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The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults—An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses

An American Academy of Sleep Medicine Clinical Practice Guideline

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A systematic literature review and meta-analyses (where appropriate) were performed to update the previous AASM practice parameters on the treatments, both dopaminergic and other, of RLS and PLMD. A considerable amount of literature has been published since these previous reviews were performed, necessitating an update of the corresponding practice parameters. Therapies with a STANDARD level of recommendation include pramipexole and ropinirole. Therapies with a GUIDELINE level of recommendation include levodopa with dopa decarboxylase inhibitor, opioids, gabapentin enacarbil, and cabergoline (which has additional caveats for use). Therapies with an OPTION level of recommendation include carbamazepine, gabapentin, pregabalin, clonidine, and for patients with low ferritin levels, iron supplementation. The committee recommends a STANDARD AGAINST the use of pergolide because of the risks of heart valve damage. Therapies for RLS secondary to ESRD, neuropathy, and superficial venous insufficiency are discussed. Lastly, therapies for PLMD are reviewed. However, it should be mentioned that because PLMD therapy typically mimics RLS therapy, the primary focus of this review is therapy for idiopathic RLS.

Keywords: Restless legs syndrome, RLS, periodic limb movement disorder, PLMD, sleep-related movement disorders

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1.0 INTRODUCTION

The purpose of this review is to survey and provide an evidence-based update of the literature and corresponding practice parameters in the area of the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). Two previous reviews have been published by the American Academy of Sleep Medicine (AASM): the first was in 1999 and called "The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder,"[2] and the most recent was published in 2004 called "An Update on the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder."[3] Two practice parameters have also been published: "Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder"[4] and "Practice Parameters for the Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder."[5]

2.0 BACKGROUND

2.1 Diagnosis

Most studies published after 2003 reference either the ICSD-2[6] or the International RLS Study Group (IRLS)[7] diagnostic criteria. The four cardinal diagnostic features of RLS include (1) an urge to move the limbs that is usually associated with paresthesias or dysesthesias, (2) symptoms that start or become worse with rest, (3) at least partial relief of symptoms with physical activity, and (4) worsening of symptoms in the evening or at night. RLS frequently also has a primary motor symptom that is characterized by the occurrence of periodic leg movements in sleep (PLMS). PLMS occur in approximately 80% to 90% of patients who have RLS and support the diagnosis of RLS. These criteria are based on the published report by Allen et al.[7] (IRLS) from a workshop held at the National Institutes of Health and are endorsed by the ICSD-2.

PLMD is characterized by periodic episodes of repetitive limb movements during sleep, which most often occur in the lower extremities, including the toes, ankles, knees, and hips, and occasionally in the upper extremities. These movements may be associated with an arousal, and if so, sleep disruption can cause excessive daytime sleepiness. PLMD is thought to be rare as PLMS are typically associated with RLS, REM sleep behavior disorder (RBD), or narcolepsy and represent a distinct diagnosis from PLMD.[6] It should be noted that while an extensive amount of literature on the treatment of RLS has emerged since the prior practice parameter update, the data on therapy for PLMD has essentially remained unchanged. Due to the scarcity of PLMD therapy data and the fact that the occurrence of only PLMD is uncommon, the current practice parameter primarily focuses on the therapies for RLS, while recommendation levels are not given for pharmacological therapies for PLMD.

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2.2 Treatment Efficacy Measures

Due to the multifaceted nature of RLS, many different treatment efficacy measures have been used to assess RLS severity, sleep quality, and quality of life, both subjectively and objectively. There is some consensus in recent studies to focus on the IRLS rating scale[8] (IRLS) and the Clinical Global Impression (CGI) scale.[9] Both of these are subjective rating scales. The IRLS was validated in 2003.[8] It consists of a 10-question assessment of RLS in a format of 0 to 4, 0 being "never" or "none," and 4 being "very severe" or "very often." The severity of RLS is rated as: 1-10 mild; 11-20 moderate; 21-30 severe; and 31-40 very severe. The CGI has 3 sections: (1) Severity of illness; (2) Global improvement (CGII) or change (CGIC), and (3) Efficacy index. Most, if not all, studies document the proportion of patients with an investigator-rated score of "much improved" (2) or "very much improved" (1) on the CGI-I (or –C) scale (defined as a "response" on this 7-point overall global improvement scale, a non-disease specific outcome measure in which 1 = very much improved and 7 = very much worse).

Other subjective measures include the RLS-6, which was used typically prior to 2003, the Patient Global Impression (PGI), the Sleep Questionnaire Form A, Quality of Life (QoL) for RLS, the Augmentation Severity Rating Scale (ASRS), Visual Analog Scales (VAS), and the Medical Outcomes Study sleep scale (MOS). A variety of other scales have been used occasionally such as the Self-Rating Zung Depression Scale (SDS) and Anxiety Scale (SAS), the SF-36 (MOS short form health survey), the work productivity and activity impairment (WPAI) survey, the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression Scale (HADS), subjective sleep and awakening quality scale (SSA), and the Epworth Sleepiness Scale (ESS).

The only objective measurements included are sleep-related parameters by polysomnography (PSG) or actigraphy. The most salient include Periodic Limb Movements in Sleep (PLMS), PLM index (PLMI), PLMs arousal index (PLMS-AI), and sleep efficiency.

3.0 METHODS

3.1 Literature Search

The literature search was performed using a combination of MeSH terms and keywords. The MeSH terms were Restless Legs Syndrome and Nocturnal Myoclonus Syndrome. The keywords were: restless legs syndrome, periodic limb movement disorder, PLMD, sleep-related movement disorder(s), leg motor activity, myoclonic hyperkinesias, nocturnal myoclonus syndrome, RLS, periodic leg movement(s), periodic limb movement(s), sleep leg movement(s), and PLM. All therapies were searched with a start date of 11-1-1997 (6 months prior to previous search). Results on dopaminergic treatments between 11-1-97 to 11-1-2001 already covered in the 2004 update were excluded. The Cochrane Highly Sensitive Search Strategy[10] for identifying randomized trials in MEDLINE was applied to the search. The search was performed first on August 12, 2010, and updated again on June 29, 2011, to capture the latest literature. The limits of the search were: humans, English, all adults (no pediatrics), randomized controlled trials (RCTs), and no editorials, letters, comments, or case reports. Studies on treatments for RLS with fewer than 10 subjects completing the study and for treatments of PLMD with fewer than 5 subjects completing the study were rejected. Also, studies with less than 1 week of treatment time were rejected. A total of 378 hits were obtained and supplemented by pearling. The final number of articles included for all treatments with either benefit/efficacy or harm data is 126.

3.2 PICO Questions

PICO (**P**opulation, **I**ntervention, **C**omparison, **O**utcome) questions were developed for the review, and are summarized in Table 1.

3.3 Meta-Analysis

To compare the range of treatment options available for RLS and PLMD, one outcome measure was chosen for which the majority of studies presented data: the International Restless Legs Syndrome Rating Scale (IRLS). Data on other outcomes measures besides IRLS are summarized and presented in a descriptive manner for further information for the reader. Thus for medications that were studied prior to the development of the IRLS, meta-analysis was not performed. All meta-analyses were performed using MIX software.[11,12] All analyses are presented using the random effects model.

The result of each meta-analysis is shown in a figure with several components. Each study of the meta-analysis is identified along the left-hand column (study ID), and adjacent to it is the year of the study, treatment (exposed, "e") results, and control ("c") results. The results are expressed as "n/M/SD" corresponding to "number/mean/standard deviation." A graphical representation of the data is shown in the center of the figure. The vertical red line indicates the average response of all studies. The zero line represents no effect. The width of the red diamond at the bottom of the plot represents the standard deviation of the meta-analysis. If the red diamond does not touch the zero line, the meta-analysis results indicate that the treatment is different from zero (i.e., it has an effect). The magnitude of the effect across all studies is given by the value of the association measure along with the 95% confidence intervals.

Tables of the data used in the meta-analyses are presented at the end of the manuscript in the Appendix.

3.4 Quality of Evidence

The assessment of evidence quality was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. The GRADE system differs from other grading systems as each study is not only evaluated for study design and risk of bias, but, additionally, an estimate of effect (see footnote following article) is generated for each outcome. Multiple aspects of quality are assessed including study limitations, imprecision, inconsistency of results, indirectness of evidence, and likeliness of publication bias. The quality of evidence from observational studies can be adjusted by the presence of large magnitudes of effect, evidence of dose-response associations, and all plausible confounders that increase the confidence in the estimated effects.[13] Quality refers to the confidence that the estimates of the effects are correct, and the quality rating is applied to a body of evidence and not to individual studies.[1]

Table 1—PICO question parameters

Population	Intervention	Comparison	Outcome
Adults diagnosed with RLS using the ICSD-2 or the International RLS Study Group (IRLS) diagnostic criteria	Pramipexole Ropinirole Levodopa Pergolide Cabergoline Opioids Gabapentin Enacarbil Gabapentin Pregabalin Carbamazepine Clonidine Iron supplementation Rotigotine Lisuride Amantadine Talipexole Peribedil Alpha-dihydroergocryptine Clonazepam Valproic acid Valerian Antidepressants	Control group, those with untreated RLS, or those with RLS using an alternate treatment	Subjective measures: 1. IRLS rating scale 2. Clinical Global Impression (CGI) Scale 3. RLS-6 4. Patient Global Impression (PGI) 5. Sleep Questionnaire Form A 6. Quality of Life (QoL) for RLS 7. Augmentation Severity Rating Scale (ASRS) 8. Visual Analog Scales (VAS) 9. Medical Outcomes Study Sleep Scale (MOS) 10. Self-Rating Zung Depression Scale (SDS) 11. Anxiety Scale (SAS) 12. SF-36 13. Work productivity and activity impairment (WPAI) 14. Pittsburgh Sleep Quality Index (PSQI) 15. Hospital Anxiety and Depression Scale (HADS) 16. Subjective sleep and awakening quality scale (SSA) 17. Epworth Sleepiness Scale (ESS) Objective measures: 1. Sleep-related parameters by polysomnography a. PLMS b. PLMI c. PLMS-AI d. Sleep efficiency e. TST f. % TIB without leg movements g. PLMWI 2. Sleep-related parameters by actigraphy a. Leg movements b. Sleep efficiency

Briefly, risk of bias includes aspects of study design (randomized control trials [RCTs] versus non-randomized controlled trials or before-after trials)[14] and conduct such as blinding, allocation concealment, large loss to follow-up, or selective outcome reporting.[15] Imprecision refers to wide confidence intervals around the estimate of effect when there are relatively few patients and few events. Indirectness occurs when the question being addressed is different than the available evidence regarding population, intervention, comparator, or outcome. There is inconsistency when there is unexplained heterogeneity of the results. Reporting bias can occur if there is selective reporting of studies or outcomes, which may occur if the published evidence is limited to a small number of trials funded by a for-profit organization.[15]

As a first step, all individual studies were assessed by 2 task force members for study design, and limitations to validity (bias) for each outcome of interest.[16,17] Randomized control trials (RCTs) were considered a higher level of evidence than observational, nonrandomized, or before-after interventional studies (Table 2). Subsequently, the body of evidence for each outcome was assessed and graded, taking into account the results of the meta-analysis (if applicable) and other factors as described above. The final assessment, as defined in Box 1, was determined for each treatment and outcome measure.

The results are reported as evidence profiles in each section that include the number of studies, study design, limitations, inconsistency, indirectness, imprecision, and other considerations that went into the quality of evidence for each outcome of interest. Also reported are the number of patients that were studied, the overall effect that was calculated in the meta-analysis (reported as the *mean difference* [MD]), and a qualitative assessment of the relative importance of the outcome.

One reviewer extracted the data and graded the studies and another verified this compiled information. The systematic review of the evidence was additionally reviewed by an outside expert who was an author on both previous review papers (2004 and 1999). The AASM Standards of Practice Committee (SPC) then reviewed the assessments of bodies of evidence as well.

3.5 Strength of Recommendations

The SPC developed these practice parameters based on the strength of evidence for efficacy of each therapy counterbalanced by an assessment of the relative benefits of each treatment versus the potential risks as delineated in Table 3. The Board of Directors of the AASM subsequently approved these practice parameters. All members of the AASM SPC and Board of Directors completed detailed conflict-of-interest statements and were found to have no conflicts of interest with regard to this subject. The recommendations were also critically reviewed by an outside expert, and the concerns that were raised were addressed by the SPC prior to approval by the Board.

Table 2—A summary of GRADE's approach to rating quality of evidence[1]

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Radomized trials	High →	Risk of bias	Large effect	High (four plus:⊕⊕⊕⊕)
		−1 Serious	+1 Large	
		−2 Very serious	+2 Very large	
		Inconsistency	Dose response	Moderate (three plus:⊕⊕⊕○)
		−1 Serious	+1 Evidence of a gradient	
		−2 Very serious	All plausible residual confounding	
Observational studies	Low →	Indirectness	+1 Would reduce a demonstrated effect	Low (two plus:⊕⊕○○)
		−1 Serious	+1 Would suggest a spurious effect if no effect was observed	
		−2 Very serious		
		Imprecision		Very Low (one plus:⊕○○○)
		−1 Serious		
		−2 Very serious		
		Publication bias		
		−1 Likely		
		−2 Very likely		

Table 3—AASM levels of recommendations

Assessment of benefit/harm/burden	Overall quality of evidence: High	Moderate	Low	Very Low
Benefits clearly outweigh harm/burden	Standard	Standard	Guideline	Option
Benefits closely balanced with harm/burden OR uncertainty in the estimates of benefit/harm/burden	Guideline	Guideline	Option	Option
Harm/burden clearly outweighs benefits	Standard	Standard	Standard	Standard

Box 1—Final assessments of level of bodies of evidence[1]

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding propriety of any specific care must be made by the physician, in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.

The AASM expects these guidelines to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. These practice parameters reflect the state of knowledge at the time of publication and will be reviewed, updated, and revised as new information becomes available. Definitions of levels of recommendations used by the AASM appear in Table 3. Particularly noteworthy on this table is that when harm/burden clearly outweighs benefit, a STANDARD level of recommendation **against** the proposed therapy is given regardless of the overall quality of evidence. ***Sections titled "Values and Trade-offs" appear under each individual practice parameter. The Values and Trade-offs discussion elucidates the rationale leading to each recommendation. These sections are an integral part of the GRADE system and offer transparency to the process***.[18]

4.0 RECOMMENDATIONS FOR THERAPIES FOR RLS

The salient detailed data from the studies was extracted and can be found in evidence tables, available at http://www.aasmnet.org/practiceguidelines.aspx. Table 4 shows a summary of the recommendation statements organized by strength of recommendation, including the body of evidence level, the assessment of the harm/benefit balance and the FDA status of the intervention.

Table 4—Summary of recommendation statements

Practice Parameter	Strength of Recommendation	Body of Evidence Level	Harm/burden Assessment	FDA status
Standards for use in RLS				
Clinicians should treat patients with RLS with pramipexole.	(STANDARD)	High	Benefits clearly outweigh harms	Approved for indication
Clinicians should treat patients with RLS with ropinirole.	(STANDARD)	High	Benefits clearly outweigh harms	Approved for indication
Standards against use in RLS				
Clinicians should not treat RLS patients with pergolide because of the risks of heart valve damage.	(STANDARD)	High	Harms clearly outweigh benefits	Discontinued
Guidelines for use in RLS				
Clinicians can treat RLS patients with levodopa with dopa decarboxylase inhibitor.	(GUIDELINE)	High	Benefits closely balanced with harms. This is particularly true for those with intermittent RLS who use this medication sporadically.	Approved, but off-label use
Clinicians can treat RLS patients with opioids.	(GUIDELINE)	Low	Benefits clearly outweigh harms	Approved, but off-label use
Clinicians can treat patients with RLS with gabapentin enacarbil.	(GUIDELINE)	High	Uncertainty in balance between benefits and harms	Approved for indication
Given the potential of side effects, including heart valve damage, clinicians can treat RLS patients with cabergoline *only if* other recommended agents have been tried first and failed, and close clinical follow-up is provided.	(GUIDELINE)	High	Benefits closely balanced with harms	Approved, but off-label use
Options for use in RLS				
Clinicians may treat RLS patients with gabapentin.	(OPTION)	Low	Unclear benefit/harm balance	Approved, but off-label use
Clinicians may treat patients with RLS with pregabalin.	(OPTION)	Low	Benefits closely balanced with harms	Approved, but off-label use
Clinicians may treat RLS patients with carbamazepine.	(OPTION)	Low	Benefits closely balanced with harms	Approved, but off-label use
Clinicians may treat RLS patients with clonidine.	(OPTION)	Low	Unclear benefit/harm balance	Approved, but off-label use
Clinicians may use supplemental iron to treat RLS patients with low ferritin levels.	(OPTION)	Very Low	Unclear benefit/harm balance	Approved, but off-label use
PLMD				
There is insufficient evidence at present to evaluate the use of pharmacological therapy in patients diagnosed with PLMD alone.	(NO RECOMMENDATION)	Insufficient	N/A	N/A

4.1 Introduction to Therapies for RLS

There are 2 types of therapies for RLS: pharmacotherapy and non-pharmacotherapy. The use of pharmacotherapy has been more widespread. Newer non-pharmacotherapies, such as cognitive behavioral therapy or exercise therapy, are still being investigated.

One interesting recent study has highlighted the importance of the placebo effect in RLS studies. Fulda and Wetter[19] performed a meta-analysis on the treatment of RLS and estimated the magnitude of this effect at 40%. This reinforces the need for placebo-controlled studies to determine the true effect of any treatment.

4.2 Pharmacotherapy

4.2.1 Dopaminergic medications

Overall, dopaminergic agents are the most extensively investigated and used therapies for the treatment of RLS. Since the

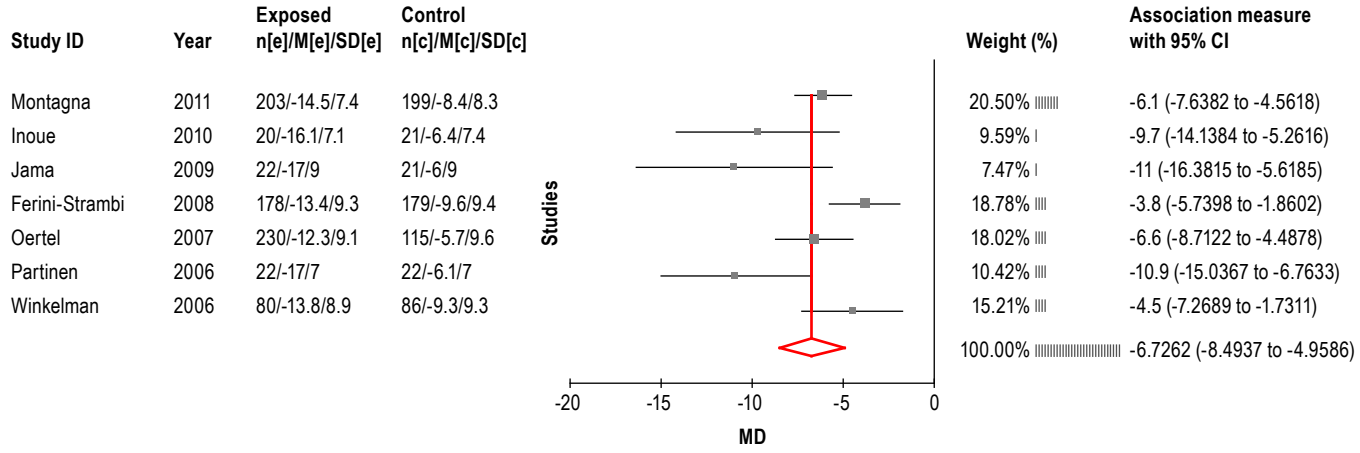

Figure 1—Meta-analysis of pramipexole IRLS data, improvement over placebo.

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pramipexole	Control	Absolute	
IRLS Rating Scale (follow-up 3 to 12 weeks; range of scores: 0-40; Better indicated by lower values)										
7	RCTs	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	possible reporting bias	755	643	MD 6.7 lower (4.9 to 8.5 lower)	⊕⊕⊕⊕ HIGH

Figure 2—Evidence profile for pramipexole.

prior practice parameter update, the literature has advanced considerably with regards to both the number and quality of studies for dopaminergic treatment of RLS. While these agents confer many benefits, there are some adverse effects that should be recognized. Similar to patients with Parkinson's disease, RLS patients treated with dopamine agonists may develop dopamine dysregulation syndrome.[20-25] These patients may exhibit an addictive pattern of dopamine replacement therapy use and/or behavioral disturbances including punding and impulse control disorders such as pathologic gambling, compulsive shopping, compulsive eating, and hypersexuality. One report[20] indicated a prevalence of 7% for pathologic gambling and 23% for compulsive eating in RLS subjects treated with a dopaminergic medication. Case reports indicate that discontinuation of the dopamine agonist results in resolution or improvement of the impulse control disorder,[26-28] although these patients may be particularly susceptible to dopamine agonist withdrawal syndrome.[29] The levodopa review encompassed an aggregate of medications with varying dopa decarboxylase inhibitor types (DDCI).

4.2.1.1 Non-ergot derived dopamine agonist: pramipexole

The dopamine agonist pramipexole is effective in the treatment of moderate-to severe RLS. (*Level of evidence:* High) This recommendation was a guideline in the previous practice parameter. An additional 8 short-term studies[30-37] (3 to 12 weeks) of treatment of patients with moderate-to-severe idiopathic RLS and 2 studies[38,39] on long-term efficacy up to 1 year have been published. All studies showed improved RLS symptom severity according to IRLS[30-37] as well as other measures of RLS including: MOS sleep disturbance and sleep adequacy[30]; CGI-I[30-32,34,37]; PGI-I[30,33,34,37]; RLS QoL[30,31,33]; PLM index[33-35]; PSQI[37]; and VAS.[31] In patients with RLS-related mood disturbance, Montagna et al.[36] also reported an improvement in mood impairment (Beck Depression Inventory II). In patients with RLS and mood impairment, Hornyak et al.[40] reported a statistically significant decrease in RLS-related limb pain as assessed by VAS. Lastly, Inoue et al.[37] reported that older age and mild RLS severity were significantly associated with early response to low-dose pramipexole therapy in their study of Japanese patients.

A meta-analysis was performed on all RCT studies with placebo control, and the results are shown in Figure 1. The results show an average improvement of 6.7 points (95% CI 4.9 to 8.5) in the IRLS scale with pramipexole use over placebo. The trials with larger patient populations trend toward an approximate improvement of 5 points. Figure 2 summarizes the evidence profile.

The long-term studies (open label, 26 to 52 weeks in length) report a 17-point improvement in IRLS scores over baseline with pramipexole use. See the online supplement at http://www.aasmnet.org/practiceguidelines.aspx for the detailed data.

Some other studies have been published that were low level evidence (Saletu et al.,[41] Stiasny-Kolster and Oertel,[42] Silber et al.[43]), and all reported improvements in RLS symptoms with pramipexole use. The study by Trenkwalder et al.[44] on the effects of pramipexole withdrawal after 6 months of use showed that patients switched to placebo experienced worsening symptoms over those who continued to receive pramipexole.

Pramipexole is well tolerated.[30-34,36,45] Inoue et al.,[38] Montagna et al.,[36] and Partinen et al.[39] also reported that adverse events (AEs) were mild to moderate in intensity and typical for non-ergot dopamine agonists. These included nausea and somnolence, which typically decreased in frequency over time, and nasopharyngitis. Winkelman and Johnston[46] and Silber et al.[43]

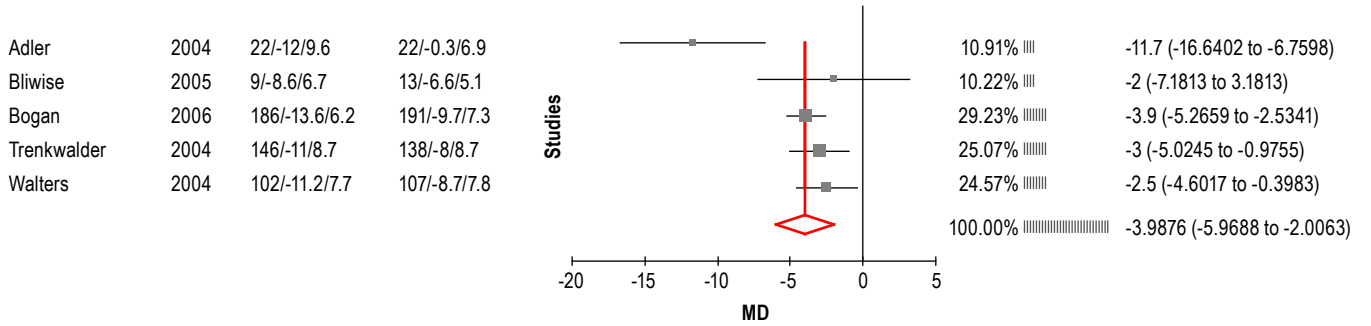

Figure 3—Meta-analysis of ropinirole IRLS data, improvement over placebo.

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ropinirole	Control	Absolute	
IRLS Rating Scale (follow-up 2-12 weeks; measured with: Points; range of scores: 0-40; Better indicated by lower values)										
5	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	Possible reporting bias	465	471	MD 4.0 lower (2.0 to 6.0 lower)	⊕⊕⊕⊕ HIGH

Figure 4—Evidence profile for ropinirole.

reported that augmentation occurred in one-third of the patients on extended pramipexole use, but was manageable by earlier dosing in the day, small dose increases,[46] or increased doses earlier in the day.[43] Silver et al.[47] reported that (1) over 10 years the average annual rate of augmentation leading to discontinuation of pramipexole was 7% in the 164 patients studied; (2) the percentage continuing medication over 5 years was 58%; and (3) the daily dose of pramipexole at the time of discontinuation for augmentation, as opposed to all other reasons, was 1.28 ± 1.0 vs. 0.66 ± 0.5 mg. Trenkwalder et al.[44] reported no augmentation after 9 months of use in 150 patients, and Inoue et al.[38] reported no augmentation in 140 patients after 1 year of use.

4.2.1.1a: Clinicians should treat patients with RLS with pramipexole. (STANDARD)

Values and Trade-Offs: Pramipexole is upgraded to standard from the previous practice parameter based on multiple studies showing efficacy in RLS. Pramipexole is typically well tolerated and side effects are self-limited with cessation of pramipexole therapy.

4.2.1.2 Non-ergot derived dopamine agonist: ropinirole

The dopamine agonist ropinirole is effective in the treatment of moderate-to-very severe RLS (*Level of evidence*: High). This recommendation was an option in the previous practice parameter. Since then an additional 5 RCTs [48-52] have been published. The studies were well conducted and reported consistent results, with just one[48] outlier as shown in Figure 3. This study included only 22 patients. Four other studies reported results that could not be used in the meta-analysis: Allen et al.[53] gave only the adjusted treatment difference without any standard deviations or details; Kushida et al.[54] provided imprecise data with very large standard deviations; Montplaisir et al.[55] reported results compared to 24 weeks treated instead of baseline; and Garcia-Borreguero et al.[56] reported a non-randomized treatment trial without placebo control. All data can be found in the online supplement at http://www.aasmnet.org/practiceguidelines.aspx.

The data from the RCT studies were combined into a meta-analysis. The average improvement in IRLS score over placebo was 4 points (95% CI: 2 to 6) as shown in Figure 3. The body of evidence level is judged to be high. The evidence profile is summarized in Figure 4.

The patients had moderate-to-severe idiopathic RLS. Eight studies showed significant improvement with ropinirole versus placebo on IRLS[48-52,54-56] and other measures (RLS symptom diary,[48] PLMS,[52,53] PLM with arousal,[53] PLM while awake,[53] ability to initiate sleep,[53] sleep adequacy [MOS],[49,50,53,56] PLMI [actigraphy],[49] CGII responders,[49,50,54,56] PGI,[54] MOS sleep disturbance,[50,55,56] MOS somnolence,[50,55,56] MOS sleep quantity,[50,55,56] RLS QoL,[50,55,56] anxiety [HADS],[49] WPAI,[56] SF-36,[56] and patient relapse[55]).

Ropinirole is also effective in the treatment of severe-to-very severe RLS. This conclusion is based on an analysis of pooled data[57] from four 12-week clinical trials[49-51,53] of 223 patients with IRLS scores ≥ 24 compared to those receiving placebo (n = 240). The mean treatment difference was > 3 points in these patients. An increasing treatment effect with ropinirole and not placebo was reported with increasing RLS severity. Additional improvements in global symptoms, sleep, and quality of life were also reported.

Two studies did not show greater efficacy than placebo. Although IRLS was significantly better than baseline in the 4 weeks of open testing by Bliwise et al.,[52] no difference compared to placebo was noted after an additional 2 weeks of randomized testing. Allen also reported a nonsignificant effect of ropinirole on IRLS after 12 weeks.[53] Unfortunately, the data were not reported in a format that allowed inclusion in the meta-analysis.

Ropinirole was found to be effective[48-51,53,55,56] and generally well tolerated.[48-51,55,56] The most common side effects were nausea,[48,50,52-54,56] headache,[50,52-54,56] dizziness,[48,53] somnolence,[52,54] and vomiting.[54] Adverse events led to discontinuation in 8.7% of patients in one study.[56] The incidence of augmentation was reported to be between 0%[50,51] and 2.3%.[56] The mean daily dose ranged from 1.5[51] to 4.6[48] mg/d taken 1-3 hours before bedtime[50,51,53] or in divided doses.[54] A significant placebo effect was reported in one study.[54]

4.2.1.2a: Clinicians should treat patients with RLS with ropinirole. (STANDARD)

Values and Trade-Offs: This recommendation is upgraded to standard from the previous practice parameter based on multiple studies with RCT data showing efficacy in RLS therapy. Ropinirole is typically well tolerated and side effects are self limited with cessation of ropinirole therapy.

4.2.1.3 Levodopa

Levodopa is effective in the treatment of RLS, but carries the risk of augmentation (*Level of evidence:* High). This conclusion and evidence level is based primarily on the data from the previous review paper.[3] Since the last review in 2004, new formulations of levodopa have been studied (combinations of sustained and regular release L-dopa[58,59] or Stalevo,[60] which contains L-dopa, carbidopa, and entacapone [LCE]) and there has been progress in understanding augmentation.[61] The newer studies were limited by short duration RCT but followed by an open clinical trial (Saletu et al.[58]), outcome measures other than IRLS reported (Polo et al.[60]), nonrandomized and open label (Hogl et al.[61] and Trenkwalder et al.[59]).

Both Trenkwalder et al.[59] and Saletu et al.[58] found improvements in RLS symptoms with the combination of sustained release (sr) and regular release (rr) L-dopa, although Trenkwalder et al. found that roughly 66% of the subjects terminated therapy before the end of a year due to probable augmentation. The dose at 1-year in the Trenkwalder study (mean rr-L-dopa 203 ± 101 mg with 185 ± 93 mg sr-L-dopa) was higher than the 4-week dose in the Saletu study (mean rr-L-dopa 100 ± 38.5 mg with 112 ± 33.2 mg sr-L-dopa). Trenkwalder reported improved quality of sleep, reduced sleep latency, increased total sleep time, reduced severity of RLS at time of falling asleep and during the night, but increased severity of RLS during the day. Global improvement was found in 56% of patients, 30% were unchanged, and 9% were slightly worse. Saletu reported a significant reduction of PLM/h TST from 20.0 ± 14.7 to 4.5 ± 4.9 ($P < 0.01$), as well as reduction of all other objective RLS/PLM variables. However, treatment did not improve sleep efficiency or subjective sleep quality with respect to placebo. Other scales (IRLS, PSQI, SSA, VAS) also improved significantly. Trenkwalder et al.[59] recommended that other treatments be sought if more than 400 mg L-dopa is required to treat RLS patients.

In a randomized controlled crossover trial of 2 days for each treatment, Polo et al.[60] studied Stalevo, a new formulation of L-dopa that potentially provides longer symptom control throughout the night by incorporating entacapone. The mean PLMI and TIB were significantly reduced compared with placebo. Compared with levodopa/carbidopa 100/25 mg, levodopa/carbidopa/entacapone 100/25/200 mg and levodopa/carbidopa/entacapone 150/37.5/200 mg reduced PLMs during the second half ($P = 0.06$ and $P < 0.001$, respectively) or the last 3 h of the night ($P < 0.05$ and $P < 0.01$, respectively). Single doses of LCE with up to 150 mg L-dopa were effective and also well tolerated without typical side effects such as nausea. Of note, Stalevo is on an FDA watch list with concerns about possible increased risk of both prostate cancer and cardiovascular disease.

Hogl et al.[61] reported during a 6-month multi-center, open-label trial with flexible dosing of levodopa that augmentation with L-dopa occurred in 60% of the patients and caused 12% to discontinue treatment by 6 months. The median time to occurrence of augmentation was 71 days. Compared to those without augmentation, patients with augmentation were significantly more likely to be on higher doses of levodopa (≥ 300 mg, 83 vs. 54%, $P = 0.03$) and to show less improvement of symptom severity.

4.2.1.3a: Clinicians can treat RLS patients with levodopa with dopa decarboxylase inhibitor. (GUIDELINE)

Values and Trade-Offs: This recommendation is changed from the previous practice parameter, where it was given a STANDARD level of recommendation for use. Levodopa has longstanding clinical use in RLS with concomitant concerns for daytime RLS augmentation and early morning rebound of RLS symptoms. The use of levodopa may be most advantageous for those patients with intermittent RLS symptoms that do not require daily therapy. For those that require daily therapy for RLS, the newer dopaminergic agents may be a better choice. Therapy should be tailored to the individual patient's specific circumstances and needs. Vigilance for secondary impulsive behavior as an adverse reaction is needed.

4.2.1.4 Ergot-derived dopamine agonists: pergolide and cabergoline

The dopamine agonist pergolide is effective in the treatment of RLS but has been withdrawn in the U.S. because of the risk of cardiac valvulopathy. (*Level of evidence:* High) Although determined as effective based on the previous review,[3] pergolide has been voluntarily withdrawn by the manufacturer in the United States because of risk of heart valve damage. Only 1 study by Trenkwalder et al.[62] has been published since the last review was written. Pergolide was found to significantly reduce PLMS-AI, PLMI, RLS severity (IRLS), CGI response, and PGI response versus placebo; however, sleep efficiency did not improve. The mean dose for the double-blinded patients was 0.52 ± 0.22 mg/d and for the open-label patients was 0.72 ± 0.42 mg/d at 12 months. With regard to side effects; nausea and headache were more frequent with pergolide than with placebo. The authors conclude that low-dose pergolide was well tolerated and maintained its efficacy in the long term.

The dopamine agonist cabergoline is effective in the treatment of moderate-to-severe RLS. (*Level of evidence:* High) *The dopamine agonist cabergoline is more effective in the treatment of RLS than levodopa, but is not as well tolerated*. (*Level of evidence:* Moderate) The recommendation was an option in favor of cabergoline use in the previous practice parameter because of 1 low-level study. A significant amount of evidence[63-66] has been published since the previous review. These studies investigated the effects of cabergoline in patients with moderate-to-severe idiopathic RLS and one in severe-to-

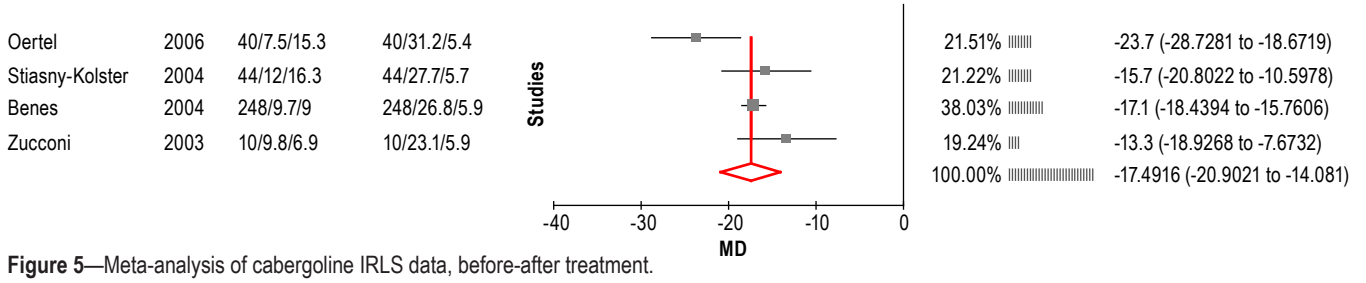

Figure 5—Meta-analysis of cabergoline IRLS data, before-after treatment.

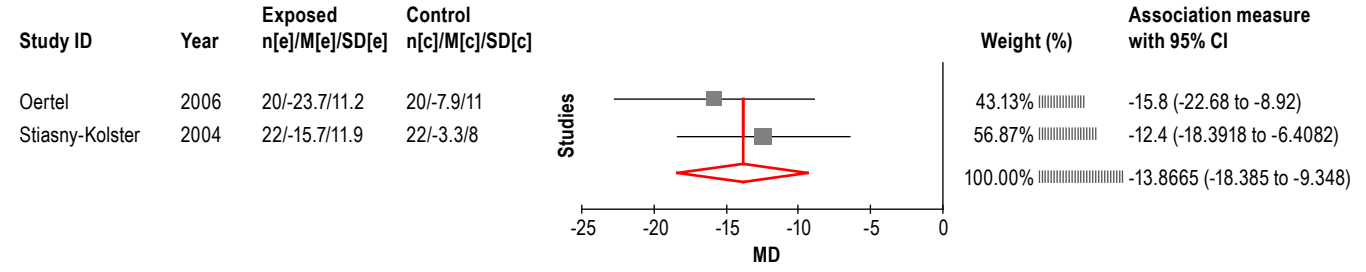

Figure 6—Meta-analysis of cabergoline IRLS data, improvement over placebo.

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cabergoline	Control	Absolute	
IRLS Rating Scale for RCTs (follow-up mean 5 weeks; measured with: points; range of scores: 0-40; Better indicated by lower values)										
2	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	42	MD 14 lower (9 to 18 lower)	⊕⊕⊕⊕ HIGH
IRLS Rating Scale for Before-After data for all trials (follow-up 2 to 12 months; range of scores: 0-40; Better indicated by lower values)										
4	2 RCT and 2 non-randomized trials	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	300	([1])	MD 17.5 lower (14 to 21 lower)	⊕⊕○○ LOW

Figure 7—Evidence profile for cabergoline. [1]Patients served as their own controls for before-after treatment effect.

very severe RLS patients.[66] The average effective dose was approximately 2 mg, at least 3 h before bedtime.[64] All studies reported significant improvement in IRLS.[63-66] The meta-analysis of the before-after treatment data show an average decrease in IRLS of 17.5 points (95% CI: 14 to 21 point improvement; see Figure 5), and the 2 RCTs show a decrease in IRLS of 16[63] and 12[64] with an average decrease of 14 (95% CI: 9 to 18 point improvement] over the control group (Figure 6). Other secondary measures including PLMS-AI, PLM-I, PLMS-I, sleep efficiency, sleep time, sleep quality,[63,62] QoL, RLS-6 (day and night),[63,64,66] CGI severity,[63,62] sleep diaries,[64] and nocturnal activity (actigraphy) also improved.[62,65] Figure 7 summarizes the evidence profile.

An additional RCT[67] compared the effect of cabergoline versus levodopa. Direct comparison[67] showed cabergoline to be superior to L-dopa with respect to efficacy (by IRLS, time to discontinuation of therapy or augmentation, RLS-6, QoL, SF-A, CGI, and ASRS). In terms of IRLS, cabergoline showed an improvement over L-dopa of 6.6 (95% CI 8.6 to 4.7) points, and, versus baseline, of 15.6 ± 10.8. However, L-dopa was found to be better tolerated: 95% of patients on L-dopa vs. 85% on cabergoline were determined to have no or mild side effects.

Cabergoline is primarily indicated in treatment of prolactinoma with associated risk of visual field loss. Cabergoline carries a comparatively much stronger risk-to-benefit ratio in prolactinoma therapy than that seen in RLS therapy. Cabergoline risks include valvular heart disease.[68] The data seem to agree that there is valve risk, but the defined risk in each study varies by incidence and degree of valve injury.[68-75] Other side effects were mostly mild and transient and included nausea, dizziness, and headache.[66] If unacceptable gastrointestinal side effects were experienced, domperidone could be prescribed.[63] Some possible or probable mild augmentation was reported.[64,66]

4.2.1.4a: Clinicians should not treat RLS patients with pergolide because of the risks of heart valve damage. (STANDARD)

Values and Trade-Offs: Pergolide risks include heart valve damage and retroperitoneal fibrosis making any future use of pergolide in RLS strongly contraindicated.

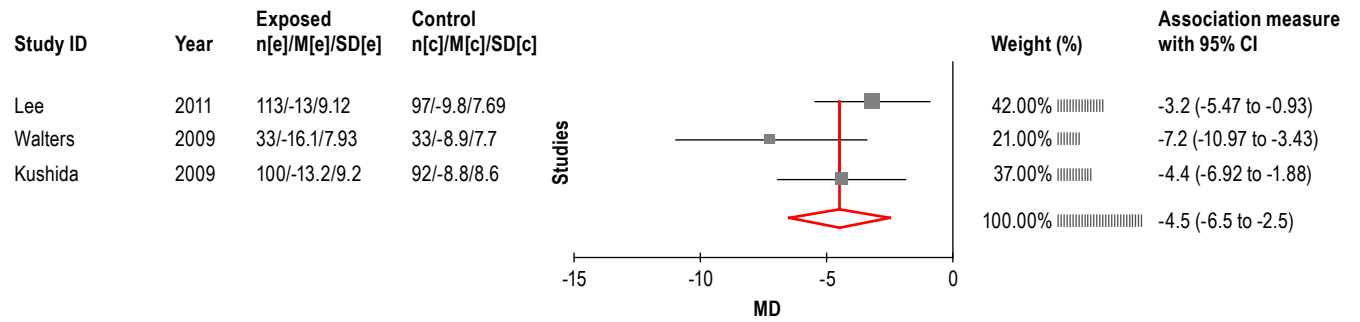

Figure 8—Meta-analysis of gabapentin enacarbil IRLS data, improvement over placebo.

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Gen	Placebo	Absolute	
IRLS Rating Scale (follow-up up to 12 weeks; measured with: Points; range of scores: 0-40; Better indicated by lower values)										
3	randomized controlled trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	Possible reporting bias	246	222	MD 4.5 lower (2.5 to 6.5 lower)	⊕⊕⊕⊕ HIGH

Figure 9—Evidence profile for gabapentin enacarbil.

4.2.1.4b: Given the potential of side effects, including heart valve damage, clinicians can treat RLS patients with cabergoline *only if* other recommended agents have been tried first and failed, and close clinical follow-up is provided. (GUIDELINE)

Values and Trade-Offs: The risks of cabergoline are sufficient to recommend cabergoline not be used in routine clinical practice for RLS particularly since there are multiple alternative RLS dopaminergic therapies with a better side effect profile. Because the risk is unclear, it is prudent to remain cautious with respect to recommending cabergoline.

4.2.2 Opioid medications

Opioids are effective in the treatment of RLS, especially for patients with RLS that is not relieved by other treatments. (*Level of evidence*: Low) In addition to 2 small RCTs that studied oxycodone and propoxyphene discussed in the 1999 review,[76,77] 3 new studies (1 open-label and 2 retrospective reviews) were found on the effects of opioids on RLS.[78-80] Lauerma and Markkula[78] reported that 10 of 12 patients found tramadol to be more effective than drugs they had tried in the past, 1 experienced some relief, and 1 had no relief. Some patients alternated tramadol with levodopa or clonazepam while other patients took "drug holidays" or used it intermittently to minimize concerns of abuse. There is one report of augmentation with long-term tramadol treatment.[81] In a retrospective review of 113 patients on long-term (up to 5 years) opioid therapy (most commonly tilidine, dihydrocodeine, codeine, propoxyphene, or methadone), Walters et al.[79] reported that opioids seem to have long-term effectiveness in the treatment of RLS and PLMS, but patients on long-term opioid therapy should be clinically or polysomnographically monitored periodically for the development of sleep apnea, as 3 of 7 subjects developed worsening sleep apnea. Lastly, Ondo[80] reported on the effect of methadone (5-40 mg/day) in 29 patients who had failed dopaminergics. Sixty-three percent of the patients remained on methadone for 23 ± 12 months, all of whom reported at least a 75% reduction in symptoms and no augmentation. Silver et al.[47] reported no augmentation leading to the end of treatment with methadone in a 10-year retrospective review of 76 patients on methadone. The median daily dose after 8-10 years on methadone treatment was no more than 10 mg greater than at 6 months, indicating minimal change in narcotic requirement over time.

4.2.2a: Clinicians can treat RLS patients with opioids. (GUIDELINE)

Values and Trade-Offs: Opioid data shows clinical effectiveness in treating RLS with a low level of evidence. As mentioned above, side effects can include an undefined potential for abuse in predisposed patients and a possible risk for the development or worsening of sleep apnea. Therefore, patients should be clinically monitored for the development of symptoms. In general, however, this medication is very well tolerated and has a lower risk of augmentation than is seen in the dopaminergic medications.

4.2.3 Anticonvulsant medications

4.2.3.1 Gabapentin enacarbil

Gabapentin enacarbil is effective in the treatment of moderate-to-severe RLS. (*Level of evidence:* High) Four studies provided data on the change in IRLS score with gabapentin enacarbil treatment over placebo.[82-85] All were well-conducted studies with no limitations. Three studies[82,84,85] provided data comparing the change in IRLS vs. baseline of 1200 mg/d of gabapentin enacarbil vs. the same change with placebo. A meta-analysis was performed on these data. Two studies[83,85] were 12 weeks in duration, and 1[84] was only 2 weeks long. The meta-analysis (Figure 8) showed an improvement in IRLS of −4.5 over placebo (95% CI −6.5, −2.5). Other doses have also been studied (600[84,85]and 1800[86] mg/d). All data are presented in the Appendix. The evidence profile is shown in Figure 9.

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Absolute	
IRLS Rating Scale (follow-up 4-6 weeks; measured with: Points; range of scores: 0-40; Better indicated by lower values)										
2	randomized controlled trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	None	32	32	MD 9.7 lower (7.4 to 12 lower)	⊕⊕⊕⊕ HIGH

Figure 10—Evidence profile for gabapentin.

The studies also reported improvements in other outcomes, including CGI-I,[82,84,85] sleep architecture, mood,[84] and sleep disturbance (MOS, PSQ, or WASO).[82,84,85] A recent multicenter, randomized, double-blind, placebo-controlled, 2-period cross-over study[87] reported the effect of 1200 mg/d gabapentin enacarbil on polysomnographically measured wake time during sleep and periodic limb movements with arousal per hour of sleep on 136 subjects after 4 and 10 weeks of treatment. There was a statistically significant decrease in both outcomes (adjusted mean treatment difference of −26 minutes for wake time during sleep and −3.1 periodic limb movements with arousal/h).

The short-term studies[83,84] reported an increase in adverse events over placebo of approximately 40%, whereas the longer-term study[82] reported an increase of only 8%. The most common adverse events were somnolence and dizziness, which were mild-to-moderate in intensity, and generally remitted. A 52-week open label trial[88] reported AEs in 80.1% of subjects, 10.3% of which led to withdrawal from the study. Most (67.7%) were mild-to-moderate in intensity, while 3.5% were serious. An additional double-blind, placebo-controlled, 9-month study[89] reported RLS relapse comparing maintenance on gabapentin enacarbil to withdrawal and introduction of placebo in gabapentin enacarbil responders. Patients on gabapentin enacarbil had fewer relapses and longer time to relapse.

An additional consideration discussed by Ellenbogan et al.[88] is the following: although their study was not prospectively designed to assess augmentation, there were no reported or suspected cases of augmentation based on a retrospective analysis of AEs. Also, there was no evidence of reemergence/rebound of symptoms and no reports of compulsive behavior or impulse control disorder.

4.2.3.1a: Clinicians can treat patients with RLS with gabapentin enacarbil. (GUIDELINE)

Values and Trade-Offs: This is a new recommendation from the prior practice parameter. Sufficient evidence has emerged since the last practice parameter to support gabapentin enacarbil as a guideline level for treatment in RLS therapy. Gabapentin enacarbil therapy is generally well tolerated with self-limited side effects. High level evidence is encouraging. However, this medication is relatively new, thereby warranting a conservative recommendation level of guideline at this time.

4.2.3.2 Gabapentin

Gabapentin is effective in the treatment of mild-to-moderate RLS. (*Level of evidence:* Low) Two small studies (16[90] and 24[91] patients) were identified on gabapentin that indicated improvement in RLS symptoms. Although the patient description was not explicitly defined, from the data it is judged that the patients in both studies were primarily in the mild-to-moderate category. In a randomized open clinical trial, Happe et al.[90] compared gabapentin to ropinirole and found gabapentin to be as effective as ropinirole (IRLS, PLMS, and PLMS index significantly improved in both groups; ESS, QoL, and SAS were not significantly changed in both groups; PLMS-AI, PSQI, and SDS were significantly better in the gabapentin but not ropinirole groups). In a 12-week randomized cross-over trial (6 weeks for each treatment), Garcia-Borreguero et al.[91] reported an improvement in IRLS for gabapentin to 9.5 ± 6.1 versus placebo to 17.9 ± 1.3 from a baseline of 20 for both groups. The evidence profile is shown in Figure 10. Sleep studies showed a significantly reduced PLMS index (11.3 ± 15.5 vs. 20.8 ± 15.5; P = 0.05) and improved sleep architecture. Patients whose symptoms included pain benefited most from gabapentin. It should be noted that gabapentin has the following potential side effects: sedation, dizziness, vision changes, and suicidal behavior and ideation.

4.2.3.2a: Clinicians may treat RLS patients with gabapentin. (OPTION)

Values and Trade-Offs: Low level evidence supports use of gabapentin for RLS therapy. Pain relief with gabapentin supports consideration of gabapentin in patients with both RLS and pain. There are some concerning potential side effects which makes the balance of benefits versus harms uncertain.

4.2.3.3 Pregabalin

Pregabalin is effective in the treatment of moderate-to-severe RLS. (Level of evidence: Low*)* Two studies have recently been published on the use of pregabalin to treat moderate-to-severe RLS. Allen et al.[92] reported the results of a dose-finding investigation of 50-450 mg/day over 6 weeks. There were 22-24 patients in each of 6 arms of the study. Calculations indicated that 123.9 mg/day would provide 90% efficacy in symptom reduction. Garcia-Borreguero et al.[93] reported the results of a 12-week RCT of 30 patients randomized to pregabalin and 28 to placebo. Twenty-four pregabalin and 19 placebo patients completed the trial. The baseline adjusted mean difference in IRLS was 4.9 (95% CI 0.7 to 9.1) with a mean dose of 337 mg/d. CGI-I showed significant improvements, as did measures of sleep quality and architecture including PLMS and PLMS-AI. Eighty-three percent of patients on pregabalin experienced AEs compared with 32% on placebo. The most common AEs were unsteadiness (39% higher with pregabalin over placebo) and daytime sleepiness (29% higher with pregabalin over placebo). More information is needed

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pgn	Placebo	Absolute	
IRLS Rating Scale (follow-up up to 12 weeks; measured with: Points; range of scores: 0-40; Better indicated by lower values)										
2	randomized controlled trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	None	110	38	MD 4.9 lower (0.7 to 9.1 lower)	⊕⊕◯◯ LOW

Figure 11—Evidence profile for pregabalin.

regarding long-term use, including augmentation occurrence. Also, the effect of pregabalin on the working population is needed.[93] The optimal dose has not yet been identified.[92,93] Figure 11 shows the evidence profile.

4.2.3.3a: Clinicians may treat patients with RLS with pregabalin (OPTION)

Values and Trade-Offs: Preliminary data shows therapeutic efficacy in pregabalin therapy for RLS. However, long-term follow up and published experience in pregabalin therapy for RLS is lacking. Thus, other better-studied RLS therapies should be considered before prescribing pregabalin.

4.2.3.4 Carbamazepine

Carbamazepine is effective in the treatment of RLS (*Level of evidence:* Low). This assessment is based on the data presented in 1999, which are considered low according to the methods of this update. Of the 3 studies, there was one large (n = 181 patients) but short-term (5 weeks) double-blind RCT[94] with placebo control that showed carbamazepine to be significantly more effective than placebo using a visual analogue scale. One study[95] did not meet current inclusion criteria because the number of patients was too small (n = 6), and the other study was a clinical series.[96] No new evidence was found on the use of carbamazepine since the last review (1999).

4.2.3.4a: Clinicians may treat RLS patients with carbamazepine. (OPTION)

Values and Trade-offs: This has been downgraded from GUIDELINE in the prior practice parameter to OPTION in this practice parameter. Although carbamazepine efficacy in RLS was shown in prior studies, these data are dated with no new additional supportive work. There are other RLS therapies with comparatively more supportive evidence, risk-to-benefit ratios, and clinical experience than carbamazepine. The benefits of carbamazepine therapy are closely balanced with potential adverse side effects which include sedation, liver abnormalities and, rarely, the potential suicidal ideation and behavior, and Stevens-Johnson syndrome.

4.2.4 Medications acting on the adrenergic systems

Clonidine is effective in the treatment of RLS (Level of evidence: Low*).* No new evidence was found on the use of clonidine since the last complete review[2] where there were 2 small studies of 11[97] and 20[98] patients. The studies were also short-term (3 days[98] to 2-3 weeks[97]). Both were double-blind and placebo controlled, but randomization was unclear in one.[98] Because of these limitations and other considerations, the data using the current methodology is considered low. The results of Wagner et al.,[97] as reported by Henning et al.,[2] are that "clonidine resulted in significant improvement compared to baseline in subjective measures and sleep latency, though PLMI was not significantly decreased. There was no correlation between plasma clonidine concentration and control of symptoms. Side effects were frequent (8 of 10 patients); however, no patients left the study due to them." Side effects were generally considered mild, and included dry mouth, decreased cognition, lightheadedness, sleepiness post dose, constipation, decreased libido, and headache. Ausserwinkler and Schmidt[98] reported that "clonidine significantly improved RLS symptoms, with 8/10 patients having complete relief of symptoms."

4.2.4a: Clinicians may treat patients with RLS with clonidine (OPTION)

Values and Trade-Offs: Clonidine has minimal supporting data in treating RLS and carries a considerable risk for side effects. Clonidine might be considered in treating hypertension and RLS concomitantly. The risk of side effects (such as hypotension in normotensive patients) associated with clonidine in the treatment of RLS makes the benefit-to-harm ratio unclear.

4.2.5 Iron supplementation

Iron supplementation has not been shown to be effective in the treatment of RLS, except perhaps in patients with iron deficiency or refractory RLS. (Level of evidence: Very low*)*

There were 6 studies in total on 3 forms of iron treatment: oral iron sulfate, IV iron sucrose, and IV iron dextran. Overall, the data are conflicting, but show some improvement in select cases, typically those with low serum ferritin levels. Davis et al.[99] and Wang et al.[100] studied oral iron sulfate. Davis et al. reported no significant effect on quality after 12 weeks. Wang et al. also examined the use of oral iron sulfate. In an RCT with 18 patients with low serum ferritin levels, the investigators showed a statistically significant improvement in IRLS with 2 doses of 325 mg/d. Earley et al.[101] and Grote et al.[102] assessed 1000 mg iron sucrose administered in 2 doses of 500 mg or 5 doses of 200 mg. Earley et al. stopped the trial early (after 2 weeks) because of no effect demonstrated on the global rating scale and PLMS. Grote et al. reported on patients with variable degrees of iron deficiency at several lengths of follow up including 2 months and 12 months. There was no statistically different change in IRLS observed at either endpoint. The dropouts for lack of treatment effect were higher in the placebo group (61% vs. 17%). The use of IV iron dextran for treatment of RLS has also been examined. Earley et al.[103] and Ondo[104] investigated IV iron dextran. The study by Earley et al. consisted of 11 patients and was open-label. Results were mixed. Ondo reported on 25 subjects in a retrospective review of severe refractory RLS. It was dem-

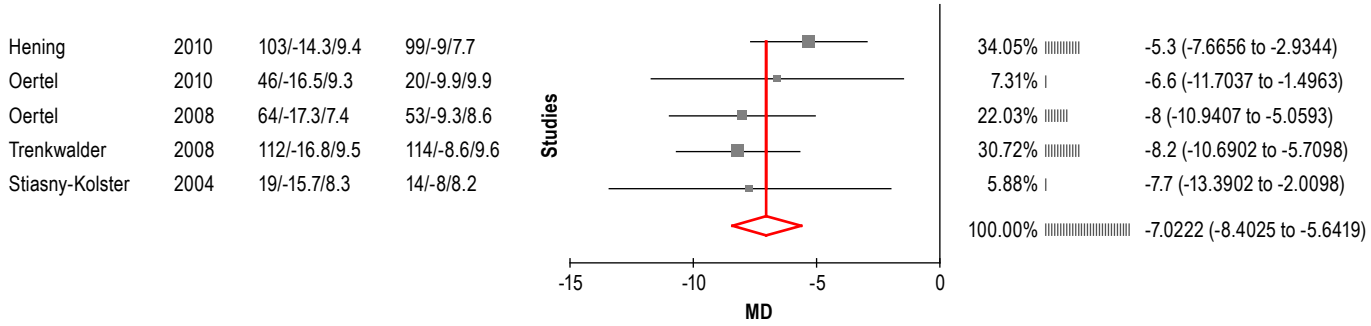

Figure 12—Meta-Analysis of rotigotine IRLS data, improvement over placebo.

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rotigotine	Control	Absolute	
IRLS Rating Scale (follow-up 1 week to 6 months; measured with: Points; range of scores: 0-40; Better indicated by lower values)										
5	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	344	300	MD 7.0 lower (5.6 to 8.4 lower)	⊕⊕⊕⊕ HIGH

Figure 13—Evidence profile for rotigotine.

onstrated that iron dextran can dramatically improve refractory RLS, but results were inconsistent and not predicted by patient demographics. Anaphylactic symptoms are a risk. In 2009, the FDA issued a warning that analphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection. The boxed warning recommends administering a test dose prior to the first therapeutic dose and observing reactions. However, it should be noted that parenteral infusion risk with low molecular weight iron dextran is lower (1 per 200,000)[105] than that with high molecular weight iron dextran. Additionally, parenteral iron therapy with iron sucrose, iron gluconate or ferumoxytol carries no anaphylactic risk.[106]

4.2.5a: Clinicians may use supplemental iron to treat RLS patients with low ferritin levels. (OPTION)

Values and Trade-Offs: RLS therapy with iron may be effective in patients with RLS associated with low ferritin levels. Parenteral high molecular weight iron dextran therapy carries the potential for anaphylactic reaction. The parenteral infusion risk with low molecular weight iron dextran is substantially lower. Moreover, parenteral iron therapy with iron sucrose, iron gluconate, or ferumoxytol carries no anaphylactic risk. However, whenever possible, oral iron replacement is recommended. Oral supplemental iron carries fewer side effects—primarily constipation and rare cases of iron overload.

4.3 Therapies For Which No Recommendations Are Made

The following section contains information on those pharmacological and nonpharmacological RLS therapies for which a recommendation level could not be given secondary to either insufficient evidence to support any recommendation or because the therapy is no longer available in the U.S.

4.3.1 Non-ergot-derived dopamine agonists: rotigotine

Rotigotine as a transdermal patch is effective in the treatment of moderate-to-severe RLS, but was withdrawn from the U.S. in 2008 (*Level of evidence*: High). This is a new treatment since the last review, and the evidence base is 5 studies[107-111] for the meta-analysis. No limitations were noted with the studies, and the results were consistent. All data are presented in the online supplement at http://www.aasmnet.org/practiceguidelines.aspx. Rotigotine was found to improve RLS symptom severity according to IRLS by 7.0 (95% CI: 5.6 to 8.4)[107-111]; the results are shown in Figure 12. Other outcomes measures including PSG-measured PLMI and PLM arousal index,[111] RLS severity (RLS-6),[108,109] CGI-I,[107-110] and QoL[107,109] also improved significantly. Figure 13 shows the evidence profile.

Two long-term continuation studies were reported, Oertel et al.[112] (220 patients for 1 year) and Hogl et al.[113] (190 patients for 2 years). The IRLS total score improved by −17.4 ± 9.9 points between baseline and end of year 1 ($P < 0.001$) and by −15.4 ± 10.3 for the 2-year study. The other measures of symptom severity, sleep satisfaction, and QoL supported the efficacy of rotigotine.

Doses ranged from 1[107] to 4.5 mg,[108] with increasing effectiveness up to approximately 3 mg/d. Oertel et al.[112] reported the mean daily dose after 1 year was 2.8 ± 1.2 mg/24 h with 4 mg/24 h (40.6%) being the most frequently applied dose. Braun et al.[114] concluded from their pharmacokinetic interaction data that rotigotine dose adjustment would not be needed if domperidone was added to the treatment regimen. In 2008, this drug was withdrawn from the U.S. market because of concerns about inconsistent absorption from the patch.

The transdermal patch was safe and generally well tolerated by the majority of patients. Oertel et al.[112] reported after 1 year of study that the tolerability was described as "good" or "very good" by 80.3% of all patients. Side effects were mostly mild to

moderate, including application site reactions (40%[112]–43%[109]), nausea (9.5%[112]), and fatigue (6.4%[112]). Hogl et al.[113] reported at a median dose of 4 mg/d that 87% of patients experienced at least 1 adverse event, the majority of which were mild or moderate, but 22% of these were severe. Additionally, the most frequent adverse event in year 2 was any application site disorder (16.4%), followed by 4.5% with back pain and 4.1% with nasopharyngitis. Transdermal rotigotine was withdrawn from the market because of drug crystallization that resulted in suboptimal absorption.

4.3.2 Other dopaminergic medications: lisuride and amantadine

There is insufficient evidence at this time to support the use of lisuride in the treatment of RLS, and it is not FDA-approved. Two small studies by Benes et al.,[115,116] 1 a non-randomized treatment trial[116] and the other a randomized controlled trial,[115] reported on the effect of lisuride on patients with severe and/or advanced RLS. The non-randomized treatment trial[116] of 20 patients reported that lisuride given orally as a monotherapy (0.3 mg) as well as in conjunction with L-dopa (150 mg) significantly improved CGI-I and PLM index. The randomized controlled trial[115] of 10 patients reported that lisuride transdermal patches significantly improved RLS-6, CGI-I, PLM index (actigraphy), and IRLS (−23.5 with lisuride and −10.6 with placebo). Side effects were typical for dopaminergic drugs. With the exception of nausea and dizziness in one patient, none of the adverse events were rated as severe.

No new studies were found on amantadine since the previous practice parameter, which reported that in 1 clinical series (Evidente et al.[117]) of 21 patients, half the patients benefited acutely by amantadine as an add-on medication, with long-term benefit in a minority. In 2004, the strength of this recommendation was OPTION level. However, currently no recommendation has been given for amantadine as several superior options are available; there was limited existing evidence, and no new evidence for the use of amantadine in RLS.

4.3.3 Other dopamine agonists

There is insufficient evidence at this time to support the use of talipexole, peribedil, and alpha-dihydroergocryptine in the treatment of RLS. In the previous practice parameter (2004), these agents were given an OPTION level of recommendation based on very low level evidence (1 small case series for each drug), one of which (Inoue, talipexole) would not have been accepted in this paper because there were only 5 patients, 2 of whom had uremia.

4.3.4 Benzodiazepines (clonazepam)

There is insufficient information on the effect of benzodiazepines on the treatment of RLS. In addition to 3 studies[118-120] discussed in the last review, 2[118,119] of which were RCTs with small numbers of patients (n = 6) and showed contradictory results, 1 non-randomized treatment trial on 10 patients with RLS by Saletu et al.[121] reported that 1 mg clonazepam improved objective sleep efficiency and subjective sleep quality but did not reduce the PLM index. The authors concluded that clonazepam had an acute therapeutic effect on insomnia, which is a different mode of action than dopamine agonists. An additional paper[122] suggested that clonazepam was not as effective as pramipexole in the treatment of RLS.

Although clonazepam received an OPTION level of recommendation in 1999 as described in the evidence review, benzodiazepines lack clinical data necessary to assess efficacy in treating RLS. The committee strongly recommends that alternate and better studied RLS medications be considered in RLS therapy. The "no recommendation" status applies to the use of benzodiazepines as a first line agent. For example, clonazepam could still be considered as an adjunctive medication in treatment of RLS.

4.3.5 Valproic acid

There is insufficient evidence at present to evaluate the use of valproic acid for RLS. A single, small RCT by Eisensehr et al.[123] reported no major difference between the efficacy of valproic acid (VPA) and levodopa on 20 patients with moderate-to-severe idiopathic RLS. Follow-up 6 to 18 months after the study end revealed that VPA was still effective in 75% (9 of 12 patients), whereas only 29% (2 of 7 patients) were still satisfied with levodopa (P = 0.048). The authors conclude that slow-release VPA provides an alternative or adjunctive treatment for patients unable to tolerate dopaminergics or those suffering from augmentation, and not as a first-line treatment for RLS. In 2009, the FDA issued a warning that there is an increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular malformations, in babies exposed to valproate sodium and related products (valproic acid and divalproex sodium) during pregnancy.

4.3.6 Valerian

There is insufficient evidence at present to evaluate the use of valerian for RLS. In one RCT by Cuellar and Ratcliffe on 48 patients,[124] it was reported that although PSQI, ESS, and IRLS all decreased, no significant differences were found between placebo and 800 mg/d valerian. In patients with ESS > 10, valerian significantly improved symptoms of RLS and decreased daytime sleepiness. Higher doses should be considered in future studies.

4.3.7 Avoidance of antidepressants

The evidence on the issue of whether or not antidepressant use can cause or exacerbate RLS symptoms is conflicting. Three studies were identified that reported there is an association between antidepressants and the occurrence of RLS. Baughman et al.[125] interviewed 1693 veterans and reported on the relationship between antidepressants and gender. Men were found to have an increased risk of developing RLS with antidepressant use, RR = 1.77 (95% CI 1.26, 2.48), whereas for women, there was no increased risk—RR = 0.79 (0.43, 1.47). For men, the highest odds ratios were found for citalopram, paroxetine, and amitryptiline. One antidepressant, fluoxetine, was found to show an increased odds ratio for women (RR = 2.47 [1.33, 4.56]). Kim et al.[126] performed a retrospective chart review of 181 charts and found that 8% of patients who were treated with mirtazapine developed RLS symptoms, typically within a few days after introduction of the drug. A higher odds ratio was found with the concomitant use of tramadol and dopamine-blocking agents. Lastly, Rottach et al.[127] studied second-generation antidepressants in a prospective observational study of 271 participants. Nine percent of patients developed RLS as a side effect with the

use of these second generation antidepressants with the exception of reboxetine. Twenty-eight percent of mirtazapine users reported RLS. In another investigation, 243 subjects with affective and anxiety disorders were studied systematically for the emergence of symptoms of RLS after antidepressant use. In contrast to the previously discussed studies, in this study antidepressants were not found to be a major risk factor for RLS.[128] Furthermore, Brown et al.[129] reported the results of a retrospective chart review of 200 consecutive patients presenting with insomnia. There were no statistically significant associations between RLS and antidepressant use or any specific class of antidepressant.

4.3.8 Non-pharmacological therapy

There is insufficient evidence at present to evaluate the use of non-pharmacological therapy for RLS, including accommodative strategies, sleep hygiene, behavioral and stimulation therapies, compression devices, exercise, and nutritional considerations.

No studies were found on accommodative strategies, sleep hygiene, or nutritional considerations since the last review. Regarding cognitive behavioral therapy, one non-randomized, non-blinded treatment trial (Hornyak et al.[130]) reported that IRLS, QoL-RLS, and mental health status (SCL-90-R) scores improved significantly through 3 months with 8 weekly 90-min sessions in group therapy consisting of mindfulness-based exercises, stress-reduction strategies, diary-based analysis, and medical education.

Lettieri and Eliasson[131] (RCT) and Eliasson and Lettieri[132] (non-randomized, non-blinded treatment trial) reported that wearing compression devices a minimum of 1 h per day for 1 to 3 months was significantly superior to sham treatment on IRLS, JHRLSS, RLS-QoL, ESS, and the Fatigue Visual Analog Scale; furthermore, one-third of patients experienced complete resolution of symptoms. The authors suggested that these devices may be potential adjunctive or alternative therapies for RLS patients.

One small (11 therapy and 12 controls) unblinded RCT by Aukerman et al.[133] reported that 12 weeks of exercise therapy (aerobic and lower-body resistance training for 3 days/week) significantly decreased RLS symptoms (IRLS rating scale and an ordinal RLS scale) versus the control group. The exercise program was shown to be an effective treatment to improve the symptoms of RLS.

4.3.9 Secondary RLS and special patient groups

There is insufficient evidence on the effectiveness of any one therapy or the balance of benefits to harm in the treatment of secondary RLS, children, pregnant women, or other special patient groups for a recommendation to be made.

End Stage Renal Disease (ESRD)—Six studies discussed the treatment of patients with ESRD and/or those on hemodialysis who also had RLS. Various treatments were used in the studies. The first was an RCT by Thorp et al.,[134] who reported that 200-300 mg **gabapentin** after each hemodialysis session on 13 patients significantly improved RLS symptoms according to an author-developed questionnaire based on the IRLS rating scale. A small (14 patients) unblinded RCT by Micozkadioglu et al.[135] compared the effects of 200 mg/d **gabapentin** versus 125 mg/d L-dopa on hemodialysis patients. They reported that gabapentin was significantly superior to L-dopa on RLS symptom severity relief, improvement of general health, body pain, social functions, and sleep parameters according to the IRLS rating scale, SF-36, and PSQI. Sloand et al.[136] reported in an RCT on 25 patients that 4 weeks of 1000 mg **IV iron dextran** during dialysis resulted in significant, but transient, reduction in symptoms of RLS in patients with ESRD according to an author-developed questionnaire. Pellecchia et al.[137] reported in an unblinded RCT on the effects of 6 weeks each of **ropinirole** (mean dosage 1.45 mg/d) versus sustained-release levodopa (mean dosage 190 mg/d) in 10 patients on chronic hemodialysis with RLS. Ropinirole resulted in a significantly higher improvement (73.5% vs. 33.5%) in IRLS scores, sleep time, and PGI. No adverse events were reported during ropinirole treatment. Mirada et al.[138] reported in a nonrandomized treatment trial on the effects of 0.125-0.75 mg of **pramipexole** on 10 patients with RLS that was severe enough to interfere with their dialysis treatment such that they required disconnection. At a mean follow-up time of 8 months, the IRLS and PLMI were significantly reduced, whereas differences in sleep latency, total hours of sleep, number of awakenings, and sleep efficiency were not statistically significant. Lastly, 2 small studies (14[139] and 18[140] patients) showed promising results of the effect of **exercise** on IRLS[139] and PLM during hemodialysis[140] in hemodialysis patients.

Other information from the 1999 review paper[2] includes: "Dialysis itself does not appear to alter the RLS or PLMD secondary to end-stage renal disease, but the **dialysate temperature** may influence symptoms.[141] **Erythropoietin** supplementation may reduce symptoms, and symptoms often largely resolve with **kidney transplantation** as reported in a case report and abstract.[142,143] Two clinical trials meeting study criteria included patients with end-stage renal disease and found efficacy for **levodopa**.[144,145] One did not.[146] One trial[98] with **clonidine** revealed efficacy in this group of patients. Some case reports suggest efficacy for **benzodiazepines (clonazepam)**.[147] Nephrologists, noting that carbidopa is a pyridoxine (B6) inhibitor, suggest providing an additional daily B6 supplement of 10 mg.[148] In considering other potential medications for dialysis patients, the elimination patterns of the medications and their active metabolites need to be considered (e.g., gabapentin is dialyzable, whereas meperidine, propoxyphene, valproic acid and carbamazepine are not[148])."

Neuropathy—In a nonrandomized treatment trial, Sommer et al.[149] reported on the effect of pregabalin on 16 patients with secondary RLS, most with neuropathy and neuropathic pain and 3 with idiopathic RLS. The final mean daily dose was 305 ± 185 mg. All patients self-rated a satisfactory or good alleviation of RLS symptoms and maintained pregabalin, 5 with additional medication, for a mean duration of 217 ± 183 days.

Superficial venous insufficiency (SVI)—A study by Hayes et al.[150] reported that RLS symptoms were alleviated in 18 treatment subjects but not in 15 controls who all had concurrent moderate-to-very severe RLS (IRLS rating scale ≥ 15) and duplex-proven SVI. The treatment consisted of endovenous laser ablation of refluxing superficial axial veins and ultrasound-guided sclerotherapy of the associated varicose veins with post-operative ACE wrap for 48 h followed by compression stockings for 2 weeks. The mean IRLS score decreased significantly by 21.4 points from 26.9 to 5.5 for treatment subjects, whereas control scores

did not decrease. Fifty-three percent of patients had a 6-week follow-up score ≤ 5, and 31% had a follow-up score of 0, indicating a complete relief of RLS symptoms. The 1999 review included the results of an unblinded study[151] on 113 selected patients with documented SVI and complaints of RLS. After 1-10 treatments of intravenous sclerotherapy with sodium tetradecyl sulfate, 98% of patients reported notable improvement in RLS symptoms, although 28% of these relapsed by the 2-year follow up.

5.0 THERAPIES FOR PLMD

Periodic limb movements of sleep (PLMS) are frequently seen as an incidental finding during sleep studies. In some cases in which there are frequent PLMS and a subjective perception of poor sleep in the absence of RLS or sleep-related breathing disorder, PLMD can be diagnosed.[6] Although there are no studies of dopaminergic treatment of PLMD, many of the studies of dopaminergic medication effects on RLS looked at PLMS and periodic limb movements during wakefulness (PLMW). Some studies demonstrated statistically significant falls in PLM indices with Stalevo,[60] pramipexole,[35,41,42,45] ropinorole,[49,52,53] and rotigotine.[111] In addition, gabapentin[90,91] and pregabalin[93] were also shown to decrease PLM indices in subjects with RLS. Thus, although there were no studies on the efficacy of these medications in a population with PLMD, they have been noted to decrease PLM indices in subjects with RLS and might be effective in treating the sleep dysfunction of PLMD. The following sections review medications tried in subjects with PLMD.

5.1 Clonazepam

In a nonrandomized treatment trial, Saletu et al.[121] discussed the acute effects of 1 mg clonazepam (1 night each of trial drug and placebo) on idiopathic PLMD. Clonazepam significantly improved objective sleep efficiency and subjective sleep quality, PLM during time in bed, PLM during REM, and PLM during wake-time, but did not reduce the PLM index. The authors concluded that clonazepam had an acute therapeutic effect on insomnia rather than limb movements.

5.2 Melatonin

In a 6-week open clinical trial on 9 patients, Kunz et al.[152] reported that 3 mg of melatonin taken 30 min prior to bedtime significantly improved the movement parameters associated with PLMD (4 severe [PLM index > 50], 3 moderate [PLM index 26-50], and 2 mild [PLM index 5 thru 25]). Melatonin improved Zerssen well-being (a self-rating mood scale) in 7 of the 9 patients; significantly reduced PLMs, PLM index, PLMs with arousals and PLM-arousal index; and significantly reduced movement rate and minutes with movements during time in bed as measured by actigraphy.

5.3 Valproate

In a nonrandomized treatment trial, Ehrenberg et al.[153] reported on the effects of low-dose valproate (125-600 mg at bedtime) on 6 patients with PLMD for a mean of 6 months of treatment. All patients experienced statistically significant improvement in subjective daytime alertness and objective sleep parameters including sleep efficiency (76% to 88%), stage 1 sleep (26% to 13%), stage 3 and 4 sleep (19% to 30%). REM sleep was unchanged, and non-significant reductions in the number of PLMs per hour of sleep and in the percentage of arousals associated with PLMs were observed.

5.4 Selegiline

In the 2004 practice parameters, 1 study (Grewal et al.,[154] a case series on 31 patients) was discussed where selegiline was used successfully to treat PLMD. No new studies were found on selegiline.

5.0a: There is insufficient evidence at present to comment on the use of pharmacological therapy in patients diagnosed with PLMD alone. (NO RECOMMENDATION)

Values and Trade Offs: There is insufficient evidence to comment on pharmacologic therapies in isolated PLMD. Existing data in RLS therapy does, in some cases, support some medical interventions in both RLS and PLMD. Clinical judgment must be used in any pharmacologic intervention in PLMD.

6.0 CONCLUSIONS AND FUTURE DIRECTIONS

Since the prior practice parameter, a considerable amount of literature has been published on the effects of dopaminergic medications for RLS. However, there were a significant number of therapies, both pharmacological and nonpharmacological, that received "no recommendation" due to the dearth of information regarding their use in the setting of RLS. Furthermore, there is a paucity of data comparing medications in head-to-head trials to determine their relative effectiveness and adverse event profiles. For this reason, and the fact that therapy should always be tailored to the individual, a dopaminergic "drug of choice" cannot be recommended. It is worth noting that the late development of augmentation (even after one year of continuous therapy on dopaminergic agents) remains a significant concern, and patients need to be monitored throughout therapy for this particular side effect.

Additionally, Godau et al.[155] have noted that the RLS treatment successes that have been demonstrated in pharmacological trials have not been consistently replicated in the clinical setting. The authors suggest that this could be related to the fact that approximately two-thirds of the patients with idiopathic RLS evaluated in clinical practice are excluded from pharmacological trials secondary to the presence of neuropsychiatric comorbidities. These comorbidities include anxiety, depression, chronic pain, and various somatoform disorders. A possible way to circumvent this limitation is to include cognitive behavioral therapies or psychotherapy as part of the treatment regimens. Investigations including patients with both RLS and neuropsychiatric comorbidities would be more clinically germane.

Finally, randomized controlled trials evaluating treatment options for patients with secondary RLS and PLMD are lacking. Multiple medications that can be considered for idiopathic RLS do not have sufficient evidence in the setting of secondary RLS or PLMD to warrant a recommendation level. These practice parameters highlight the need for further investigations assessing treatments for secondary RLS and PLMD.

FOOTNOTE

Estimate of effect: The observed relationship between an intervention and an outcome expressed as, for example, a

number needed to treat, odds ratio, risk difference, risk ratio, relative risk reduction, standardized mean difference, or weighted mean difference.

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Appendix—Data for meta-analyses

IRLS rating scale total scores for cabergoline, treatment vs. baseline

Study	Study Length	# Pts Completed	Dose, mg/d	IRLS Baseline Avg ± SD	IRLS Cabergoline Avg ± SD	P
Oertel, 2006[63]	5 wks	20 each tx	2	31.2 ± 5.4	7.5 ± 15.3*	< 0.01
Stiasny-Kolster, 2004[64]	52 wks	22†	2.2 ± 1.1	27.7 ± 5.7	12.0 ± 16.3*	< 0.001
Benes, 2004[66]	6 mo	248	1.5	26.8 ± 5.9	9.7 ± 9.0	< 0.001
Zucconi, 2003[65]	2 mo	10	1.1	23.1 ± 5.9**	9.8 ± 6.9	0.005

†Number of patients on 2 mg dose, out of 85 patients in complete dose-finding trial. *Back calculated from difference data. **After 1 week of placebo treatment (24.3 ± 2.9 at baseline). tx, treatment.

IRLS rating scale total scores for cabergoline vs. placebo

Study	Study Length / # Pts Completed	Dose, mg/d	IRLS Comparison Avg (SD)	IRLS Cabergoline Avg (SD)	P
Cabergoline vs. placebo					
Oertel, 2006[63]	5 wks / 40 (20 each tx)	2	-7.9 ± 11.0	-23.7 ± 11.2	0.0002
Stiasny-Kolster, 2004[64]	5 wks / 44 (22 each tx)	2	-3.3 ± 8.0	-15.7 ± 11.9	< 0.001
Cabergoline vs. levodopa					
Trenkwalder, 2007[67]	30 wks / 204	2-3 cabergoline 200+ L-dopa	-8.8 ± 10.7	-15.6 ± 10.8	< 0.0001

tx, treatment.

Appendix continues on the following page

Appendix (*continued*)—Data for meta-analyses

IRLS rating scale total scores for pramipexole

Study	Study Length / # Pts Completed	Dose quoted, mg/day	IRLS Baseline Avg (SD)	Δ IRLS Placebo Avg (SD)	Δ IRLS Pramipexole Avg (SD)	P
Large studies with placebo control						
Montagna 2011[36]	12 weeks / 199 placebo, 203 pramipexole	0.125 to 0.75	Placebo: 25.8 ± 5.4 Pramipexole: 25.9 ± 5.2	-8.4 ± 8.3	-14.5 ± 7.4	< 0.0001
Ferini-Strambi, 2008[30]	12 weeks / ITT 179 placebo, 178 pramipexole (278 completed)	0.42*	Placebo: 24.6 ± 5.7 Pramipexole: 24.2 ± 5.2	-9.6 ± 9.4	-13.4 ± 9.3	< 0.0001
Oertel, 2007[32]	6 weeks / 115 placebo, 230 pramipexole (338 completed)	0.35**	Placebo: 24.9 ± 5.4 Pramipexole: 24.7 ± 5.2	-5.7 ± 9.6	-12.3 ± 9.1	< 0.0001
Winkelman, 2006[31]	12 weeks / 86 placebo, 80 pramipexole (281 total completed all doses)	0.5	Placebo: 23.5 ± 5.2 Pramipexole: 22.9 ± 5.1	-9.3 ± 9.3	-13.8 ± 8.9	< 0.01
Large study without placebo control						
Inoue 2011[37]	6 weeks / 154 divided into 3 dose groups	0.25, 0.5 and 0.75	22.3 ± 4.7	N/A	-12.3‡ [95% CI: -13.4, -10.9]	Not stated
Small studies with placebo control						
Inoue 2010[34]	6 weeks / 21 placebo, 20 pramipexole	0.125-0.75	Placebo: 25.1 ± 5.8 Pramipexole: 23.4 ± 6.4	-6.4 ± 7.4	-16.1 ± 7.1	< 0.001
Jama 2009[35,39]	3 weeks / 21 placebo, 22 pramipexole	0.5 mg (0.125 to 0.75 tested)	Placebo: 22.9 ± 4.2 Pramipexole: 23.6 ± 3.7	-6 ± 9†	-17 ± 9†	< 0.0001
Partinen, 2006[33]	3 weeks / 22 each pramipexole 0.5 mg and placebo (107 total completed all doses)	0.5	Placebo: 22.9 ± 4.2 Pramipexole: 23.6 ± 3.7	-6.1 ± 7.0	-17.0 ± 7.0	< 0.0001
Long-term trial data						
Inoue 2010[38]	52 weeks / 140	0.125 to 0.75	22.3 ± 4.7	N/A	-17.4 ± 5.3	Not stated
Partinen 2008[39]	26 weeks / 107	0.125 to 0.75	23.0 ± 4.3	N/A	-17.0 ± 5.5	Not stated

*Calculated from 0.125 mg for 15.4% (28/182), 0.25 mg for 33.0% (60/182), 0.5 mg for 26.9% (49/182), and 0.75 mg for 24.7% (45/182). **Median dose. †Calculated from SE data given. ‡Mean of all doses.

Appendix continues on the following page

Appendix (*continued*)—Data for meta-analyses

IRLS rating scale total scores for ropinirole

Study	Study Length / # Pts Completed	Dose, mg/d	IRLS Baseline Avg (SD)	IRLS Placebo Avg (SD)	IRLS Ropinirole Avg (SD)	P
Adler, 2004[48]	4 wks each / 22 each tx	4.6 ± 2.0	25.0 ± 7.0	24.7 ± 7.2	13.0 ± 12.0	< 0.001
				-0.3 ± 6.9	-12.0 ± 9.6	
Bliwise, 2005[52]	2 wks / 13 placebo, 9 ropinirole	1.4	22.6 ± 4.6	16 ± 6*	14 ± 9*	ns
				-6.6 ± 5.1	-8.6 ± 6.7	
Bogan, 2006[49]	12 wks / 186 ropinirole, 191 placebo	2.1 ± 1.2	Ropinirole: 22.0 ± 5.0 Placebo: 21.6 ± 4.8	11.9 ± 9.2 LOCF	8.4 ± 7.3 LOCF	< 0.001
				-9.7 ± 7.3	-13.6 ± 6.2	
Trenkwalder, 2004[50]	12 wks / 146 ropinirole, 138 placebo	1.9 ± 1.1	Ropinirole: 24.4 ± 5.75 Placebo: 25.2 ± 5.63	-8.0 ± 8.7	-11.0 ± 8.7	0.0036
Walters, 2004[51]	12 wks / 102 ropinirole, 107 placebo	1.5	Ropinirole: 23.6 ± 5.9 Placebo: 24.8 ± 5.4	-8.7 ± 7.8	-11.2 ± 7.7	0.0197
Other data not used in meta-analysis						
Garcia-Borreguero, 2007[56]	1 year / 233 OC and 307 LOCF	1.9	22.0 ± 8.66	Not applicable	10.9 ± 7.71 OC 12.0 ± 8.60 LOCF	Not stated
Kushida, 2008[54]	12 wks / 175 ropinirole, 184 placebo	3.1 ± 2.0 Divided doses	Not stated	-11 ± 13* OC	-15 ± 20* OC	< 0.001
Montplaisir, 2006[55]	12 wks / 92	2.05 ± 1	Baseline = 24 weeks treated	+8.2	+4.1	0.0246
Allen, 2004[53]	12 wks / 59	0.25-4.0	Adjusted treatment difference in favor of ropinirole at week 12 LOCF = -1.2			ns, P = 0.56

*Estimated from figure in paper, SD calculated from graph data. OC, observed case; LOCF, Last observation carried forward.

IRLS rating scale total scores for rotigotine

Study	Study Length / # Pts Completed	Dose,* mg/d	IRLS Baseline Avg (SD)	IRLS Placebo Avg (SD)	IRLS Rotigotine Avg (SD)	P
Hening 2010[110]	6 mo / 99 placebo, 103 rotigotine	3.0	Placebo: 23.1 ± 5.1 Rotigotine: 23.6 ± 5.0	14.5 ± 8.0	9.3 ± 8.5	< 0.0001
				-9.0 ± 7.7	-14.3 ± 9.4	
Oertel 2010[111]	4 wks / 20 placebo, 46 rotigotine	Mean 2.1	Placebo: 25.4 ± 6.3 Rotigotine: 26.3 ± 6.4	-9.9 ± 9.9	-16.5 ± 9.3	Not stated
Oertel, 2008[107]	6 wks / 333 total-53 placebo, 64 rotigotine	3.0	Placebo: 28.0 ± 6.3 Rotigotine:: 27.4 ± 6.1	18.7 ± 10.6	10.1 ± 8.6	< 0.0001
				-9.3 ± 8.6	-17.3 ± 7.4	
Stiasny-Kolster, 2004[108]	1 wk / 62 total-14 placebo,19 rotigotine	4.5	Placebo: 25.0 ± 18.7 Rotigotine: 25.9 ± 23.5	-8.0 ± 8.2	-15.7 ± 8.3	< 0.01
Trenkwalder, 2008[109]	6 mo / 114 placebo, 112 rotigotine	3.0	Placebo: 28.1 ± 6.3 Rotigotine: 28.0 ± 5.9	-8.6 ± 9.6	-16.8 ± 9.5	< 0.0001

*Data for other doses are listed in the evidence table available online at http://www.aasmnet.org/practiceguidelines.aspx.

Appendix continues on the following page

Appendix (*continued*)—Data for meta-analyses

IRLS rating scale total scores for gabapentin enacarbil (GEn)

Study	Study Length / # Pts Completed	Dose, mg/d	IRLS Baseline Avg (SD)	IRLS Placebo Avg (SD)	IRLS Gabapentin Enacarbil Avg (SD)	P
Kushida 2009[82]	12 wks / 92 placebo, 100 Gen	1200	Placebo: 22.6 ± 4.9	-8.8 ± 8.6	-13.2 ± 9.2	0.0003
			GEn: 23.1 ± 4.9			
Kushida 2009[86]	2 wks / 24 each treatment (crossover)	1800	Placebo: 20.4	-1.9 ± 6.3	-12.1 ± 6.5	< 0.0001
			GEn: 20.4			
Walters 2009[84]*	2 wks / 33 placebo, 33 Gen	1200	Placebo: 22.4 ± 4.6	-8.9 ± 7.7	-16.1 ± 7.93	< 0.0001
			GEn: 22.4 ± 4.4			
Ellenbogan 2011[88]	52 wks / 376 in safety population	600-1800	23.2 ± 5.03	N/A	-16.8 ± 8.21 OC	Not stated
					-15.2 ± 8.85 LOCF	
Lee 2011[85]	12 wks / 77/97 placebo, 104/115 GEn	600	Placebo: 23.8 ± 4.58	-9.8 ± 7.69	-13.8 ± 8.09	< 0.0001
			GEn: 23.1 ± 4.93			
	12 wks / 77/97 placebo, 98/113 GEn	1200	Placebo: 23.8 ± 4.58	-9.8 ± 7.69	-13.0 ± 9.12	0.0015
			GEn: 23.2 ± 5.32			

*Data for other doses are reported in the paper.