0.09) with an absolute risk of 40 events/1000 patients (95% CI: 0 to 90 events/1000 patients) with use of pramipexole (see supplemental material, **Figure S85**).

One observational study[77] reported on the incidence of impulse control order in a total of 50 participants. The duration of patient follow-up after treatment ranged from 6 months to 12 years. The meta-analysis demonstrated a clinically significant risk difference of 0.10 (95%: 0.01 to 0.19) with an absolute risk of 100 events/1000 patients (95% CI: 10 to 190 events/1000 patients) with use of pramipexole (see supplemental material, **Figure S86**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies, imprecision and inconsistency.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of pramipexole in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies, imprecision and inconsistency. (see supplemental material, **Table S11**).

Benefits vs harms

The potential benefits of pramipexole in adults with RLS include a clinically significant improvement in disease severity, quality of life and sleep quality. The potential harms include a clinically significant risk of somnolence, dizziness, impulse control order and augmentation that may or may not resolve over time. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either pramipexole or the comparison.

Resource use

The current unit costs for pramipexole ranges from $0.05 for a 0.5 mg tablet to $6.32 for a 1.5 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant risks, the TF judged that most with RLS would generally not be accepting of treatment with pramipexole.

Transdermal Rotigotine

A total of 8 RCTs[16, 82-88] and 3 observational studies[16, 87, 89] investigated the use of rotigotine in adults with RLS to improve one or more of the following outcomes: disease severity, QOL, sleep quality, and unwanted side effects. Participants in the RCTs had a mean age of 55 years (63% female) and were diagnosed with moderate to severe RLS. Participants received dosages of transdermal rotigotine from 0.5 mg to 4.5 mg. All observational studies were before-and-after treatment design with participants diagnosed with moderate to severe RLS and serving as their own controls. Meta-analyses were performed to assess the efficacy of rotigotine as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S87** through **Figure S94**. A summary of findings table is provided in the supplemental material, **Table S12**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of rotigotine to treat adults with RLS: disease severity, QOL, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of rotigotine to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 8 RCTs[16, 82-88] in a total of 1,905 participants. The duration of patient follow-up after treatment ranged from 1 week to 6 months. The meta-analysis demonstrated a clinically significant reduction in disease severity of -4.7 points (95% CI: -6.2 to -3.2 points) as measured by the IRLS (see supplemental material, **Figure S87**). The certainty of evidence was high.

QOL: The efficacy of rotigotine to improve QOL was evaluated from an analysis of 4 RCTs[84-86, 90] that reported on the RLS-QOL Kohnen scale in a total of 1,310 participants. The duration of patient follow-up after treatment ranged from 10 weeks to 6 months. The analysis demonstrated a clinically significant improvement in QOL of -4.5 points (95% CI: -8.2 to -0.9 points) as measured by the RLS-QOL Kohnen scale (see supplemental material, **Figure S88**). The certainty of evidence was moderate due to imprecision.

SLEEP QUALITY: The efficacy of rotigotine to improve sleep quality was evaluated based on an analysis of 4 RCTs[16, 84, 86, 91] that reported on the Pittsburgh Sleep Quality Index (PSQI) and Medical Outcomes Study Sleep (MOSS) scale in a total of 995 participants. The duration of patient follow-up after treatment ranged from 3 to 6 months. The meta-analysis demonstrated a clinically significant improvement in sleep quality of 0.2 (95% CI: 0.06 to 0.34) as measured by the PSQI and MOSS scales (see supplemental material, **Figure S89**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 8 RCTs [16, 82-88] reported on the total adverse events that led to study withdrawal in a total of 1,927 participants. The duration of patient follow-up after treatment ranged from 1 week to 6 months. The meta-analysis demonstrated a clinically significant risk ratio of adverse events leading to study withdrawal of 1.7 (95% CI: 0.8 to 3.7) with an absolute risk of 30 events/1000 patients (95% CI: -8 to 115 events/1000 patients) with use of rotigotine (see supplemental material, **Figure S90**).

A meta-analysis of 3 RCTs[16, 84, 86] reported on the incidence of somnolence in a total of 855 participants. The duration of patient follow-up after treatment ranged from 3 to 6 months. The meta-analysis demonstrated a clinically significant risk ratio of somnolence of 2.3 (95%: 1.0 to 5.3) with an absolute risk of 60 events/1000 patients (95% CI: 0 to 199 events/1000 patients) with use of rotigotine (see supplemental material, **Figure S91**).

A meta-analysis of 4 RCTs[84-86, 90] reported on the incidence of dizziness/vertigo in a total of 1,369 participants. The duration of patient follow-up after treatment ranged from 3 to 6 months. The meta-analysis demonstrated a clinically significant risk ratio of somnolence of 1.0 (95%: 0.6 to 1.9) with an absolute risk of 0 events/1000 patients (95% CI: -18 to 35 events/1000 patients) with use of rotigotine (see supplemental material, **Figure S92**).

A meta-analysis of 5 RCTs[85-87, 90, 92] reported on the incidence of application site reaction in a total of 1,205 participants. The duration of patient follow-up after treatment ranged from 1 week to 6 months. The meta-analysis demonstrated a clinically significant risk ratio of 5.2 (95%: 1.4 to 19.4) with an absolute risk of 210 events/1000 patients (95% CI: -=20 to 920 events/1000 patients) with use of rotigotine (see supplemental material, **Figure S93**).

A meta-analysis of 3 observational studies [16, 87, 89] reported on the incidence of augmentation in a total of 1,164 participants. The duration of patient follow-up after treatment ranged from 12 weeks to 5 years. The meta-analysis demonstrated a clinically significant risk difference of 0.06 (95%: -0.05 to 0.17) with an absolute risk of 60 events/1000 patients (95% CI: 050 to 170 events/1000 patients) with use of rotigotine (see supplemental material, **Figure S94**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies, imprecision and inconsistency.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of rotigotine in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies, imprecision and inconsistency. (see supplemental material, **Table S12**).

Benefits vs harms

The potential benefits of rotigotine in adults with RLS include a clinically significant improvement in disease severity, QOL and sleep quality. The potential harms include a clinically significant risk of somnolence, dizziness/vertigo, augmentation, and application site reaction that may or may not resolve over time. Other side effects including nausea, headache, and asthenia have been reported.[93] Although rates of augmentation reported in the clinical trials was low, study duration may have led to an underestimation of its occurrence. Furthermore, the shared clinical experience of the TF suggests that actual rates of augmentation for rotigotine are likely higher than what is reported in the above trials. Based on their combined clinical experience, the TF judged taking into account the class effect of harms associated with this group, the TF concluded that it was unable to exclude a net harm.

Resource use

The current unit costs of rotigotine ranges from $22.66 for a 4 mg/24 hr patch to $22.88 for a 8 mg/24 hr patch.[26] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with rotigotine.

Ropinirole

A total of 12 RCTs[94-104] and 2 observational studies[100, 105] investigated the use of ropinirole in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCTs had a mean age of 55 years (62% female) and were diagnosed with moderate to severe RLS. Participants received flexible dosages of ropinirole from 0.25 mg to 6 mg. All observational studies were before-and-after treatment design with participants diagnosed with moderate to severe RLS and serving as their own controls. Meta-analyses were performed to assess the efficacy of ropinirole as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S95** through **Figure S103**. A summary of findings table is provided in the supplemental material, **Table S13**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of ropinirole to treat adults with RLS: disease severity, quality of life, sleep quality and unwanted side effects.

DISEASE SEVERITY: The efficacy of ropinirole to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 7 RCTs[94, 96-99, 103, 104] in a total of 1,314 participants. The duration of patient follow-up after treatment ranged from 2 to 26 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -4.0 points (95% CI: -5.4 to -2.6 points) as measured by the IRLS (see supplemental material, **Figure S95**). The certainty of evidence was moderate due to imprecision.

QOL: The efficacy of ropinirole to improve QOL was evaluated from an analysis of 3 RCTs[98, 100, 104] that reported on the RLS-QOL scale in a total of 768 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a non-clinically significant improvement in QOL of 3.8 points (95% CI: 1.8 to 5.8 points) as measured by the RLS-QOL scale (see supplemental material, **Figure S96**). The certainty of evidence was moderate due to imprecision.

SLEEP QUALITY: The efficacy of ropinirole to improve sleep quality was evaluated based on an analysis of 3 RCTs[95, 98, 100] that reported on the Medical Outcomes Study Sleep (MOS) scale in a total of 615 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a non-clinically significant improvement in sleep quality of 0.17 points (95% CI: -0.00 to 0.35 points) as measured by the MOSS scale (see supplemental material, **Figure S97**). The certainty of evidence for sleep quality was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 8 RCTs[28, 95, 96, 98, 100, 101, 103, 104, 106] reported on the total adverse events that led to study withdrawal in a total of 2,067 participants. The duration of patient follow-up after treatment ranged from 3 days to 12 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.03 (95% CI: -0.01 to 0.06) with an absolute risk of 30 events/1000 patients (95% CI: -10 to 60 events/1000 patients) with use of ropinirole (see supplemental material, **Figure S98**).

A meta-analysis of 3 RCTs[98, 100, 103] reported on the incidence of augmentation in a total of 1,072 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.02 (95%: -0.01 to 0.04) with an absolute risk of 20 events/1000 patients (95% CI: -10 to 40 events/1000 patients) with use of ropinirole (see supplemental material, **Figure S99**).

One observational study[100] reported on the incidence of augmentation in a total of 269 participants. The duration of patient follow-up after treatment was 12 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.03 (95%: -0.01 to 0.05) with an absolute risk of 30 events/1000 patients (95% CI: 10 to 50 events/1000 patients) with use of ropinirole (see supplemental material, **Figure S100**).

One observational study[37] reported on the definite/highly suggestive likelihood of augmentation in a total of 266 participants. The duration of patient follow-up after treatment was 2.7 ± 2.4 years. The meta-analysis demonstrated a clinically significant risk difference of 0.67 (95%: 0.61 to 0.73) with an absolute risk of 670 events/1000 patients (95% CI: 610 to 730 events/1000 patients) with use of ropinirole (see supplemental material, **Figure S101**).

A meta-analysis of 4 RCTs[98, 100, 101, 103] reported on the incidence of somnolence in a total of 1,430 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant risk difference of 0.06 (95% CI: 0.01 to 0.11) with an absolute risk of 60 events/1000 patients (95% CI: 10 to 110 events/1000) with use of ropinirole (see supplemental material, **Figure S102**).

A meta-analysis of 4 RCTs[96, 98, 100, 104] reported on the incidence of dizziness in a total of 1,315 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a clinically significant risk difference of 0.07 (95% CI: 0.04 to 0.09) with an absolute risk of 70 events/1000 patients (95% CI: 40 to 90 events/1000) with use of ropinirole (see supplemental material, **Figure S103**).

The certainty of evidence for unwanted side effects ranged from low to moderate due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of ropinirole in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S13**).

Benefits vs harms

The potential benefits of ropinirole in adults with RLS include a clinically significant reduction in disease severity. The potential harms include a clinically significant risk of somnolence, dizziness and augmentation that may or may not resolve over time. Based on their combined clinical experience, the TF judged that the potential harms of ropinirole in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for ropinirole ranges from $0.05 for a 0.5 mg tablet to $2.54 for a 12 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with ropinirole.

Bupropion

One RCT[107] investigated the use of bupropion in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCT (29:31 intervention: control group) received 150 mg of sustained-release bupropion for 6 weeks. Participants had a mean age of 49 years (77% female). Meta-analyses were performed to assess the efficacy of bupropion as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S104** and **Figure S105**. A summary of findings table is provided in the supplemental material, **Table S14**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of bupropion to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of bupropion to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 1 RCT[107] in a total of 60 participants. The duration of patient follow-up after treatment was 3 weeks. The meta-analysis demonstrated a non-clinically significant reduction in disease severity of –2.8 points (95% CI: -7.3 to 1.7 points) as measured by the IRLS (see supplemental material, **Figure S104**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 1 RCT[107] reported on the total adverse events that led to study withdrawal in a total of 60 participants. The duration of patient follow-up after treatment ranged was 3-6 weeks. The meta-analysis demonstrated a non-clinically significant risk ratio of 1.1 (95% CI: 0.3 to 3.9) with an absolute risk of 13

events/1000 patients (95% CI: -92 to 374 events/1000 patients) with use of bupropion (see supplemental material, **Figure S105**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of bupropion in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S14**).

Benefits vs harms

The potential benefits of bupropion in adults with RLS were considered trivial. Side effects including nausea and gastritis have been reported. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either bupropion or the comparison.

Resource use

The current unit costs for bupropion ranges from $0.11 for a 150 mg tablet to $166.50 for a 522 mg tablet.[26] The TF judged these costs to be negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given there was no clinically significant improvement in disease severity, the TF judged that most patients with RLS would generally not be accepting of treatment with bupropion.

Carbamazepine

A total of 2 RCTs[108, 109] and 1 observational study[110] investigated the use of carbamazepine in adults with RLS to improve one or more of the following outcomes: disease severity, PLM frequency, sleep latency, WASO and unwanted side effects. Participants in the RCTs received 100mg to 300mg of carbamazepine. Participants had a mean age of 53 years (69% female). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving 3-7 mg/kg of carbamazepine per day. Meta-analyses were performed to assess the efficacy of carbamazepine as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S106** through **Figure S113**. A summary of findings table is provided in the supplemental material, **Table S15**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of carbamazepine to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of carbamazepine to reduce disease severity as measured by RL sensation frequency was reported in one RCT[108] in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a reduction in disease severity of -1.1 days/week (95% CI: -3.1 to 0.9) (see supplemental material, **Figure S106**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

The efficacy of carbamazepine to reduce disease severity as measured by subjective severity ratings was reported in one RCT[108] in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a reduction in disease severity of -3.0 (95% CI: -8.7 to 2.7) (see supplemental material,

Figure S107). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 2 RCTs[108, 109] reported on the total adverse events that led to study withdrawal in a total of 184 participants. The duration of patient follow-up after treatment ranged from 4 to 5 weeks. The meta-analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.05 (95% CI: -0.02 to 0.11) with an absolute risk of 50 events/1000 patients (95% CI: -20 to 110 events/1000 patients) with use of carbamazepine (see supplemental material, **Figure S108**).

One observational study[110] reported on the total adverse events that led to study withdrawal in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: -0.19 to 0.19) with an absolute risk of 0 events/1000 patients (95% CI: -190 to 190 events/1000 patients) with use of carbamazepine (see supplemental material, **Figure S109**).

One RCT[108] reported on the incidence of dizziness in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.17 (95%: -0.19 to 0.53) with an absolute risk of 170 events/1000 patients (95% CI: 190 to 530 events/1000 patients) with use of carbamazepine (see supplemental material, **Figure S110**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of carbamazepine: sleep latency, WASO and PLM frequency.

PLM FREQUENCY: The efficacy of carbamazepine to decrease PLM frequency was reported in one observational study[110] in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated an increase of 1.4 PLMs/hour (95% CI: -19.3 to 22.1 PLMs/hour) as measured by the Myoclonus Index (see supplemental material, **Figure S111**). The clinical significance of this increase was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

SLEEP LATENCY: The efficacy of carbamazepine to decrease sleep latency was reported in one observational study [47] in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. Meta-analysis demonstrated a clinically significant decrease of -25.7 minutes (95% CI: -48.3 to 3.1 minutes) (see supplemental material, **Figure S112**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

WASO: The efficacy of carbamazepine to decrease WASO was reported in one observational study[110] in a total of 9 participants. The duration of patient follow-up after treatment was 6 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of -65.1 minutes (95% CI: -126.4 to -3.8 minutes) with carbamazepine (see

supplemental material, **Figure S113**). The certainty of evidence very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of carbamazepine in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S15**).

Benefits vs harms

The potential benefits of carbamazepine in adults with RLS include a reduction in disease severity (not measured by iRLS), sleep latency and WASO. The potential harms include a clinically significant risk of dizziness that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential harms of carbamazepine in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for carbamazepine ranges from $0.31 for a 100 mg tablet to $5.19 for a 400 mg tablet.[26] The TF judged these costs as moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. The TF judged that most patients with RLS would generally not be accepting of treatment with carbamazepine.

Clonazepam

A total of 3 RCTs [48-50] investigated the use of clonazepam in adults with RLS to improve one or more of the following outcomes: sleep latency, PLM frequency, WASO and unwanted side effects. Participants in the RCTs received 0.5mg to 2mg of clonazepam. Participants had a mean age of 52 years (53% female). Meta-analyses were performed to assess the efficacy of clonazepam as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S114** through **Figure S118**. A summary of findings table is provided in the supplemental material, **Table S16**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of clonazepam to treat adults with RLS: unwanted side effects.

ADVERSE EFFECTS: A meta-analysis of 3 RCTs[111-113] reported on the total adverse events that led to study withdrawal in a total of 44 participants. The duration of patient follow-up after treatment ranged from 3 days to 4 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI -0.13 to 0.13) with an absolute risk of 0 events/1000 patients (95% CI: -130 to 130 events/1000 patients) with use of clonazepam (see supplemental material, **Figure S114**).

One RCT[113] reported on the incidence of sleepiness in a total of 12 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.33 (95%: -0.17 to 0.83) with an absolute risk of 330 events/1000 patients (95% CI: -170 to 830 events/1000 patients) with use of clonazepam (see supplemental material, **Figure S115**).

The certainty of evidence for unwanted side effects was moderate.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of clonazepam: PLM frequency, sleep latency, and WASO.

PLM FREQUENCY: The efficacy of clonazepam to decrease PLM frequency was reported in one RCT[113] in a total of 20 participants. The duration of patient follow-up after treatment was 3 days. The meta-analysis demonstrated a decrease of -0.6 PLMs/hour (95% CI: -20.7 to 19.4 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S116**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate.

SLEEP LATENCY: The efficacy of clonazepam to decrease sleep latency was reported in one RCT[113] in a total of 20 participants. The duration of patient follow-up after treatment was 3 days. Meta-analysis demonstrated a non-clinically significant decrease of -3.2 minutes (95% CI: -14.8 to 8.4 minutes) (see supplemental material, **Figure S117**). The certainty of evidence was moderate.

WASO: The efficacy of clonazepam to decrease WASO was reported in one[113] in a total of 20 participants. The duration of patient follow-up after treatment ranged from 2 to 12 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of -28.3 minutes (95% CI: -40.0 to -16.8 minutes) with clonazepam (see supplemental material, **Figure S118**). The certainty of evidence was moderate.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of clonazepam in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S16**).

Benefits vs harms

The potential benefits of clonazepam in adults with RLS include a clinically significant improvement in WASO. The potential harms include the risk of sleepiness that may or may not resolve over time. Other side effects including cognitive impairment and chemical dependence have been reported. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential harms of clonazepam in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for clonazepam ranges from $0.02 for a 0.5 mg tablet to $1.00 for a 2 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is important uncertainty or variability in how much patients value the main outcomes.

Valerian

One RCT[114] investigated the use of valerian in adults with RLS to improve one or more of the following outcomes: disease severity, sleep quality and unwanted side effects. Participants in the RCT received 800mg of valerian. Participants had a mean age of 49 years (75% female). Meta-analyses were performed to assess the efficacy of valerian as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S119** through **Figure S122**. A summary of findings table is provided in the supplemental material, **Table S17.** A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of valerian to treat adults with RLS: disease severity, sleep quality and unwanted side effects.

DISEASE SEVERITY: The efficacy of valerian to reduce disease severity as measured by IRLS was reported in one RCT[114] in a total of 37 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a non-clinically significant increase in disease severity of 1.3 points (95% CI: -5.1 to 7.7 points) as measured by the IRLS (see supplemental material, **Figure S119**). The certainty of evidence was low due to very serious imprecision.

SLEEP QUALITY: The efficacy of valerian to improve sleep quality was evaluated based on one RCT[114] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 37 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a non-clinically significant decline in sleep quality of 0.1 points (95% CI: -3.2 to 3.4) as measured by the PSQI scale (see supplemental material, **Figure S120**). The certainty of evidence was low due to very serious imprecision.

ADVERSE EFFECTS: One RCT[114] reported on the total adverse events that led to study withdrawal in a total of 37 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.08 (95% CI: -0.07 to 0.24) with an absolute risk of 80 events/1000 patients (95% CI: -70 to 240 events/1000 patients) with use of valerian (see supplemental material, **Figure S121**).

One RCT[114] reported on the incidence of dizziness in a total of 24 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.04 (95% CI: -0.07 to 0.15) with an absolute risk of 40 events/1000 patients (95% CI: -70 to 150 events/1000 patients) with use of valerian (see supplemental material, **Figure S122**).

The certainty of evidence for unwanted side effects was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of valerian in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S17**).

Benefits vs harms

The potential benefits of valerian in adults with RLS were considered trivial by the TF. The potential harms include a clinically significant risk of dizziness that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential harms of valerian in adults with RLS outweigh the potential benefits.

Resource use

The TF judged the costs of valerian are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the trivial benefits and potential harms, the TF judged that most with RLS would generally not be accepting of treatment with valerian.

Valproic Acid

One observational study[52] investigated the use of valproic acid in adults with RLS to improve one or more of the following outcomes: disease severity, PLM frequency, WASO and unwanted side effects. The observational study was a before-and-after treatment design with participants diagnosed with moderate to severe RLS, receiving 600mg valproic acid, and serving as their own controls. Analyses were performed to assess the efficacy of valproic acid as a treatment for adults with RLS. The analyses are provided in the supplemental material, **Figure S123** through **Figure S127**. A summary of findings table is provided in the supplemental material, **Table S18**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of valproic acid to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of valproic acid to reduce disease severity as measured by RLS intensity score was reported in one observational study[52] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a reduction in disease severity of -1.7 (95% CI: -3.9 to 0.5) (see supplemental material, **Figure S123**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

The efficacy of valproic acid to reduce disease severity as measured by RLS duration was reported in one observational study[52] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a reduction in disease severity of -51.5 minutes (95% CI: -292.8 to 189.8) (see supplemental material, **Figure S124**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

The certainty of evidence for disease severity was low due to imprecision.

ADVERSE EFFECTS: One observational study[52] reported on the total adverse events that led to study withdrawal in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: -0.24 to 0.24) with an absolute risk of 0 events/1000 patients (95% CI: -240 to 240 events/1000 patients) with use of valproic acid (see supplemental material, **Figure S125**). The certainty of evidence was low due to very serious imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of valproic acid: WASO and PLM frequency.

PLM FREQUENCY: The efficacy of valproic acid to decrease PLM frequency was reported in one observational study[52] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a decrease of -5.2 PLMs/hour (95% CI: -41.5 to 31.1 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S126**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was low due to very serious imprecision.

WASO: The efficacy of valproic acid to decrease WASO was reported in one observational study[52] in a total of 7 participants. The duration of patient follow-up after treatment was 3 weeks. The results demonstrated a non-clinically significant decrease in WASO of -3.3 minutes (95% CI: -22.4 to 15.8 minutes) with valproic acid (see supplemental material, **Figure S127**). The certainty of evidence was low due to very serious imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of valproic acid in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S18**).

Benefits vs harms

The potential benefits of valproic acid in adults with RLS include changes in disease severity and WASO. There was changes in PLM frequency of uncertain clinical significance as no clinical significance threshold was set. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential harms of valproic acid in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for valproic acid ranges from $0.02 for a 250 mg/5 ml solution to $0.24 for a 250 mg capsule.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is important uncertainty or variability in how much patients value the main outcomes. Given the potential harms, the TF judged that most with RLS would generally not be accepting of treatment with valproic acid.

Cabergoline

A total of 2 RCTs[115, 116] and 4 observational studies[59, 116-118] investigated the use of cabergoline in adults with RLS to improve one or more of the following outcomes: disease severity, quality of life, PLM frequency, sleep latency and unwanted side effects. Participants in the RCTs had a mean age of 56 years (71% female) and were diagnosed with moderate to severe RLS. Participants received titrated dosages of cabergoline from 0.25 mg to 2 mg. All observational studies were before-and-after treatment design with participants diagnosed with moderate to severe RLS and serving as their own controls. Meta-analyses were performed to assess the efficacy of cabergoline as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S128** through **Figure S134**. A summary of findings table is provided in the supplemental material, **Table S19**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of cabergoline to treat adults with RLS: disease severity, quality of life and unwanted side effects.

DISEASE SEVERITY: The efficacy of cabergoline to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 RCTs[115, 116] in a total of 124 participants. The duration of patient follow-up after treatment ranged from 5 to 47 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -12.5 points (95% CI: -17.2 to -7.9 points) as measured by the IRLS (see supplemental material, **Figure S128**). The certainty of evidence was moderate due to imprecision.

QOL: The efficacy of cabergoline to improve QOL was reported in one RCT[115] on the RLS-QOL Kohnen scale in a total of 40 participants. The duration of patient follow-up after treatment was 5 weeks. The analysis demonstrated a clinically significant improvement in QOL of -12.3 points (95% CI: -22.3 to 2.3 points) as measured by the RLS-QOL Kohnen scale (see supplemental material, **Figure S129**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS A meta-analysis of 2 RCTs[115, 116] reported on the total adverse events that led to study withdrawal in a total of 128 participants. The duration of patient follow-up after treatment ranged from 5 to 47 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 4.4 (95% CI: 0.6 to 34.4) with an absolute risk of 0 events/1000 patients (95% CI: 0 to 0 events/1000 patients) with use of cabergoline (see supplemental material, **Figure S130**).

A meta-analysis of 4 observational studies[59, 116-118] reported on the incidence of augmentation in a total of 558 participants. The duration of patient follow-up after treatment ranged from 5 to 30 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 12.1 (95% CI: 2.2 to 65.7) with an absolute risk of 36 events/1000 patients (95% CI: 21 to 51events/1000 patients) with use of cabergoline (see supplemental material, **Figure S131**).

A meta-analysis of 2 RCTs[115, 116] reported on the incidence of dizziness or vertigo in a total of 128 participants. The duration of patient follow-up after treatment ranged from 5 to 47 weeks. The meta-analysis demonstrated a clinically significant risk ratio of 0.73 (95% CI: 0.02 to 25.58) with an absolute risk of 26 events/1000 patients (95% CI: -93 to 1,000 events/1000 patients) with use of cabergoline (see supplemental material, **Figure S132**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies, imprecision and inconsistency.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of cabergoline: PLM frequency and sleep latency.

PLM FREQUENCY: The efficacy of cabergoline to decrease PLM frequency was evaluated reported in one RCT[115] in a total of 40 participants. The duration of patient follow-up after treatment was 5 weeks. The meta-analysis demonstrated a decrease of -32.8 PLMs/hour (95% CI: -56.8 to -8.8 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S133**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

SLEEP LATENCY: The efficacy of cabergoline to decrease sleep latency was evaluated reported in one RCT[115]in a total of 40 participants. The duration of patient follow-up after treatment was 5 weeks. Meta-analysis demonstrated a clinically significant decrease of -17.7 minutes (95% CI: -6.9 to 42.3 minutes) (see supplemental material, **Figure S134**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of cabergoline in adults with RLS was moderate based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies, imprecision and inconsistency. (see supplemental material, **Table S19**).

Benefits vs harms

The potential benefits of cabergoline in adults with RLS include a clinically significant improvement in disease severity, QOL and sleep latency. The potential harms include a clinically significant risk of dizziness/vertigo and augmentation that may or may not resolve over time. Other side effects including nausea, depression, and valvular heart disease have been reported.[119, 120] Based on their combined clinical experience and largely based upon its association with valvular heart disease, the TF judged that the potential harms of cabergoline in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs for cabergoline ranges from $2.44 to $2.87 for a 0.5 mg tablet.[26] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. The TF was not certain whether adults with RLS would generally be accepting of treatment with cabergoline.

PICO 2: Adult Populations with RLS and ESRD

Gabapentin

One RCT[121] and 2 observational studies[122, 123] investigated the use of gabapentin in adults with RLS and ESRD to improve one or more of the following outcomes: disease severity, sleep quality, and unwanted side effects. Participants in the RCT received dosages of gabapentin 300mg three times weekly after hemodialysis. Participants had a mean age of 64 years (94% male). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving dosages of 200 mg gabapentin three times weekly after hemodialysis. Meta-analyses were performed to assess the efficacy of gabapentin as a treatment for adults with RLS and CKD/ESRD. The meta-analyses are provided in the supplemental material, **Figure S135** through **Figure S140**. A summary of findings table is provided in the supplemental material, **Table S20**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of gabapentin to treat adults with RLS and CKD: disease severity, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of gabapentin to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[122, 123] in a total of 56 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -18.6 points (95% CI: -21.6 to -15.5 points) as measured by the IRLS (see supplemental material, **Figure S135**). The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

SLEEP QUALITY: The efficacy of gabapentin to improve sleep quality was evaluated based on an analysis of 2 observational studies[122, 123] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 56 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of -10.3 points (95% CI: -13.3 to -7.3) as measured by the PSQI scale (see supplemental material, **Figure S136**. The certainty of evidence for sleep quality was very low due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: One RCT[121] reported on the total adverse events that led to study withdrawal in a total of 16 participants. The duration of patient follow-up after treatment was 6 weeks. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.13 (95% CI: -0.06 to 0.31) with an absolute risk of 130 events/1000 patients (95% CI: -60 to 310 events/1000 patients) with use of gabapentin (see supplemental material, **Figure S137**).

A meta-analysis of 2 observational studies[122, 123]reported on the total adverse events that led to study withdrawal in a total of 58 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of 0.03 (95% CI: -0.03 to 0.10) with an absolute risk of 30 events/1000 patients (95% CI: -30 to 100 events/1000) with use of gabapentin (see supplemental material, **Figure S138**).

One RCT [121]reported on the incidence of somnolence in a total of 16 participants. The duration of patient follow-up after treatment was 6 weeks. The meta-analysis demonstrated a clinically significant risk difference of 0.13

(95%: -0.06 to 0.31) with an absolute risk of 130 events/1000 patients (95% CI: -60 to 310 events/1000 patients) with use of gabapentin (see supplemental material, **Figure S139**).

One observational study[123] reported on the incidence of somnolence in a total of 44 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a clinically significant risk difference of 0.14 (95% CI: 0.03 to 0.24) with an absolute risk of 140 events/1000 patients (95% CI: 30 to 240 events/1000) with use of gabapentin (see supplemental material, **Figure S140**).
The certainty of evidence for adverse effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of gabapentin in adults with RLS and CKD/ESRD was very low based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S20**).

Benefits vs harms

The potential benefits of gabapentin in adults with RLS and ESRD include a clinically significant improvement in disease severity and sleep quality. The potential harms include a clinically significant risk of somnolence that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential benefits of gabapentin in adults with RLS and ESRD outweigh the potential harms.

Resource use

The current unit costs for gabapentin ranges from $0.03 for a 100 mg capsule to $9.20 for a 600 mg tablet.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS and CKD/ESRD would generally be accepting of treatment with gabapentin.

IV Iron Sucrose

One RCT[124] investigated the use of IV iron sucrose in adults with RLS and ESRD to improve one or more of the following outcomes: disease severity. Participants in the RCT received 1000 mg of iron sucrose. Participants had a mean age of 63 years with 20 females and 12 males. Analyses were performed to assess the efficacy of IV iron sucrose as a treatment for adults with RLS and ESRD. The analyses are provided in the supplemental material, **Figure S141** through **Figure S142**. A summary of findings table is provided in the supplemental material, **Table S21**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron sucrose to treat adults with RLS: disease severity and adverse effects.

DISEASE SEVERITY: The efficacy of IV iron sucrose to reduce disease severity as measured by the IRLS was reported in one RCT[124] in a total of 32 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a clinically significant reduction in disease severity of -6.6 points (95% CI: -8.2 to -5.0 points)

as measured by the IRLS (see supplemental material, **Figure S141**). The certainty of evidence was moderate due to small sample size.

ADVERSE EFFECTS: One RCT[124] reported on the total adverse events that led to study withdrawal in a total of 32 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.0 (95% CI: -0.11 to 0.11) with an absolute risk of 0 events/1000 patients (95% CI: -110 to 110 events/1000 patients) with use of IV iron sucrose (see supplemental material, **Figure S142**).

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV iron sucrose in adults with RLS and ESRD was moderate based on the critical outcomes and downgrading of the evidence due to small sample size. (see supplemental material, **Table S21**).

Benefits vs harms

The potential benefits of IV iron sucrose in adults with RLS and ESRD include a clinically significant improvement in disease severity. Based on their combined clinical experience, the TF judged that the potential benefits of IV iron sucrose in adults with RLS and ESRD outweigh the potential harms.

Resource use

The TF judged the costs for IV iron sucrose to be moderate due to cost of infusion at a treatment center.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS and ESRD would generally be accepting of treatment with IV iron sucrose.

Vitamin C

One RCT[125] investigated the use of vitamin C in adults with RLS and ESRD to improve one or more of the following outcomes: disease severity. Participants in the RCT received 200 mg of vitamin C. Participants had a mean age of 56 years (1:1 female-to-male). Meta-analyses were performed to assess the efficacy of vitamin C as a treatment for adults with RLS and ESRD. The meta-analyses are provided in the supplemental material, **Figure S143**. A summary of findings table is provided in the supplemental material, **Table S22**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin C to treat adults with RLS: disease severity.

DISEASE SEVERITY: The efficacy of vitamin C to reduce disease severity as measured by the IRLS was reported in one RCT[125] in a total of 30 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant reduction in disease severity of -6.9 points (95% CI: -9.2 to -4.6 points) as

measured by the IRLS (see supplemental material, **Figure S143**). The certainty of evidence was low due to imprecision and indirectness.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin C in adults with RLS and ESRD was low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, **Table S22**).

Benefits vs harms

The potential benefits of vitamin C in adults with RLS and ESRD include a clinically significant improvement in disease severity. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential benefits of vitamin C in adults with RLS and ESRD outweigh the potential harms.

Resource use

The TF judged the costs for vitamin C are negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most with RLS and ESRD would generally be accepting of treatment with vitamin C.

Levodopa

One RCT[53] and 4 observational studies[122, 123, 126, 127] investigated the use of levodopa in adults with RLS and ESRD to improve one or more of the following outcomes: disease severity, sleep quality, PLM frequency, and unwanted side effects. Participants in the RCT received 100 mg or 200 mg/50 mg of levodopa (with phosphodiesterase inhibitor carbidopa or benserazide). Participants had a mean age of 52 years (56% male). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving 100 mg to 200 mg of levodopa (with phosphodiesterase inhibitor carbidopa or benserazide). Meta-analyses were performed to assess the efficacy of levodopa as a treatment for adults with RLS and ESRD. The meta-analyses are provided in the supplemental material, **Figure S144** through **Figure S149**. A summary of findings table is provided in the supplemental material, **Table S23**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of levodopa to treat adults with RLS and ESRD: disease severity, sleep quality, and unwanted side effects.

DISEASE SEVERITY: The efficacy of levodopa to reduce disease severity as measured by the CGI-S was reported in one RCT[53] in a total of 11 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a non-clinically significant improvement of -0.2 (95% CI: -1.0 to 0.6) as measured by the CGI-S (see supplemental material, **Figure S144**).

The efficacy of levodopa to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[122, 123] in a total of 52 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -14.1 points (95% CI: -16.4 to -11.9 points) as measured by the IRLS (see supplemental material, **Figure S145**).

The certainty of evidence for disease severity ranged from very low to low due to risk of bias associated with observational studies and imprecision.

SLEEP QUALITY: The efficacy of levodopa to improve sleep quality was evaluated based on an analysis of 2 observational studies[122, 123] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 52 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a clinically significant improvement in sleep quality of -7.2 points (95% CI: -10.1 to -4.3) as measured by the PSQI scale (see supplemental material, **Figure S146**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: There were no adverse events leading to study withdrawal reported from the 11 participants in the one RCT[53]. The duration of patient follow-up after treatment ranged was 4 weeks. (see supplemental material, **Figure S147**).

A meta-analysis of 3 observational studies[122, 123, 126, 127] reported on the total adverse events that led to study withdrawal in a total of 69 participants. The duration of patient follow-up after treatment ranged from 4 to 14 weeks. The meta-analysis demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.02 (95% CI: -0.03 to 0.08) with an absolute risk of 20 events/1000 patients (95% CI: -30 to 80 events/1000 patients) with use of levodopa (see supplemental material, **Figure S148**).

The certainty of evidence for unwanted side effects ranged from very low to moderate due to risk of bias associated with observational studies and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of levodopa: PLM frequency.

PLM FREQUENCY: The efficacy of levodopa to decrease PLM frequency was reported in one RCT[53] in a total of 11 participants. The duration of patient follow-up after treatment was 4 weeks. The meta-analysis demonstrated a decrease of -28.0 PLMs/hour (95% CI: -75.0 to 18.9 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S149**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of levodopa in adults with RLS and ESRD was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S23**).

Benefits vs harms

The potential benefits of levodopa in adults with RLS and ESRD include a clinically significant improvement in disease severity and sleep quality, and improvement in PLM frequency. The results also reported significant results

of adverse events leading to study withdrawal. Based on their combined clinical experience, the TF judged that the potential harms of levodopa in adults with RLS and ESRD outweigh the potential benefits.

Resource use

The current unit costs for levodopa was $0.10 for a 25/100 mg tablet. [26]The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the potential harms with augmentation, the TF judged that most with RLS and ESRD would generally not be accepting of treatment with levodopa.

Rotigotine

One RCT[128] investigated the use of rotigotine in adults with RLS and end-stage renal disease to improve one or more of the following outcomes: disease severity, QOL, PLM frequency, sleep latency, WASO and unwanted side effects. Participants in the RCT had a mean age of 55 years (67% male) and were diagnosed with moderate to severe RLS. Participants received dosages of transdermal rotigotine from 1 mg to 3 mg. Meta-analyses were performed to assess the efficacy of rotigotine as a treatment for adults with RLS and end-stage renal disease. The meta-analyses are provided in the supplemental material, **Figure S150** through **Figure S155**. A summary of findings table is provided in the supplemental material, **Table S24**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of rotigotine to treat adults with RLS and end-stage renal disease: disease severity, QOL, and unwanted side effects.

DISEASE SEVERITY: The efficacy of rotigotine to reduce disease severity as measured by the IRLS was reported in one RCT[128] in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant reduction in disease severity of -7.3 points (95% CI: -13.7 to -0.9 points) as measured by the IRLS (see supplemental material, **Figure S150**). The certainty of evidence was moderate due to imprecision.

QOL: The efficacy of rotigotine to improve QOL was evaluated in one RCT[128] that reported on the RLS-QOL Kohnen scale in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. The analysis demonstrated a non-clinically significant improvement in QOL of 0.5 points (95% CI: -8.2 to 9.2 points) as measured by the RLS-QOL Kohnen scale (see supplemental material, **Figure S151**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: One RCT[128] reported on the total adverse events that led to study withdrawal in a total of 30 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.10 (95% CI: -0.09 to 0.29) with an absolute risk of 100 events/1000 patients (95% CI: -90 to 290 events/1000 patients) with use of rotigotine (see supplemental material, **Figure S152**). The certainty of evidence was low due to very serious imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of rotigotine: PLM frequency, sleep latency, and WASO.

PLM FREQUENCY: The efficacy of rotigotine to decrease PLM frequency was evaluated using a meta-analysis of 1 RCT[128] in a total of 25 participants. The duration of patient follow-up after treatment ranged was 5 weeks. The results demonstrated a decrease of -34.0 PLMs/hour (95% CI: -57.5 to -10.5 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S153**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

SLEEP LATENCY: The efficacy of rotigotine to decrease sleep latency was reported in one RCT[128] in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant decrease of -31.7 minutes (95% CI: -79.2 to 15.8 minutes) (see supplemental material, **Figure S154**). The certainty of evidence was low due to very serious imprecision

WASO: The efficacy of rotigotine to decrease WASO was reported in one RCT[128] in a total of 25 participants. The duration of patient follow-up after treatment was 5 weeks. Meta-analysis demonstrated a clinically significant decrease in WASO of -22.8 minutes (95% CI: -64.2 to -18.6 minutes) with rotigotine (see supplemental material, **Figure S155**). The certainty of evidence was low due to very serious imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of rotigotine in adults with RLS and end-stage renal disease was low based on the critical outcomes and downgrading of the evidence due to serious imprecision. (see supplemental material, **Table S24**).

Benefits vs harms

The potential benefits of rotigotine in adults with RLS and end-stage renal disease include a clinically significant reduction in disease severity, QOL, sleep latency and WASO, and improvement in PLM frequency. Side effects including nausea, headache, and asthenia have been reported with the rotigotine transdermal patch. [93]. Augmentation was not considered; however, the study duration was insufficient (5 weeks) to properly assess augmentation. Shared clinical experience of the TF suggests that augmentation does certainly occur with rotigotine. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS and end-stage renal disease does not favor either rotigotine or the comparison.

Resource use

The current unit costs of rotigotine ranges from $22.66 for a 4 mg/24 hr patch to $22.88 for a 8 mg/24 hr patch.[26] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the TF clinical experience, they judged that most with RLS and end-stage renal disease would generally not be accepting of treatment with rotigotine.

PICO 3: Adults with PLMD

Triazolam

A total of 2 RCTs[129, 130] investigated the use of triazolam in adults with PLMD to improve one or more of the following outcomes: excessive daytime sleepiness, sleep latency, WASO, PLM frequency, and unwanted side effects. Participants in the RCTs had a mean age of 53 years (67% male). Participants received 0.25 mg to 0.5 mg triazolam. Meta-analyses were performed to assess the efficacy of triazolam as a treatment for adults with PLMD. The meta-analyses are provided in the supplemental material, **Figure S156** through **Figure S160**. A summary of findings table is provided in the supplemental material, **Table S25**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of triazolam to treat adults with PLMD: excessive daytime sleepiness and unwanted side effects.

EXCESSIVE DAYTIME SLEEPINESS: The efficacy of triazolam to improve excessive daytime sleepiness was evaluated from an analysis of 1 RCT[130] that reported on the Multiple Sleep Latency Test (MSLT) in a total of 24 participants. The duration of patient follow-up after treatment ranged from 4 to 7 days. The analysis demonstrated a clinically significant improvement in excessive daytime sleepiness of 3.4 minutes (95% CI: -0.1 to 6.9) as measured by the MSLT (see supplemental material, **Figure S156**). The certainty of evidence was moderate due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 2 RCTs[130] reported on the total adverse events that led to study withdrawal in a total of 24 participants. The duration of patient follow-up after treatment ranged from 4 days to 12 weeks. In both studies there were no adverse events leading to study withdrawal with use of triazolam (see supplemental material, **Figure S157**). The certainty of evidence was moderate due to imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of triazolam: PLM frequency, sleep latency, and WASO.

PLM FREQUENCY: The efficacy of triazolam to decrease PLM frequency was reported in one RCT[130] in a total of 15 participants. The duration of patient follow-up after treatment ranged from 4 to 7 days. The meta-analysis demonstrated a decrease of -21.3 PLMs/hour (95% CI: -44.5 to 1.9 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S158**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure.

SLEEP LATENCY: The efficacy of triazolam to decrease sleep latency was reported in one RCT[130] in a total of 15 participants. The duration of patient follow-up after treatment ranged from 4 to 7 days. The results demonstrated a non-clinically significant increase of 1.7 minutes (95% CI: -1.06 to 4.5 minutes) (see supplemental material, **Figure S159**). The certainty of evidence was moderate due to imprecision.

WASO: The efficacy of triazolam to decrease WASO was reported in one RCT[130] in a total of 15 participants. The duration of patient follow-up after treatment ranged from 4 to 7 days. Results demonstrated a clinically significant increase in WASO of 11.7 minutes (95% CI: -8.5 to 31.9 minutes) with triazolam (see supplemental material, **Figure S160**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of triazolam in adults with PLMD was moderate based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S25**).

Benefits vs harms

The potential benefits of triazolam in adults with PLMD include a clinically significant improvement in excessive daytime sleepiness. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with PLMD does not favor either triazolam or the comparison.

Resource use

The TF judged the costs of triazolam are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF judged that most patients with PLMD would generally not be accepting of treatment with triazolam.

Valproic Acid

One observational study[131] investigated the use of valproic acid in adults with PLMD to improve one or more of the following outcomes: PLM frequency and unwanted side effects. The observational study is a before-and-after treatment design with participants receiving 150mg to 600mg of valproic acid and serving as their own controls. Analysis were performed to assess the efficacy of valproic acid as a treatment for adults with PLMD. The results are provided in the supplemental material, **Figure S161** and **Figure S162**. A summary of findings table is provided in the supplemental material, **Table S26**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of valproic acid to treat adults with PLMD: unwanted side effects.

ADVERSE EFFECTS: One observational study[131] reported on the total adverse events that led to study withdrawal in a total of 6 participants. The duration of patient follow-up after treatment ranged from 3 months to 3 years. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.33 (95% CI: -0.07 to 0.74) with an absolute risk of 330 events/1000 patients (95% CI: -70 to 740 events/1000 patients) with use of valproic acid (see supplemental material, **Figure S161**). The certainty of evidence was very low due to imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of valproic acid: PLM frequency.

PLM FREQUENCY: The efficacy of valproic acid to decrease PLM frequency was reported in one observational study[131] in a total of 6 participants. The duration of patient follow-up after treatment ranged from 3 months to 3 years. The meta-analysis demonstrated a decrease of -11.3 PLMs/hour (95% CI: -17.5 to -5.1 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S162**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of valproic acid in adults with PLMD was very low based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S26**).

Benefits vs harms

The potential benefits of valproic acid in adults with PLMD include an improvement in PLM frequency. Based on their combined clinical experience, the TF judged that the potential harms of valproic acid in adults with PLMD outweigh the potential benefits.

Resource use

The current unit costs for valproic acid ranges from $0.02 for a 250 mg/5 ml solution to $0.24 for a 250 mg capsule.[26] The TF judged these costs are negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. The TF judged that most with PLMD would generally not be accepting of treatment with valproic acid.

PICO 4: Pediatric Populations with RLS

Oral Iron

A total of 2 observational studies[132, 133] investigated the use of oral iron in children with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. One observational study is a retrospective design and one is a clinical cohort. All participants received 3mg/kg/day of ferrous sulfate and served as their own controls. Meta-analyses were performed to assess the efficacy of oral iron as a treatment for children with RLS. The meta-analyses are provided in the supplemental material, **Figure S163** through **Figure S167**. A summary of findings table is provided in the supplemental material, **Table S27**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of oral iron to treat children with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of oral iron to reduce disease severity as measured by the P-RLS-SS was reported in one observational study[133] in a total of 16 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a reduction in disease severity of -2.5 points (95% CI: -4.7 to -0.3 points) as measured by the P-RLS-SS (see supplemental material, **Figure S163**). The clinical significance of this reduction was not determined as the TF could not reasonably estimate a threshold for this measure.

The efficacy of oral iron to reduce disease severity as measured by the IRLS reported one observational study[132] in a total of 21 participants. The duration of patient follow-up after treatment ranged from 1 to 2 years. The results demonstrated a clinically significant reduction in disease severity of -10.5 points (95% CI: -15.4 to -5.6 points) as measured by the IRLS (see supplemental material, **Figure S164**).

The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: One observational study[133] reported on the total adverse events that led to study withdrawal in a total of 65 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a non-clinically significant risk difference of adverse events leading to study withdrawal of 0.02 (95% CI: -0.03 to 0.06) with an absolute risk of 20 events/1000 patients (95% CI: -30 to 60 events/1000 patients) with use of oral iron (see supplemental material, **Figure S165**).

One observational study[132] reported on the total adverse events that led to study withdrawal in a total of 30 participants. The duration of patient follow-up after treatment ranged from 1 to 2 years. The results reported of no adverse events leading to study withdrawal with use of oral iron (see supplemental material, **Figure S166**).

The certainty of evidence for disease severity was very low due to risk of bias associated with observational studies and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of oral iron to treat children with RLS: PLM frequency.

PLM FREQUENCY: The efficacy of oral iron to decrease PLM frequency was evaluated using a meta-analysis of 1 observational study[132] in a total of 21 participants. The duration of patient follow-up after treatment ranged from 1 to 2 years. The results demonstrated a decrease of 10.5 PLMs/hour (95% CI: -15.4 to -5.6 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S167**). The clinical significance of this increase was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of oral iron in children with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S27**).

Benefits vs harms

The potential benefits of oral iron in children with RLS include a clinically significant reduction in disease severity. Side effects including constipation have been reported. Based on their combined clinical experience, the TF judged that the potential benefits of oral iron in children with RLS outweigh the potential harms.

Resource use

The TF judged the costs of oral iron to be negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in disease severity, the TF judged that most with RLS would generally be accepting of treatment with oral iron.

PICO 5: Special Pediatric Populations with RLS

The task force did not identify any studies reporting evidence for special pediatric populations with RLS.

PICO 6: Pediatric Populations with PLMD

The task force did not identify any studies reporting evidence for pediatric populations with PLMD.

No Recommendations

The following interventions are those for which the task force deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.

PICO 1: Adults with RLS

Intravenous (IV) Iron Sucrose

A total of 2 RCTs[134, 135] investigated the use IV iron sucrose in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. Participants in the RCTs received 1000mg of IV iron sucrose and had a mean age of 51 years (82% female). Meta-analyses were performed to assess the efficacy of intravenous iron (IV) as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S168** through **Figure S169**. A summary of findings table is provided in the supplemental material, **Table S28**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron sucrose to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of IV iron sucrose to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 RCTs[134, 135] in a total of 78 participants. The duration of patient follow-up after treatment ranged from 2 to 11 weeks. The meta-analysis demonstrated a non-clinically significant reduction in disease severity of -1.0 points (95% CI: -5.2 to 3.3 points) as measured by the IRLS (see supplemental material, **Figure S168**). The certainty of evidence for disease severity was low due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 2 RCTs[134, 135] reported on the total adverse events that led to study withdrawal in a total of 78 participants. The duration of patient follow-up after treatment ranged from 2 to 11 weeks. The meta-analysis demonstrated a non-clinically significant risk ratio of adverse events leading to study withdrawal of 3.21 (95% CI: -0.35 to 29.11) with an absolute risk of 84 events/1000 patients (95% CI: 9 to 766 events/1000 patients) with use of IV iron sucrose (see supplemental material, **Figure S169**). The certainty of evidence for unwanted side effects was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV iron sucrose in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to imprecision. (see supplemental material, **Table S28**).

Benefits vs harms

The potential benefits of IV iron sucrose in adults with RLS include a non-clinically significant improvement in disease severity. The potential harms include a non-clinically significant risk of adverse events that lead to study withdrawal. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either IV iron sucrose or the comparison.

Resource use

The TF judged the costs for IV iron sucrose to be moderate.

Clonidine

One RCT[136] investigated the use of clonidine in adults with RLS to improve one or more of the following outcomes: PLM frequency, sleep latency and unwanted side effects. There were no identified studies that investigated the use of clonidine to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received dosages of clonidine from 0.1 mg to 1 mg. Participants had a mean age of 45 years (73% male). Meta-analyses were performed to assess the efficacy of clonidine as a treatment for adults with RLS. The results are provided in the supplemental material, **Figure S170** through **Figure S174**. A summary of findings table is provided in the supplemental material, **Table S29**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of clonidine to treat adults with RLS: unwanted side effects.

ADVERSE EFFECTS: One RCT[136] reported on the total adverse events that led to study withdrawal in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The participants did not have adverse events leading to study withdrawal with use of clonidine (see supplemental material, **Figure S170**).

One RCT[136] reported on the incidence of sleepiness in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a clinically significant risk difference of 0.50 (95% CI: 0.18 to 0.82) with an absolute risk of 500 events/1000 patients (95% CI: 180 to 820 events/1000 patients) with use of clonidine (see supplemental material, **Figure S171**).

One RCT[136] reported on the incidence of lightheadedness in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated a clinically significant risk difference of 0.40 (95% CI: 0.01 to 0.79) with an absolute risk of 400 events/1000 patients (95% CI: 10 to 790 events/1000 patients) with use of clonidine (see supplemental material, **Figure S172**).

The certainty of evidence for unwanted side effects ranged from very low to low due to risk of bias associated with lack of effective blinding and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of clonidine: PLM frequency and sleep latency.

PLM FREQUENCY: The efficacy of clonidine to decrease PLM frequency was reported in one RCT[136] in a total of 10 participants. The duration of patient follow-up after treatment was 2 weeks. The results demonstrated an increase of 12.2 PLMs/hour (95% CI: -15.6 to 40.0 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S173**). The clinical significance of this increase was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

SLEEP LATENCY: The efficacy of clonidine to decrease sleep latency was evaluated reported in one RCT[136] in a total of 10 participants. The duration of patient follow-up after treatment ranged was 2 weeks. Meta-analysis demonstrated a clinically significant decrease of -17.5 minutes (95% CI: -33.7 to -1.3 minutes) (see supplemental material, **Figure S174**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of clonidine in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision. (see supplemental material, **Table S29**).

Benefits vs harms

The potential benefits of clonidine in adults with RLS include a clinically significant improvement in sleep latency. The potential harms include a clinically significant risk of sleepiness and lightheadedness that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either clonidine or the comparison.

Resource use

The current unit costs of clonidine is $0.07 for a 10 mg tablet. [136] The TF judged these costs to be negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with clonidine would be effective for adults with RLS.

Botulinum

A total of 2 RCTs[137, 138] investigated the use of botulinum in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. There were no identified studies that investigated the use of botulinum to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCTs had a mean age of 61 years (54% female) and were diagnosed with moderate to severe RLS. Participants received 70mU to 320mU botulinum toxin injection in their legs. Meta-analyses were performed to assess the efficacy of botulinum as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S175** and **Figure S176**. A summary of findings table is provided in the supplemental material, **Table S30**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of botulinum to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of botulinum to reduce disease severity as measured by the IRLS was reported in 1 RCT[138] in a total of 6 participants. The duration of patient follow-up after treatment was 12 weeks. The results

demonstrated a non-clinically significant reduction in disease severity of -2.3 points (95% CI: -9.0 to 4.4 points) as measured by the IRLS (see supplemental material, **Figure S175**). The certainty of evidence was low due to imprecision.

ADVERSE EFFECTS: A meta-analysis of 2 RCTs[137, 138] reported on the total adverse events that led to study withdrawal in a total of 30 participants. The duration of patient follow-up after treatment was 12 weeks. The results did not have any adverse events leading to study withdrawal. (see supplemental material, **Figure S176**). The certainty of evidence was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of botulinum in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with imprecision. (see supplemental material, **Table S30**).

Benefits vs harms

The potential benefits of botulinum in adults with RLS include a non-clinically significant improvement in disease severity. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either botulinum or the comparison.

Resource use

The TF judged the costs of botulinum are moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with botulinum would be effective for adults with RLS.

Perampanel

One observational study[139] investigated the use of perampanel in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. There were no identified studies that investigated the use of perampanel to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. The observational study is a prospective clinical cohort. All participants received 2 mg to 4 mg of perampanel and served as their own controls Meta-analyses were performed to assess the efficacy of perampanel as a treatment for adults with RLS. The results are provided in the supplemental material, **Figure S177** through **Figure S183**. A summary of findings table is provided in the supplemental material, **Table S31**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of perampanel to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of perampanel to reduce disease severity as measured by the IRLS reported in 1 observational study[139] in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated clinically significant reduction in disease severity of -12.2 points (95% CI: -15.1 to -9.3 points) as measured by the IRLS (see supplemental material, **Figure S177**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

UNWANTED SIDE EFFECTS: One observational study[139] reported on the total adverse events that led to study withdrawal in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant risk difference of adverse events leading to study withdrawal of 0.05 (95% CI: -0.08 to 0.18) with an absolute risk of 50 events/1000 patients (95% CI: -80 to 180 events/1000 patients) with use of perampanel (see supplemental material, **Figure S178**).

One observational study[139] reported on the incidence of dizziness in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant risk difference of 0.30 (95% CI: -0.09 to 0.51) with an absolute risk of 300 events/1000 patients (95% CI: 90 to 510 events/1000 patients) with use of perampanel (see supplemental material, **Figure S179**).

An analysis of 1 observational study[139] reported on the incidence of somnolence in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant risk difference of 0.10 (95% CI: -0.05 to 0.25) with an absolute risk of 100 events/1000 patients (95% CI: -50 to 250 events/1000) with use of perampanel (see supplemental material, **Figure S180**).

The certainty of evidence of disease severity was very low due to risk of bias associated with observational studies and imprecision.

Important Outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for evaluating the efficacy of perampanel: PLM frequency, sleep latency, and WASO.

PLM FREQUENCY: The efficacy of perampanel to decrease PLM frequency was reported in 1 observational study[139] in a total of 20 participants. The duration of patient follow-up after treatment ranged was 8 weeks. The meta-analysis demonstrated a decrease of -23.4 PLMs/hour (95% CI: -26.5 to -20.3 PLMs/hour) as measured by the PLMI (see supplemental material, **Figure S181**). The clinical significance of this decrease was not determined as the TF could not reasonably estimate a threshold for this measure. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

SLEEP LATENCY: The efficacy of perampanel to decrease sleep latency was reported in 1 observational study[139] in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant decrease of -11.9 minutes (95% CI: -18.1 to -5.7 minutes) (see supplemental material, **Figure S182**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

WASO: The efficacy of perampanel to decrease WASO was evaluated reported in 1 observational study[139] in a total of 20 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant decrease in WASO of -49.2 minutes (95% CI: -63.5 to -35.0 minutes) with perampanel (see supplemental material, **Figure S183**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of perampanel in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see supplemental material, **Table S31**).

Benefits vs harms

The potential benefits of perampanel in adults with RLS include a clinically significant improvement in disease severity, PLM frequency, sleep latency and WASO. The potential harms include a clinically significant risk of dizziness and somnolence that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential harms of perampanel in adults with RLS outweigh the potential benefits.

Resource use

The current unit costs of perampanel range from $17.85 for a 2 mg tablet to $35.29 for a 12 mg tablet.[26] The TF judged these costs are moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with perampanel would be effective for adults with RLS.

Vitamin D

A total of 1 RCT[140] and 2 observational studies[141, 142] investigated the use of vitamin D in adults with RLS to improve one or more of the following outcomes: disease severity. There were no identified studies that investigated the use of vitamin D to treat adults with PLMD, and children with RLS or PLMD. Participants in the RCT received dosages of 50,000 IU vitamin D and had a mean age of 43 years (69% male). All observational studies were before-and-after treatment design with participants serving as their own controls and receiving dosages of 28,000 IU or 50,000 IU vitamin D. Meta-analyses were performed to assess the efficacy of vitamin D as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S184** and **Figure S185**. A summary of findings table is provided in the supplemental material, **Table S32**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin D to treat adults with RLS: disease severity.

DISEASE SEVERITY: The efficacy of vitamin D to reduce disease severity as measured by the IRLS was reported in 1 RCT[140] in a total of 22 participants. The duration of patient follow-up after treatment was 12 weeks. The results

demonstrated a clinically significant increase in disease severity of 4.2 points (95% CI: -4.1 to 12.5 points) as measured by the IRLS (see supplemental material, **Figure S184**). The certainty of evidence was low due to imprecision.

The efficacy of vitamin D to reduce disease severity as measured by the IRLS was evaluated using a meta-analysis of 2 observational studies[141, 142] in a total of 24 participants. The duration of patient follow-up after treatment ranged from 2 to 8 months. The meta-analysis demonstrated a clinically significant reduction in disease severity of -9.8 points (95% CI: -21.7 to 2.0 points) as measured by the IRLS (see supplemental material, **Figure S185**).

The certainty of evidence for disease severity ranged from very low to low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin D in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see supplemental material, **Table S32**).

Benefits vs harms

The potential benefits of vitamin D in adults with RLS include a clinically significant improvement in disease severity. The potential harms include a clinically significant risk of dizziness and somnolence that may or may not resolve over time. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either vitamin D or the comparison.

Resource use

The TF judged the costs of vitamin D to be negligible.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with vitamin D would be effective for adults with RLS.

Yoga

A total of 1 RCT[143] and 1 observational study[144] investigated the use of yoga in adults with RLS to improve one or more of the following outcomes: disease severity and sleep quality. There were no identified studies that investigated the use of yoga to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT completed a 12-week yoga program and had a mean age of 51 years (78% female). The observational study is a before-and-after treatment design with participants serving as their own controls and completing an 8-week yoga program. Meta-analyses were performed to assess the efficacy of yoga as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S186** through **Figure S188**. A summary of findings table is provided in the supplemental material, **Table S33**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of yoga to treat adults with RLS: disease severity and sleep quality.

DISEASE SEVERITY: The efficacy of yoga to reduce disease severity as measured by the IRLS was reported in 1 RCT[143] in a total of 40 participants. The duration of patient follow-up after treatment was 12 weeks. The results demonstrated a clinically significant reduction in disease severity of -5.3 points (95% CI: -9.6 to -1.1 points) as measured by the IRLS (see supplemental material, **Figure S186**). The certainty of evidence was low due to imprecision and risk of bias associated with inadequate blinding.

SLEEP QUALITY: The efficacy of yoga to improve sleep quality was evaluated based on an analysis of 1 RCT[143] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 40 participants. The duration of patient follow-up after treatment was 12 weeks. The analysis demonstrated a non-clinically significant improvement in sleep quality of -1.2 points (95% CI: -3.2 to 0.8 points) as measured by the PSQI scale (see supplemental material, **Figure S187**).

The efficacy of yoga to improve sleep quality was evaluated based on an analysis of 1 observational study[144] in a total of 10 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant improvement in pooled sleep quality of 1.1 points (95% CI: 0.2 to 1.2 points) (see supplemental material, **Figure S188**).

The certainty of evidence for sleep quality ranged from very low due to risk of bias associated with observational studies and imprecision, to low due to imprecision and risk of bias associated with inadequate blinding.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of yoga in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision (see supplemental material, **Table S33**).

Benefits vs harms

The potential benefits of yoga in adults with RLS include a clinically significant improvement in disease severity and sleep quality. Based on their combined clinical experience, the TF judged that the potential benefits of yoga in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of yoga to be moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with yoga would be effective for adults with RLS.

Acupuncture

One RCT[32] investigated the use of acupuncture in adults with RLS to improve one or more of the following outcomes: disease severity and sleep quality. There were no identified studies that investigated the use of

acupuncture to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 10 sessions of medical acupuncture along with 300mg of gabapentin daily. Participants in the control arm of the trial also received 300mg of gabapentin daily. Participants had a mean age of 48 years (82% male). Meta-analyses were performed to assess the efficacy of acupuncture as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S189** and **Figure S190**. A summary of findings table is provided in the supplemental material, **Table S34**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of acupuncture to treat adults with RLS: disease severity and sleep quality.

DISEASE SEVERITY: The efficacy of acupuncture to reduce disease severity as measured by the IRLS was reported in 1 RCT[32] in a total of 33 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a difference in disease severity of -2.5 points (95% CI: -10.0 to 5.0 points) as measured by the IRLS (see supplemental material, **Figure S189**). The certainty of evidence was very low due to imprecision and risk of bias associated with inadequate blinding.

SLEEP QUALITY: The efficacy of acupuncture to improve sleep quality was evaluated based on an analysis of 1 RCT[32] that reported on the Pittsburgh Sleep Quality Index (PSQI) scale in a total of 33 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a difference in sleep quality of 2.5 points (95% CI: -1.9 to 6.9 points) as measured by the PSQI scale (see supplemental material, **Figure S190**). The certainty of evidence was low due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of acupuncture in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision. (see supplemental material, **Table S34**).

Benefits vs harms

The potential benefits of acupuncture in adults with RLS include an improvement in disease severity and sleep quality. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either acupuncture or the comparison.

Resource use

The TF judged the costs of acupuncture to be moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with acupuncture would be effective for adults with RLS.

Cognitive Behavioral Therapy

A total of 1 observational study[145] investigated the use of CBT in adults with RLS to improve one or more of the following outcomes: disease severity and quality of life. There were no identified studies that investigated the use

of CBT to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. The observational study is a prospective clinical cohort in a proof-of-concept trial. All participants received eight, 90-minute group sessions and served as their own controls. Meta-analyses were performed to assess the efficacy of CBT as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S191** and **Figure S192**. A summary of findings table is provided in the supplemental material, **Table S35**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of CBT to treat adults with RLS: disease severity and quality of life.

DISEASE SEVERITY: The efficacy of CBT to reduce disease severity as measured by the IRLS was reported in 1 observational study[145] in a total of 25 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant reduction in disease severity of -7.0 points (95% CI: -10.8 to -3.2 points) as measured by the IRLS (see supplemental material, **Figure S191**). The certainty of evidence for disease severity was very low to low due to risk of bias associated with observational studies and imprecision.

QUALITY OF LIFE: The efficacy of CBT to improve QOL was evaluated from an analysis of 1 observational study[145] that reported on the QOL-RLS Kohnen scale in 25 participants. The duration of patient follow-up after treatment was 8 weeks. The analysis demonstrated a clinically significant improvement in QOL of -7.4 points (95% CI: -13.7 to -1.1) as measured by the QOL-RLS Kohnen scale (see supplemental material, **Figure S192**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of CBT in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with observational studies and imprecision. (see supplemental material, **Table S35**).

Benefits vs harms

The potential benefits of CBT in adults with RLS include a clinically significant improvement in disease severity and quality of life. Based on their combined clinical experience, the TF judged that the potential benefits of CBT in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of CBT to be moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with cognitive behavioral therapy would be effective for adults with RLS.

Near Infrared Light Therapy

One RCT[146] investigated the use of near infrared light therapy in adults with RLS to improve the outcome of disease severity. There were no identified studies that investigated the use of near infrared light therapy to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the

RCT received 3 treatments per week for 4 weeks. Participants had a mean age of 48 years (1:1 female-to-male). Meta-analyses were performed to assess the efficacy of near infrared light therapy as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure 193**. A summary of findings table is provided in the supplemental material, **Table S36**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of near infrared light therapy to treat adults with RLS: disease severity.

DISEASE SEVERITY: The efficacy of near infrared light therapy to reduce disease severity as measured by the IRLS was reported in 1 RCT[146] in a total of 34 participants. The duration of patient follow-up after treatment was 5 weeks. The results demonstrated a clinically significant reduction in disease severity of -8.3 points (95% CI: -12.3 to -4.3 points) as measured by the IRLS (see supplemental material, **Figure S193**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of near infrared light therapy in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision. (see supplemental material, **Table S36**).

Benefits vs harms

The potential benefits of near infrared light therapy in adults with RLS include a clinically significant improvement in disease severity. The TF judged the potential harms of near infrared light therapy are small. Based on their combined clinical experience, the TF judged that the potential benefits of near infrared light therapy in adults with RLS probably outweigh the potential harms.

Resource use

The unit costs of near infrared light therapy range in price between $400 and $1,200. The TF judged these costs as moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with near infrared light therapy would be effective for adults with RLS.

Tramadol

One observational study[147] investigated the use of tramadol in adults with RLS to improve one or more of the following outcomes: disease severity and unwanted side effects. There were no identified studies that investigated the use of tramadol to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the observational study received dosages of tramadol from 50 mg to 150 mg. Participants had a mean age of 56 years (66% female). Meta-analyses were performed to assess the efficacy of tramadol as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S194** through

Figure S196. A summary of findings table is provided in the supplemental material, **Table S37**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of tramadol to treat adults with RLS: disease severity and unwanted side effects.

DISEASE SEVERITY: The efficacy of tramadol to reduce disease severity as measured by the IRLS was reported in 1 observational study[147] in a total of 10 participants. The duration of patient follow-up after treatment was between 15 and 24 months. The results demonstrated a significant reduction in disease severity of -80.2 points (95% CI: -90.7 to -69.7 points) as measured by subjective distress scale (see supplemental material, **Figure S194**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision.

ADVERSE EFFECTS: One observational study[147] reported on the total adverse events that led to study withdrawal in a total of 12 participants. The duration of patient follow-up after treatment was between 15 and 24 months. The results demonstrated a non-significant risk difference of adverse events leading to study withdrawal of 0.00 (95% CI: -0.15 to 0.15) with an absolute risk of 0 events/1000 patients (95% CI: -150 to 150 events/1000 patients) with use of tramadol (see supplemental material, **Figure S195**).

One observational study[147] reported on the incidence of dizziness in a total of 12 participants. The duration of patient follow-up after treatment was 15 to 24 months. The results demonstrated a non-significant risk difference of 0.08 (95% CI: -0.12 to 0.29) with an absolute risk of 83 events/1000 patients (95% CI: -73 to 240 events/1000 patients) with use of tramadol (see supplemental material, **Figure S196**).

The certainty of evidence for unwanted side effects was very low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of tramadol in adults with RLS was very low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision. (see supplemental material, **Table S37**).

Benefits vs harms

The potential benefits of tramadol in adults with RLS include a significant improvement in disease severity. The potential harms include a risk of dizziness that may or may not resolve over time. No risk of augmentation was reported. Based on their combined clinical experience, the TF judged that the potential benefits of tramadol in adults with RLS outweigh the potential harms.

Resource use

The current unit costs of tramadol range from $0.02 for a 50 mg tablet to $2.19 for a 300mg tablet.[21] The TF judged these costs as negligible.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with tramadol would be effective for adults with RLS.

Transcranial Magnetic Stimulation

One RCT[148] investigated the use of transcranial magnetic stimulation in adults with RLS to improve disease severity. There were no identified studies that investigated the use of transcranial magnetic stimulation to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 10 treatments total, one every day for 3 days, across thirty days. Participants had a mean age of 56 years. Meta-analyses were performed to assess the efficacy of clonidine as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S197**. A summary of findings table is provided in the supplemental material, **Table S38**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of transcranial magnetic stimulation to treat adults with RLS: disease severity.

DISEASE SEVERITY: The efficacy of transcranial magnetic stimulation to reduce disease severity as measured by the IRLS was reported in 1 RCT[148] in a total of 19 participants. The duration of patient follow-up after treatment was 4 weeks. The results demonstrated a clinically significant reduction in disease severity of -15.9 points (95% CI: -19.9 to -11.9 points) as measured by the IRLS (see supplemental material, **Figure S197**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of transcranial magnetic stimulation in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision. (see supplemental material, **Table S38**).

Benefits vs harms

The potential benefits of transcranial magnetic stimulation in adults with RLS include a clinically significant improvement in disease severity. The TF judged the potential harms of transcranial magnetic stimulation are small. Based on their combined clinical experience, the TF judged that the potential benefits of transcranial magnetic stimulation in adults with RLS probably outweigh the potential harms.

Resource use

The TF judged the costs of transcranial magnetic stimulation as moderate.

Patient values and preferences

The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with transcranial magnetic stimulation would be effective for adults with RLS.

Transcutaneous Spinal Direct Current Stimulation

One RCT[149] investigated the use of transcutaneous spinal direct current stimulation in adults with RLS to improve one or more of the following outcomes: disease severity and sleep quality. There were no identified studies that investigated the use of transcutaneous spinal direct current stimulation to treat special populations of adults with RLS, adults with PLMD, and children with RLS or PLMD. Participants in the RCT received one treatment daily, for 14 days. Participants had a mean age of 62 years (77% female). Meta-analyses were performed to assess the

efficacy of transcutaneous spinal direct current stimulation as a treatment for adults with RLS. The meta-analyses are provided in the supplemental material, **Figure S198** and **Figure 199**. A summary of findings table is provided in the supplemental material, **Table S39**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of transcutaneous spinal direct current stimulation to treat adults with RLS: disease severity and sleep quality.

DISEASE SEVERITY: The efficacy of transcutaneous spinal direct current stimulation to reduce disease severity as measured by the IRLS was reported in 1 RCT[149] in a total of 30 participants. The duration of patient follow-up after treatment was 2 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -8.4 points (95% CI: -13.6 to -3.2 points) as measured by the IRLS (see supplemental material, **Figure S198**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

SLEEP QUALITY: The efficacy of transcutaneous spinal direct current stimulation to improve sleep quality was reported in 1 RCT[149] in 30 participants that reported on the Pittsburgh Sleep Quality Index (PSQI) scale. The duration of patient follow-up after treatment was 2 weeks. The analysis demonstrated a non-clinically significant improvement in sleep quality of -1.6 points (95% CI: -4.2 to 1.0) as measured by the PSQI scale (see supplemental material, **Figure S199**). The certainty of evidence was low due to risk of bias associated with lack of effective blinding and imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of transcutaneous spinal direct current stimulation in adults with RLS was low based on the critical outcomes and downgrading of the evidence due to risk of bias associated with lack of effective blinding and imprecision. (see supplemental material, **Table S39**).

Benefits vs harms

The potential benefits of transcutaneous spinal direct current stimulation in adults with RLS include a clinically significant improvement in disease severity. The TF judged the potential harms of transcutaneous spinal direct current stimulation are small. Based on their combined clinical experience, the TF judged that the potential benefits of transcutaneous spinal direct current stimulation in adults with RLS outweigh the potential harms.

Resource use

The TF judged the costs of transcutaneous spinal direct current stimulation as moderate.

Patient values and preferences

The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with transcutaneous spinal direct current stimulation would be effective for adults with RLS.

PICO 2: Adult Populations with RLS and ESRD

Intravenous (IV) Iron Dextran

One RCT[150] investigated the use IV iron dextran in adults with RLS and ESRD to improve one or more of the following outcomes: disease severity and adverse effects. Participants in the RCTs received 1000mg of IV iron

dextran and had a mean age of 56 years (37% female). Analyses were performed to assess the efficacy of IV iron dextran as a treatment for adults with RLS and ESRD. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of IV iron dextran to treat adults with RLS: disease severity and adverse effects.

DISEASE SEVERITY: The efficacy of IV iron dextran to reduce disease severity as measured by a non-validated disease severity score was evaluated using analysis of 1 RCT[150] in a total of 25 participants. The duration of patient follow-up after treatment was 4 weeks. The analysis demonstrated a reduction in disease severity but by 4 weeks they showed worsening in both groups. The TF was unable to determine clinician significance as the RLS scale used was not a validated tool. The certainty of evidence for disease severity was low due to imprecision.

ADVERSE EFFECTS: The one RCT[150] reported on adverse events but did not lead to study withdrawal in a total of 25 participants. The duration of patient follow-up after treatment was 4 weeks. The adverse events reported were nausea, headache and vomiting.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of IV iron dextran in adults with RLS and ESRD was low based on the critical outcomes and downgrading of the evidence due to imprecision.

Benefits vs harms

The potential benefits of IV iron dextran in adults with RLS and ESRD include a non-clinically significant improvement in disease severity. The potential harms include a non-clinically significant risk of adverse events that lead to study withdrawal. Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults with RLS does not favor either IV iron dextran or the comparison.

Resource use

The TF judged the costs for IV iron dextran to be moderate.

Vitamin C + Vitamin E

1 RCT[125] investigated the use of vitamin C + vitamin E in adults on hemodialysis with RLS to improve one or more of the following outcomes: disease severity. There were no identified studies that investigated the use of vitamin C + vitamin E to treat adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 200 mg vitamin C and 400 mg vitamin E. Participants had a mean age of 53 years (63% female). Meta-analyses were performed to assess the efficacy of vitamin C + vitamin E as a treatment for adults on hemodialysis with RLS. The meta-analyses are provided in the supplemental material, **Figure S200**. A summary of findings table is provided in the supplemental material, **Table S40**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin C + vitamin E to treat adults on hemodialysis with RLS: disease severity.

DISEASE SEVERITY: The efficacy of vitamin C + vitamin E to reduce disease severity as measured by the IRLS was reported in 1 RCT[125] in a total of 30 participants. The duration of patient follow-up after treatment was 8 weeks. The results demonstrated a clinically significant reduction in disease severity of -7.2 points (95% CI: -10.3 to -4.1 points) as measured by the IRLS (see supplemental material, **Figure S200**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin C + vitamin E in adults on hemodialysis with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see supplemental material, **Table S40**).

Benefits vs harms

The potential benefits of vitamin C + vitamin E in adults on hemodialysis with RLS include a clinically significant improvement in disease severity. The TF notes that a dose of vitamin E of 400 mg and greater may increase mortality risk in certain populations.[151, 152] Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms in adults on hemodialysis with RLS does not favor either vitamin C + vitamin E or the comparison.

Resource use

The TF judged the costs for vitamin C + vitamin E are negligible.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes. Given the limited evidence, the TF were unable to determine if treatment with vitamin C + vitamin E would be effective for adults with RLS.

Vitamin E

1 RCT[125] investigated the use of vitamin E in adults on hemodialysis with RLS to improve one or more of the following outcomes: disease severity. There were no identified studies that investigated the use of vitamin E to treat adults with PLMD, and children with RLS or PLMD. Participants in the RCT received 400 mg vitamin E and had a mean age of 53 years (63% female). Meta-analyses were performed to assess the efficacy of vitamin E as a treatment for adults on hemodialysis with RLS. The meta-analyses are provided in the supplemental material, **Figure S201**. A summary of findings table is provided in the supplemental material, **Table S41**. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of vitamin E to treat adults on hemodialysis with RLS: disease severity.

DISEASE SEVERITY: The efficacy of vitamin E to reduce disease severity as measured by the IRLS was reported in 1 RCT[125] in a total of 30 participants. The duration of patient follow-up after treatment was 8 weeks. The meta-analysis demonstrated a clinically significant reduction in disease severity of -7.0 points (95% CI: -10.4 to -3.6 points) as measured by the IRLS (see supplemental material, **Figure S201**). The certainty of evidence was moderate due to imprecision.

Overall certainty of evidence

The TF determined that the overall certainty of evidence for the use of vitamin E in adults on hemodialysis with RLS was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see supplemental material, **Table S41**).

Benefits vs harms

The potential benefits of vitamin E in adults on hemodialysis with RLS include a clinically significant improvement in disease severity. The TF notes that a dose of vitamin E of 400 mg and greater may increase mortality risk in certain populations.[151, 152] Based on their combined clinical experience, the TF judged that the balance of potential benefits and harms of vitamin E in adults on hemodialysis with RLS does not favor either vitamin E or the comparison.

Resource use

The TF judged the costs for vitamin E are negligible.

Patient values and preferences

The TF judged that there is no important uncertainty or variability in how much patients value the main outcomes.

Given the limited evidence, the TF were unable to determine if the balance of effects with vitamin E treatment would be effective for adults with RLS.

OTHER INTERVENTIONS

The TF also identified studies reporting evidence for interventions where the GRADE process was not applied, and these interventions were not considered for recommendations in the accompanying clinical practice guideline. These studies had limited data on critical or important outcomes or biased study designs or methods. These interventions, in alphabetical order, are as follows: alpha-dihydroergocryptine, [153] bromocriptine,[67, 154] cryotherapy,[155] deep brain stimulation (in patients with Parkinson's),[156] exercise,[157-163] foot massage,[164] heat therapy,[164] hot/cold baths,[165] hypericin,[166] hydrocortisone,[167] intrathecal morphine,[168] istradefylline,[169] levetiracetam (in children with ADHD),[170] light therapy,[171] magnesium (in patients with PLMD),[172] melatonin,[171] methadone,[173, 174] olive oil massage or lavender oil massage,[175, 176] pneumatic compression,[177, 178] pramipexole (in patients with spinal cord injury or type II diabetes)[179, 180], refaximine,[181] vibration pads[182] and foot compression wrap.[177]

DISCUSSION AND FUTURE DIRECTIONS

This systematic review delivers an updated and comprehensive assessment of published research on the treatment of RLS and PLMD in both adults and children. The use of the GRADE methodology offers a systematic approach that minimizes bias with recommendations based on the balance between the benefits and harms of each treatment intervention. Initially, the TF determined six PICO questions relevant to this systemic review. No studies meeting inclusion criteria were found for three of the six PICO questions (adults with PLMD, special populations of children with RLS, and children with PLMD) and two (children with RLS and adults with PLMD) had very few studies, leaving the majority of the analyzed studies on RLS in adults and special populations of adults with RLS.

For each PICO, the TF identified critical outcomes, and then measurement tools for each outcome. For RLS in both adults in children, disease severity was the primary focus along with sleep quality and quality of life in most categories. The most heavily weighted outcome measure was the International RLS Study Group Scale (IRLS), as this tool has been used in the vast majority of clinical trials in the past three decades. It is a validated clinical scale, demonstrating concurrent criterion validity with the clinical global impression of severity. Further, it incorporates all three of these critical outcomes in one scale. Adverse effects (AEs) were also a critical outcome shared by all six PICOs. Within adverse effects, the TF elected to focus on those most relevant to clinical practice, including AEs leading to study withdrawal to capture all major side effects. There was a focus on augmentation, drowsiness/somnolence, and dizziness, with the latter two being among the most common for classes of drugs with central nervous system effects. AEs specific to a drug, but not shared among other drug classes, were also highlighted, such as cardiac valvulopathy in the case of cabergoline.

The development of clinical significance thresholds (CST) was a challenge for this guideline as there were inadequately established relationships between treatment-related changes in scales and underlying clinical symptoms, even in the most widely employed instruments. Further, some non-validated measurements, including many visual analogue scales, used primarily in studies predating the IRLS, could not be used at all given the lack of such validation between CST and a meaningful clinical change. Because of the wide variety of metrics available to assess aspects of RLS, some of the less utilized or clinically relevant tools were only employed when higher quality ones such as the IRLS or Epworth Sleepiness Scale (ESS) were not available. As a result of these shortcomings, a small number of treatments could not be evaluated. However, the TF did not find that this affected the results of the overall recommendations.

Perhaps the biggest change from the previous systematic review in 2012[1] was the focus on augmentation as a critical adverse effect of dopaminergic medications. This assessment led to conditional recommendations against the use for all non-ergotamine dopamine agonists and levodopa as initial therapy in the treatment of RLS in adults and in special populations of adults with RLS. In this systematic review, RCTs generally resulted in higher quality evidence over observational studies. However, as noted in the clinical practice guidelines, augmentation is a complication that generally develops only after long-term treatment. RCT durations are generally on the order of weeks or months, rather than a year or several years that it may take for augmentation to become apparent. Thus, the vast majority of RCTs did not assess, and could not capture, augmentation. The TF analyzed augmentation incidence in the few clinical trials that did assess this outcome, but determinations were also supported by high-quality retrospective studies as well as the extensive experience of the TF members.

Prior to literature search, the TF sought to maintain broad inclusion criteria. Larger RCTs took precedence in the evaluation process, but observational studies with as few as five subjects were included. However, many of the RLS treatments had very small observational or even randomized samples that met inclusion criteria but provided insufficient data for any recommendations. Other treatments had more clinical evidence, but the TF could not make any recommendation based on the available research and instead gave “no recommendation,” signifying the need and encouragement for further research on these approaches. The lack of recommendation for or against these treatments should not be a barrier to use, when clinically indicated, nor should it be an obstacle to further research regarding their harms and benefits.

The systematic review includes information on periodic limb movements in sleep (PLMS), though these did not contribute to our clinical recommendations in the clinical practice guidelines. Currently, the index of PLMS

(PLMI) measured in polysomnography has no clear utility in the evaluation of RLS disease severity, as the two are poorly correlated both cross-sectionally and as changed with treatment. However, in the future, research may demonstrate that PLMI is relevant in this condition in either short- or long-term outcomes.

There were very few studies that met inclusion criteria for the treatment of PLMD in adults, and none in children, and no new treatment studies were identified since the last systematic review. PLMD cannot be diagnosed unless RLS, REM sleep behavior disorder, untreated OSA, and narcolepsy are excluded in the patient. This sets a high standard for PLMD diagnosis, which makes research in this area difficult.

Within the broad category of special populations of adults with RLS, most studies meeting inclusion were in adults with RLS and comorbid chronic kidney disease/end-stage renal disease. There were no studies found for the PICO questions of special populations of children with RLS or children with PLMD. There was very little published on the treatment of RLS in children outside of oral iron supplementation, though this is an important addition to the new guidelines. Though intravenous iron and many of the same medications used in adults are employed clinically in children, currently there have been no published trials meeting inclusion criteria to be assessed in this systematic review.

Future Directions

With widespread prescribing of dopaminergic medications over the past quarter century and a significant portion of those with RLS now having augmentation, prospective, randomized clinical trials specific to those having RLS with augmentation are needed. Studies assessing the relative efficacy and long-term safety of iron, alpha-2-delta ligands, and opioids, and their ability to allow taper and discontinuation of dopaminergic agents in such patients will be of substantial clinical value. More use of quantitative measurements of augmentation severity in such treatment trials would be particularly helpful aside from the gold-standard measurements of RLS disease severity.

Very few clinical trials were identified in this systematic review for pediatric and special populations with RLS, highlighting the need for future studies to focus on identifying the underlying causes of pediatric RLS and developing targeted treatments that address these causes. Equally, patients with RLS comorbid with other medical conditions may provide challenges for our existing clinical trial protocols and efficacy outcomes. For instance, patients with Parkinson's Disease and RLS may already be taking dopaminergic agents and trials of add-on therapy may be appropriate. Further, in this population, assessment of an intervention's effect on the underlying movement disorder may be appropriate. Similarly, treatment studies with pregnant women may want to include outcomes for the pregnancy and the fetus. Beyond special populations, sub-typing of RLS, for instance those with a "painful" variant of RLS, with linkage to specific genetic polymorphisms, may provide more personalized treatments.

Given the complexities in the diagnosis of PLMD, in order for high level research to be conducted on this disorder, it is critical to lay forth specific criteria for the evaluation and diagnosis of PLMD. Currently these research criteria for PLMD are being developed by a task force commissioned by the International RLS Study Group. These consensus criteria will standardize assessment for a disorder in which diagnosis has historically been challenged by numerous clinical confounders. The introduction of these criteria will allow studies to be conducted to outline prevalence of PLMD and then beyond these studies to assess efficacy of different treatments of PLMD.

RLS is a clinical diagnosis, and its severity is assessed clinically. However, objective tests would be welcome in sub-typing RLS, in complementing RLS severity scales, and for assessing changes with treatment. Currently, there is ongoing research with imaging in RLS including the assessment of iron in the central nervous system, but other diagnostic techniques that may correlate with symptoms are needed as well. Further development in interpreting and employing limb movement analysis could also fill the void in objective assessment. The single night PLMI measured by polysomnography is presently lacking in utility, but devices capable of longitudinal nightly measurement of sleep-related limb movements may be coming and may provide better clinical relevance. Lastly, as RLS severity instruments are entirely obtained through self-report, it is essential that non-pharmacological treatment trials incorporate adequate masking, particularly for devices and procedures, where strong placebo effects are present.

Forty years ago, RLS was generally unknown to the medical community. The dramatic acute efficacy and associated FDA approvals of the dopaminergic agents increased awareness of RLS within both the public and medical community. Consequently, there was an initial surge of enthusiasm and satisfaction about RLS treatment. Subsequently, the discovery of clear genetic associations from large GWAS and demonstrations of brain iron deficiency (and the efficacy of iron treatments) led to optimism about progress into further translation of RLS physiology into clinical practice. However, the increasing incidence of dopaminergically-mediated iatrogenic worsening of RLS symptoms has led to a new surge of severely affected RLS patients whose treatment is now more complex and pressing. Education, such as this systematic review, about treatment options is now particularly important given that most clinicians continue to prescribe dopaminergic agents as first-line treatment for RLS. This systematic review looks back at the last forty years with some pride at our progress, some disappointment at our naivete, but some optimism that continued research will translate into better treatments for RLS in the future.

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