Practice guideline: Treatment of restless legs syndrome in adults

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

John W. Winkelman, MD, PhD[1]; Melissa J. Armstrong, MD, MSc[2]; Richard P. Allen, PhD[3]; K. Ray Chaudhuri, MD, FRCP, DSc[4]; William Ondo, MD[5]; Claudia Trenkwalder, MD[6]; Phyllis C. Zee, MD, PhD[7]; Gary S. Gronseth, MD[8]; David Gloss, MD, MPH&TM[9]; Theresa Zesiewicz, MD[10]

1) Harvard Medical School and Massachusetts General Hospital, Boston, MA
2) Department of Neurology, University of Florida College of Medicine, Gainesville, FL
3) Department of Neurology, Johns Hopkins University, Baltimore, MD
4) King's College and King's College Hospital, London, UK
5) Methodist Neurological Institute, Houston, TX
6) Department of Neurology, University Medical Center, Goettingen, Germany
7) Northwestern University Feinberg School of Medicine, Chicago, IL
8) University of Kansas Medical Center, Kansas City, KS
9) CAMC Neurology Section, Charleston, WV
10) Department of Neurology, University of South Florida, James A Haley Veterans Administration Hospital, Tampa

Correspondence to
American Academy of Neurology:
guidelines@aan.com

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on November 7, 2015; by the Practice Committee on December 21, 2015; and by the AAN Institute Board of Directors on August 29, 2016.

STUDY FUNDING

This guideline was developed with financial support from the American Academy of Neurology. Authors who serve or served as AAN subcommittee members or methodologists (M.J.A., G.S.G., D.G., T.Z.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

AUTHOR CONTRIBUTIONS

Dr. Winkelman: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

Dr. Armstrong: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

Dr. Allen: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Chaudhuri: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Ondo: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Trenkwalder: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Zee: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Gronseth: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

Dr. Gloss: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Zesiewicz: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

DISCLOSURE

Dr. Winkelman currently serves on scientific advisory boards for Merck and Flex Pharma and has served on scientific advisory boards for UCB, Impax, Pfizer, Lacrima, Luitpold Pharmaceuticals, GlaxoSmithKline, Boehringer-Ingelheim, Xenoport, Zeo Inc., Sunovion, Insys, Takeda, Jazz, and Neurogen; currently performs neurophysiology studies as part of his practice; currently serves as a journal editor for the following publications: *Sleep, Sleep Medicine, CNS Drugs*; has received honoraria from or served on speakers bureaus for the following organizations: Boehringer-Ingelheim, GlaxoSmithKline, Pfizer, Sepracor (now Sunovion), Takeda, Luitpold Pharmaceuticals, Novartis, Neurogen, and UCB (Schwarz Pharma); has received research support from Boehringer-Ingelheim, GlaxoSmithKline, UCB (Schwarz Pharma), Sepracor (now Sunovion), and Pfizer ; holds stock in Flex Pharma; receives publishing royalties for the following publications: *Foundations of Psychiatric Sleep Medicine* (Cambridge University Press, 2010), and an UpToDate chapter on Nocturnal Leg Cramps; receives government research support from the National Institute of Mental Health (1RO1MH095792-01A1, PI); and has given expert testimony for legal cases representing generic manufacturers of pharmaceuticals approved for the treatment of insomnia and narcolepsy.

Dr. Armstrong receives compensation from the American Academy of Neurology (AAN) as an evidence-based medicine methodologist and serves on the Level of Evidence editorial board for the journal *Neurology* but is not compensated financially.

Dr. Allen has served on a volunteer basis for the International Restless Legs Syndrome Study Group and the World Association of Sleep Medicine; has served on scientific advisory boards for Pfizer, GlaxoSmithKline, Boehringer Ingelheim, Jazz Pharmaceuticals, UCB, Luitpold, and Xenoport; has received funding for travel from UCB; currently serves as a field editor for the journal *Sleep Medicine*; has served as a journal editor for the following journals: *Sleep Medicine, Sleep,* and *Movement Disorders*; receives publishing royalties from *Sleep* and *Movement Disorders*; has received honoraria from UCB for CME; currently serves as a consultant for Luitpold Pharmaceuticals; holds a patent (PCT/US15/15556) for a device and method for detection of periodic leg movements; and has received research support from GlaxoSmithKline, Pharmacosmos, and the NIH.

Dr. Chaudhuri has served as a journal editor-in-chief for *Nature Parkinson Journal* and as editor for *Basal Ganglia*; receives publishing royalties from the following publications: *Non-Motor Symptoms of Parkinson's Disease*, Oxford University Press, 2nd edition, 2014, and 1st edition, 2011; has received honoraria from Parkinson's UK, the National Institute of Health Research (NIHR), the International Parkinson and Movement Disorder Society, Parkinson's UK and EU, and UCB, and for sponsored symposiums from UCB, AbbVie, Britannia, US Worldmeds, Otsuka, Medtronic, and Zambon; has served as a consultant for AbbVie, UCB, Britannia, Medtronic, and Mundipharma; currently serves on a scientific advisory board for Mundipharma and has served on a scientific advisory board for Eli Lilly in April of 2013; has received research support from Britannia and UCB (in the form of educational grants), from the NIHR (UK and EU both, for development of a nonmotor symptoms questionnaire for RLS), and from Parkinson's UK, (in the form of the following awards: 2016–2018: Horizon 2020 award: i-PROGNOSIS: Intelligent Parkinson eaRly detectiOn Guiding NOvel Supportive InterventionS,

2015–2016: CRN South London contingency funding, and 2014–2016: International Parkinson's and Movement Disorders Society: Field Validation of the MDS-NMS Scale); and currently receives license fee payments for the following scales: the King's Parkinson's Disease Pain Scale and the revised Parkinson's Disease Sleep Scale.

Dr. Ondo serves on speakers bureaus for Teva, Lundbeck, Merz, UCB, Xenoport, and Avanir; has received research support in the form of grants from Grants: US WorldMeds, Cynapsus, Dystonia Coalition, Tremor Research Group, Huntington Study Group, Auspex, and InSightec; serves on the *Neurology* Level of Evidence editorial advisory board; and receives royalties for co-editing the UpToDate publication *Restless Legs Syndrome.*

Dr. Trenkwalder has served on scientific advisory boards for Britannia, UCB, Mundipharma, Novartis, Vifor, and Desitin; has received honoraria from UCB, Mundipharma, Desitin, Britannia, and GlaxoSmithKline; has received grants from Teva, Mundipharma, Horizon 2020 European Frame Work Program, and the Michael J. Fox Foundation; has served as a paid investigator for Mundipharma, Novartis, and Vifor; has received research support from Mundipharma and Teva; and has received publishing royalties from Schattauer for *Parkinson* and from Thieme (Georg Thieme Verlag) for *Parkinson Dise*ase and for guidelines on RLS from the German Neurological Society.

Dr. Zee currently serves on scientific advisory boards for Merck, Phillips, and Eisai; has served on scientific advisory boards for Sanofi, Merck, Aptalis, Jazz, Vanda, Ferring, Takeda, UCB, Purdue, Pernix, and Phillips; serves as the deputy editor for the journal *Sleep* and for the *Journal of Sleep Medicine*; has served as an associate editor for the journal *Sleep* and as single-issue editor for the journal *Sleep Medicine Clinics*; holds a patent on a light therapy visor; receives publishing royalties from Wolters Kluwer for various books; has received honoraria from Merck, Aptalis, Jazz, Vanda, and Ferring; has received research support from Boehringer Ingelheim Pharmaceuticals, Inc. and GlaxoSmithKline for studies related to RLS, and from Takeda Pharmaceuticals, Jazz, Philips Consumer Lifestyle International B.V., the NIH, the American Academy of Sleep Medicine, and Northwestern Memorial Foundation (for studies not related to RLS); serves on the American Board of Internal Medicine test-writing committee for the Sleep Medicine Board Exam; has received honoraria for numerous speaking engagements; and has held stock in Teva.

Dr. Gronseth serves as an associate editor for *Neurology* and as an editorial advisory board member of *Neurology Now*, and receives compensation from the AAN for work as the chief evidence-based medicine methodologist.

Dr. Gloss serves as an evidence-based medicine consultant for the AAN.

Dr. Zesiewicz serves on the editorial boards of *Tremor and Other Hyperkinetic Disorders* and *Neurodegenerative Disease Management*, and has received research support for work on the Friedreich's Ataxia Research Alliance.

BBREVIATIONS

AAN: American Academy of Neurology
AEs: adverse events
ANCOVA: analysis of covariance
BDI-II: Beck Depression Inventory II
CGI-I: Clinical Global Impression of Improvement scale
COI: conflicts of interest
GDDI: Guideline Development, Dissemination, and Implementation Subcommittee
ESRD: end-stage renal disease
ESS: Epworth Sleepiness Scale
FCM: ferric carboxymaltose
FDA: US Food and Drug Administration
HADS: Hospital Anxiety and Depression Scale
HD: hemodialysis
IQR: interquartile range
IRLS: International Restless Legs Syndrome Study Group rating scale
MOS: Medical Outcomes Study
NIRS: near-infrared spectroscopy
OR: odds ratio
PGI-I: Patient Global Impression of Improvement
PLMI: Periodic Limb Movement Index
PLMS: periodic limb movements of sleep
PSG: polysomnography
PSQ: Post Sleep Questionnaire
PSQI: Pittsburgh Sleep Quality Index
QoL: quality of life
RCT: randomized controlled trial
RD: risk difference
RLS: restless legs syndrome
RLSQoL: Restless Legs Syndrome Quality of Life scale
rTMS: repetitive transcranial magnetic stimulation
SAEs: serious AEs
SC: standard of care
SE: standard error
tDCS: transcranial direct current stimulation
TST: total sleep time
WASO: wake after sleep onset

ABSTRACT

Objective: To make evidence-based recommendations regarding restless legs syndrome (RLS) management in adults.

Methods: Articles were classified per the 2004 American Academy of Neurology evidence-rating scheme. Recommendations were tied to evidence strength.

Results and recommendations: In moderate to severe primary RLS, clinicians should consider prescribing medication to reduce RLS symptoms. Strong evidence supports pramipexole, rotigotine, cabergoline, and gabapentin enacarbil use (Level A); moderate evidence supports ropinirole, pregabalin, and IV ferric carboxymaltose use (Level B). Clinicians may consider prescribing levodopa (Level C). Few head-to-head comparisons exist to suggest agents preferentially. Cabergoline is rarely used (cardiac valvulopathy risks). Augmentation risks with dopaminergic agents should be considered. When treating periodic limb movements of sleep, clinicians should consider prescribing ropinirole (Level A) or pramipexole, rotigotine, cabergoline, or pregabalin (Level B). For subjective sleep measures, clinicians should consider prescribing cabergoline or gabapentin enacarbil (Level A), or ropinirole, pramipexole, rotigotine, or pregabalin (Level B). For patients failing other treatments for RLS symptoms, clinicians may consider prescribing prolonged-release oxycodone/naloxone where available (Level C). In patients with RLS with ferritin ≤75 μg/L, clinicians should consider prescribing ferrous sulfate with vitamin C (Level B). When nonpharmacologic approaches are desired, clinicians should consider prescribing pneumatic compression (Level B) and may consider prescribing near-infrared spectroscopy or transcranial magnetic stimulation (Level C). Clinicians may consider prescribing vibrating pads to improve subjective sleep (Level C). In patients on hemodialysis with secondary RLS, clinicians should consider prescribing vitamin C and E supplementation (Level B) and may consider prescribing ropinirole, levodopa, or exercise (Level C).

INTRODUCTION

Restless legs syndrome (RLS) is a movement disorder that is characterized by an urge to move the legs or arms, commonly in response to an uncomfortable dysesthesia. It has the following 3 features: it is present at rest (sitting or lying down), it is relieved (often only temporarily) by movement of the affected limb, and it is most pronounced in the evening or at night.[e1] Clinical mimics (e.g., positional discomfort, leg cramps) cannot solely account for the symptoms. Diagnosis is made by clinical interview. RLS severity exists along a continuum from occasionally annoying to severely disruptive to quality of life (QoL). The prevalence of clinically important RLS is approximately 2.5% of adults in the United States and Northern Europe, with higher prevalence in women and with increasing age.[e2]

RLS is often classified as primary or secondary in origin, with the latter generally reserved for those with comorbid iron deficiency, end-stage renal disease (ESRD), or pregnancy. The etiology of primary RLS remains unknown. The primary and secondary phenotypes are nearly identical,[e3] and there is no evidence that primary and secondary RLS are distinct disease entities. Most patients with RLS have periodic limb movements of sleep (PLMS), which are repetitive dorsiflexion movements of the foot occurring every 5 to 90 seconds during sleep that are measured by EMG during polysomnography (PSG) and may be associated with EEG-defined arousals from sleep.[e4] Clinical consequences of RLS include impairment in sleep quality and quantity,[e5] mood and anxiety disorders,[e6] deterioration of health-related QoL,[e7] and loss of work productivity.[e8]

An accepted standardized outcome measure for treatment studies in RLS (the International Restless Legs Syndrome Study Group rating scale [IRLS]) was first published in 2003[e9]; before that time, various nonvalidated scales were used. The IRLS is composed of 10 questions addressing different aspects of RLS symptoms and consequences and is administered by clinical interview, with each item having a 0 to 4 range. Generally, a score greater than 10 is considered moderate RLS, greater than 20 is considered severe RLS, and greater than 30 is considered very severe RLS. When discussing the studies reviewed here, however, the guideline panel reflects the vocabulary used in the source literature. The IRLS is validated only for longitudinal or cross-sectional assessment of RLS severity and cannot be used for diagnosis. A change score of at least 3 points is considered clinically important.[e10] A similar scale, the RLS-6,[e11] has also been used as an outcome measure in a number of clinical trials. The RLS-6 consists of 6 scales designed as 11-point Likert assessments for the severity of different RLS symptoms. A clinically important change has not been established for this scale.

The first US Food and Drug Administration (FDA)–approved medication to treat RLS was ropinirole in 2005. Before then, levodopa/carbidopa, codeine, and clonazepam were the most commonly prescribed medications for treating RLS. Currently, there are 4 FDA-approved medications to treat primary moderate to severe RLS (defined as an IRLS score >15) in the United States, though additional agents have approval in other countries. The FDA-approved medications for RLS treatment are ropinirole, pramipexole, rotigotine patch, and gabapentin enacarbil. The vast majority of patients with RLS currently treated in the United States are prescribed the first 2 approved dopamine agonists (ropinirole and pramipexole). In 2014, the FDA approved a device with a vibrating pad for RLS-related sleep disturbance.

Augmentation is a major side effect of long-term treatment of RLS with dopaminergic medication (levodopa and dopamine agonists).[e12] Augmentation refers to an iatrogenic worsening of RLS and is most commonly characterized by an advance of symptom onset by at least 2 to 4 hours. It may also be manifested by increased intensity of RLS symptoms, wider anatomical distribution, shorter latency to symptom onset, or shorter duration of medication benefit.[e13,e14] Its likelihood of occurrence increases with longer duration of dopaminergic medication use; it does not usually occur before 6 months of treatment. Results of three 6-month double-blind studies comparing active medication with placebo suggest that augmentation can occur in an average of 2.4% (11/456) of patients treated with placebo,[e15–e17] with the average being driven by a 6.0% placebo augmentation rate in the first study[e15] and a rate of 1% or less in the other 2 studies.[e16,e17] This base rate of augmentation with placebo probably reflects a combination of natural progression of RLS symptoms and fluctuation of RLS symptoms related to other medical and lifestyle factors. There is no convincing evidence that augmentation occurs with other classes of medications for RLS. Augmentation exists along a continuum of severity. Most individuals with this complication experience a few hours of intermittent advanced symptom onset, although some may develop severe symptoms most of the day and night. Because augmentation is the major long-term complication of RLS treatment, its incidence (defined by guideline criteria from Allen et al. and Garcia-Borreguero et al.)[e13,e14] is noted subsequently for each treatment modality. Another potential limitation of long-term pharmacologic treatment of RLS is loss of efficacy.[e12] This has only recently been defined, so most studies do not address it specifically.

This practice guideline addresses the following question: What are safe and effective therapies, including both pharmacologic and nonpharmacologic approaches, for the symptoms and clinical consequences (disturbed sleep, PLMS, depression/anxiety, and decreased QoL) of RLS in adults? Data on each of the major therapeutic approaches for primary RLS (dopamine agonists, α2δ ligands, levodopa, iron treatments, opioids, and miscellaneous treatments) are addressed in turn, followed by data from therapeutic trials of secondary RLS.

DESCRIPTION OF THE ANALYTIC PROCESS

This practice guideline follows the methodologies outlined in the 2004 edition of the AAN's guideline development process manual.[e18] The guideline panel summarizes the process here and provides a detailed description in the appendices referenced in this document. In 2007, the Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) of the American Academy of Neurology (AAN) (appendices e-1 and e-2) assembled a panel of clinicians and investigators from the United States and Europe who had published extensively on RLS and who represented a broad range of relevant expertise and opinion. According to the 2004 process, panel members may have conflicts of interest (COI) if these conflicts are disclosed in the guideline and the panel is balanced. For this practice guideline, experts in RLS with possible COIs were accompanied on the panel by an RLS expert without relevant conflicts and a former guideline subcommittee member (TZ) and three evidence-based medicine methodologists (MJA, GG, DG) without conflicts. The GDDI leadership determined presence of COI by reviewing updated COI forms before final approval of the manuscript. In accordance with the 2004 process, the guideline panel based recommendations strictly on the evidence and did not involve expert

opinion. During the classification of evidence, panel members were not permitted to rate their own work, and classification for all articles included in the practice guideline was confirmed by at least one evidence-based medicine methodologist.

Panel members developed the clinical question, the data extraction template, and the search terms. An independent medical librarian performed a systematic literature search in all languages in December 2007 (see appendix e-3 for the complete search strategy) for pharmacologic and nonpharmacologic RLS therapies. Three databases (MEDLINE, Embase, and Science Citation Index) were searched from 1966 to December 2007. The guideline panel subsequently performed an identical search in order to include articles published from December 2007 to August 2011. The independent librarian performed a final identical search in July 2015. The chair of the panel reviewed each of the retrieved 2,729 abstracts to establish whether an article met the basic inclusion criteria: (1) original article described treatment of RLS, (2) study lasted longer than a single night (for each treatment arm), and (3) article was not a single-patient case report. Articles meeting these basic criteria were reviewed and classified by 2 panel members, working independently of each other, for quality of evidence on the basis of the AAN therapeutic classification scheme rating risk of bias pertaining to study characteristics (appendix e-4). Two additional committee members adjudicated discrepancies between reviewers. Studies involving only interventions that have been withdrawn from the market (e.g., pergolide, which was removed from the market in the United States in 2007 because of concerns regarding associated valvulopathy) were excluded. Recommendations were derived from the conclusions and are strictly tied to the evidence (appendix e-5).

For each intervention, data were extracted for results regarding efficacy for RLS symptoms and efficacy for sleep, mood, and QoL. For RLS efficacy, the IRLS was the preferred outcome, if available, and a change of 3 points was considered clinically meaningful.[e10] For sleep outcomes, the most commonly used subjective scales were the RLS-6 and the Medical Outcomes Study (MOS) Sleep Scale, for which clinically meaningful changes have not been established. The MOS Sleep Scale includes 4 subscales: sleep disturbance (decrease indicates improvement), sleep quantity (in hours; increase indicates improvement), sleep adequacy (increase indicates improvement), and daytime somnolence (decrease indicates improvement). For studies reporting PSG results, the panel chose to evaluate the Periodic Limb Movement Index (PLMI), total sleep time (TST), sleep efficiency, sleep latency, and wake after sleep onset (WASO) for uniformity between studies. PLMI is a PSG measure calculated by dividing the total number of PLMS by sleep time in hours. The clinical importance of PLMI is uncertain, however, and optimal PSG parameters for assessing clinically meaningful changes in sleep in RLS have not been established.

Even in the face of uncertainty regarding the clinical importance of any given change score on sleep and QoL measures, when considering these outcomes, one must assess not only statistical significance but also clinical relevance in order to decide whether a given result should inform a conclusion for or against use of an agent for that outcome or whether the evidence is insufficient to draw conclusions. Statistical significance, clinical significance, and precision were all considered when deriving conclusions from the evidence. This resulted in 6 possible outcomes, 4 occurring in the context of statistical significance and 2 occurring when there is not statistical significance:

1. The point estimate of the difference between 2 interventions is clinically important, and the CI around this point estimate is both statistically significant and clinically important: conclusion developed in favor of the superior intervention.

2. The point estimate of the difference between 2 interventions is clinically important, and the CI is statistically significant but include values that are not clinically important or are of uncertain clinical relevance: conclusion developed in favor of the superior intervention, but text includes a description of the limitation in interpretation due to CIs.

3. The point estimate of the difference between 2 interventions is *not* clinically important, but the difference is statistically significant and the CI includes a clinically important difference: conclusion states insufficient evidence because the point estimate is not clinically important (regardless of statistical significance), but CIs include a difference that is clinically important, so clinical importance remains possible.

4. The point estimate of the difference between 2 interventions is *not* clinically important, the difference is statistically significant, and the CI includes only values that also are not clinically important: conclusion states that the 2 interventions are essentially equivalent because the difference between them is not clinically important; if one of the interventions is placebo, conclude that the active intervention does not result in a clinically meaningful improvement.

5. The difference between 2 interventions is *not* statistically significant, and the CI does *not* include clinically important values: conclusion states that the active intervention does not result in benefit vs the comparator.

6. The difference between 2 interventions is *not* statistically significant, but the CI includes clinically important (or potentially clinically important) values: conclude that there is insufficient evidence because, although the results were not statistically significant, there remains the possibility for an important difference between interventions (this is often the case when studies have insufficient precision [e.g., because they are underpowered]).

With the exception of the IRLS, where a 3-point difference was considered clinically meaningful/relevant, these judgments were made by guideline panel members on the basis of a subjective assessment of the change (e.g., a difference of 30 minutes of night sleep was considered to be potentially clinically important; an odds ratio [OR] CI including 1.01 was perceived to include an OR of dubious clinical importance). Provided or calculated CIs are available for most referenced articles (where data are sufficient to calculate CIs if they were not provided) so that readers can assess whether their judgments align with those made by the guideline panel. The practice guideline indicates when the CIs include values of potential or uncertain clinical relevance. The six categories just presented are most relevant when considering the IRLS, where a clinically important difference was prespecified. In the case of sleep and QoL outcomes, assessment of CIs was most relevant in cautioning against overinterpretation of conclusions in favor of an agent (item 2 in the previous list) or when attempting to decide whether a result that was not statistically significant had a narrow enough

CI to recommend against use or whether there was insufficient evidence (items 5 and 6 in the list). Ultimately, readers can derive their own conclusions from review of the provided CIs.

Evidence-based medicine methodology consultants performed random-effects meta-analyses when there was a need to reconcile potentially discordant results or improve statistical precision. For the purpose of establishing confidence in the evidence, results of meta-analyses were considered equivalent to the classification of the contributing studies. For example, if a meta-analysis was performed on 2 Class I studies but only one of those studies had statistical significance, the results of that meta-analysis were considered equivalent to a single Class I study. If a meta-analysis was performed on Class I and Class II studies and none of the studies achieved statistical significance on their own, the results of that meta-analysis were deemed equivalent to a single Class II study.

Results are presented for each dose according to the results extracted from reviewed studies. For the formulation of conclusions, the decision was made to write conclusions for the medication rather than considering each dose separately. This decision was based on the assumption that clinicians will follow prescribing instructions, which typically start at the smallest recommended dose and gradually titrate up to clinical effect, using the lowest effective dose to try to limit dose-dependent side effects. FDA-approved doses for each recommended medication are included in table e-1.

Recommendations were based on conclusions and class of evidence in accordance with the AAN process (appendix e-5), where Level A reflects strong evidence, Level B reflects moderate evidence, and Level C reflects weak evidence. A Level U recommendation represents insufficient evidence to support or refute the use of any given intervention. Class I and II articles are described in the text (in cases with substantial Class I evidence, Class II evidence is referenced but not described); Class III studies are described only if there are insufficient articles with a higher classification to drive conclusions and recommendations. Class IV studies are not described except in the context of side effects and long-term complications, particularly augmentation.

ANALYSIS OF EVIDENCE

Details regarding classification of evidence for all studies included in the practice guideline text are available in appendix e-4.

Dopamine agonists

Ropinirole

Ropinirole is a nonergot dopamine agonist with preferential binding to D3 receptors. The literature search identified 2 Class I, 5 Class II, and 3 Class III studies relevant to the efficacy of ropinirole for RLS.

Efficacy for RLS

Two Class I[e19,e20] and 5 Class II[e21–e25] flexible-dose studies (all over 12 weeks) examined ropinirole use vs placebo for treatment of moderate to severe primary RLS. In 1 Class I randomized controlled trial (RCT)[e19] enrolling 381 patients, the mean difference on the IRLS between the ropinirole (mean dose 2.1 mg/d) and placebo groups was -3.7 (95% CI -5.4 to -2.0). Ropinirole was also superior to placebo on the Clinical Global Impression of Improvement scale (CGI-I) at 12 weeks. Ropinirole was associated with an adjusted OR of 2.1 (95% CI 1.5–3.3) for a response to treatment (those reporting they were much or very much better after treatment). A smaller 12-week Class I study[e20] enrolled 65 patients with RLS and PLMS. In this study, there was no statistical difference in the IRLS score between groups (-1.2, 95% CI -5.2 to 2.9), but the CI included both clinically important and unimportant effects. The mean ropinirole dose was 1.8 mg in the treatment group. In a random-effects meta-analysis combining the 2 Class I studies, ropinirole treatment resulted in a mean difference of -3.1 on the IRLS (95% CI -5.2 to -1.1, I^2 21%), demonstrating a statistically significant improvement with ropinirole treatment but with the CI including a change that is not clinically important.

All 5 Class II studies demonstrated a statistically significant effect of ropinirole compared with placebo. In a 12-week RCT enrolling 284 participants,[e21] ropinirole treatment (mean dose 1.9 mg) resulted in a mean difference of -3.0 (95% CI -5.0 to -1.0) on the IRLS and an OR for response of 1.7 (95% CI 1.0–2.7). A 12-week RCT enrolling 267 patients with moderate to severe RLS[e22] found a mean difference of -2.5 (95% CI -4.6 to -0.4) on the IRLS in the ropinirole group (median dose 1.5 mg) vs placebo and an OR for response of 2.3 (95% CI 1.4–3.8). In a 12-week RCT enrolling 359 patients and using twice-daily dosing of ropinirole (mean total dose 3.1 mg),[e23] ropinirole was superior to placebo, with a mean treatment difference on the IRLS of -4.1 (95% CI -6.1 to -2.1) and an OR for improvement of 2.4 (95% CI 1.6–3.8). The mean treatment difference on the IRLS was -4.8 (95% CI -7.5 to -2.1) in a 12-week RCT of 231 patients with moderate to severe RLS and at least mild depression, again showing the superiority of ropinirole over placebo.[e24] The OR for a treatment response was 2.1 (95% CI 1.2–3.7). Finally, an RCT of 404 patients with a baseline IRLS score $\geq$24 showed superiority of ropinirole (median dose 1.8 mg) with a mean difference of -2.1 (95% CI -4.0 to -0.1) vs placebo at 12 weeks and 2.5 (95% CI -4.6 to -0.3) at 26 weeks.[e25] Ropinirole treatment was associated with an OR for response of 1.9 (95% CI 1.2–3.1) at 12 weeks and 2.7 (95% CI 1.4–5.2) at 26 weeks.

Efficacy for sleep, mood, and QoL

Both Class I studies[e19,e20] and 4 of the Class II studies[e21,e22,e24,e25] just discussed assessed sleep as measured by the MOS Sleep Scale. In the Class I study enrolling 381 patients,[e19] ropinirole was superior to placebo for sleep disturbance (mean difference -10.3, 95% CI -15.0 to -5.7), sleep quantity (0.3 hours, 95% CI 0.1–0.5), and sleep adequacy (11.4, 95% CI 6.2–16.7). The difference in daytime somnolence between groups was not statistically significant (-3.1, 95% CI -6.8 to 0.6), though the CI included a change that could potentially be clinically important. In the Class I study enrolling 65 patients with RLS and PLMS,[e20] ropinirole was superior to placebo for sleep adequacy (mean difference 12.1, 95% CI 1.1–23.1). Other comparisons were not statistically significant because they had insufficient precision to demonstrate a difference in means for sleep disturbance (-5.4, 95% CI -18.7 to 7.9), sleep quantity (2.9 hours, 95% CI -2.0 to 7.9), or daytime somnolence (-3.1, 95% CI -9.2 to 2.9) (i.e., CIs included both potentially important and unimportant effects).

In a Class II RCT of 284 patients,[e21] ropinirole was significantly better than placebo for all MOS subscales: sleep disturbance (mean difference -7.7, 95% CI -13.3 to -2.2), sleep quantity (0.38 hours, 95% CI 0.03–0.73), daytime somnolence (-5.0, 95% CI -9.4 to -0.7), and sleep adequacy (11.2, 95% CI 4.9–17.6), although some of these CIs included differences of uncertain clinical importance. Ropinirole resulted in significant improvements vs placebo in all MOS subscales in the Class II RCT of 267 patients with moderate to severe RLS[e22]: sleep disturbance (mean difference -13.4, 95% CI -18.8 to -8.1), sleep quantity (1.3 hours, 95% CI 0.3– 2.2), daytime somnolence (-6.3, 95% CI -10.5 to -2.0), and sleep adequacy (13.6, 95% CI 7.2–20.0). Although the Class II RCT of 231 patients with moderate to severe RLS and at least mild depression[e24] reported *p* values only for MOS subscales, original data obtained from the GSK Clinical Study Registry[e26] showed that all MOS subscales except daytime somnolence were significantly better in patients treated with ropinirole: sleep disturbance (mean difference-14.3, 95% CI -20.7 to -7.9), sleep quantity (0.7 hours, 95% CI 0.4–1.0), and sleep adequacy (17.6, 95% CI 9.1–26.0). Mean difference between ropinirole and placebo for daytime somnolence was -4.4 (95% CI -9.4 to 0.6). Finally, the Class II RCT of 404 patients[e25] with a baseline IRLS score $\geq$ 24 showed that ropinirole was superior to placebo at 12 weeks for sleep disturbance (mean difference -9.0, 95% CI -13.6 to -4.4), sleep adequacy (7.8, 95% CI 2.3–13.2), and daytime somnolence (-3.9, 95% CI -7.6 to -0.3), but results were not statistically significant for sleep quantity (0.2, 95% CI -0.1 to 0.5). At 26 weeks, ropinirole was superior to placebo for sleep disturbance (mean difference -8.2, 95% CI -13.3 to -3.0) and sleep adequacy (11.1, 95% CI 4.9–17.3), but results were not statistically significant for daytime somnolence (-2.3, 95% CI -6.8 to 2.2) or sleep quantity (0.2 hours, 95% CI -0.1 to 0.5).

Because many of the studies had limited statistical precision (as evidenced by CIs including both important and unimportant effects), a meta-analysis of the mean differences for each subscale was performed using all 6 studies after a meta-analysis of the 2 Class I studies failed to achieve sufficient precision. When random-effects models were used, ropinirole treatment resulted in improvements on each subscale: sleep disturbance (-4.6, 95% CI -6.4 to -2.7, I^2 0%), sleep quantity (0.4 hours, 95% CI 0.2–0.7, I^2 53%), sleep adequacy (11.6, 95% CI 8.9–14.2, I^2 0%), and daytime somnolence (-4.1, 95% CI -6.0 to -2.3, I^2 0%), though some CIs included values of uncertain clinical importance.

One Class I study using PSG found reductions in both the PLMI (adjusted mean difference -27.2, 95% CI -39.1 to -15.4) and sleep onset latency (adjusted mean difference -9.8 minutes, 95% CI -17.2 to -2.4) with ropinirole treatment. There was no significant change in TST (adjusted treatment difference 20.5 minutes, 95% CI -4.6 to 45.6) or sleep efficiency (adjusted treatment difference 4.3%, 95% CI -0.8 to 9.4), but precision was limited, with CIs that included both potentially clinically important and unimportant effects.[e20] Another Class I study found a reduction in actigraphy-recorded PLMS using a mean ropinirole dose of 2.1 mg (PLMI adjusted mean treatment difference -14.5, 95% CI -20.3 to -8.7).[e19]

One Class I study[e19] and 3 Class II studies[e21,e22,e25] found improvements in RLS-specific QoL with ropinirole treatment. At 12 weeks, ropinirole was superior to placebo as assessed on the Restless Legs Syndrome Quality of Life scale (RLSQoL) in the Class I study (mean difference 4.5, 95% CI 1.6–7.5)[e19] and all 3 Class II studies (4.4, 95% CI 0.5–8.4[e22]; 4.9, 95% CI 0.4–7.7[e25];

and 17.1 vs 12.6, $p = 0.03$).[e21] Ropinirole was also superior to placebo on the RLSQoL at 26 weeks in a Class II study (mean difference 2.0, 95% CI 1.8–5.9).[e25]

One Class I study[e19] and 1 Class II study[e24] examined patients with at least mild depression symptoms at baseline. The Class II study[e24] showed a statistically significant improvement in depression on the Montgomery-Asberg Depression Rating Scale (the primary outcome measure) with ropinirole treatment, with an adjusted mean treatment difference of -3.6 (95% CI -5.6 to -1.6). This difference was also seen on the Hospital Anxiety and Depression Scale (HADS) depression score (adjusted mean difference with ropinirole -2.7, 95% CI -4.4 to -1.1) and the Beck Depression Inventory II (BDI-II) (adjusted mean difference with ropinirole -2.6, 95% CI -4.6 to -0.7). There was no difference in the HADS depression score in the Class I study[e19] (treatment difference -1.5, 95% CI -3.6 to 0.6), but the CI included a potentially clinically important effect. A random-effects meta-analysis combining the mean difference in the HADS depression score from each study showed superiority of ropinirole over placebo, with a treatment difference of -2.2 in favor of ropinirole (95% CI -3.5 to -0.9, I^2 0%). Anxiety as measured by the HADS anxiety score was significantly reduced in the ropinirole group in a Class I study[e19] (mean treatment difference in favor of ropinirole -1.2, 95% CI -2.3 to -0.1), although the CI includes values of uncertain clinical importance.

Safety and tolerability

The most common acute adverse events (AEs) in these 12-week studies were nausea, headache, somnolence, and dizziness. Of three 12-week studies reporting augmentation rates, 2 studies described no augmentation[e21,e22] and 1 reported augmentation in 1.6% of patients taking ropinirole (vs 0.5% taking placebo).[e19] In a 26-week study,[e16] an adjudication board determined that 4% of patients taking ropinirole and 0.48% of patients taking placebo met diagnostic criteria for augmentation. Loss of efficacy was observed in 12.7% of patients taking ropinirole and 6.8% of patients taking placebo.[e16] Longer term, 2 Class IV studies[e14,e16] reported rates of augmentation of 7%–9% and loss of efficacy in 16% of patients over 1 year of open-label follow-up.

Conclusions

It is likely that ropinirole decreases IRLS scores at 12 weeks (meta-analysis of 2 Class I studies, of which 1 had sufficient precision independently). It is highly likely that ropinirole improves PLMS (2 Class I studies) and likely that it improves some other objective sleep measures (1 Class I study) and some subjective sleep measures (meta-analysis of 2 Class I and 4 Class II studies using MOS subscales). It is likely that ropinirole improves RLS-specific QoL at 12 weeks (1 Class I study and 3 Class II studies). It is possible that ropinirole improves depression (meta-analysis of 1 Class II study and 1 Class I study with insufficient precision) and likely that it improves anxiety at 12 weeks (1 Class I study).

Pramipexole

Pramipexole is a nonergot dopamine agonist with preferential binding to D3 receptors. Three Class I, 6 Class II, and 4 Class III studies related to the efficacy of pramipexole were identified.

Efficacy for RLS

Three Class I studies[e27–e29] and 6 Class II studies[e30–e35] investigated the efficacy of pramipexole (0.25 mg–0.75 mg) in the treatment of moderate to severe primary RLS. A Class I parallel-group study[e27] randomized 344 patients to 3 doses (0.25, 0.5, 0.75 mg) of pramipexole or placebo. Patients treated with pramipexole had a difference of -4.3 on the IRLS vs placebo at 12 weeks when an analysis of covariance (ANCOVA)–based model (95% CI -6.5 to -2.1) was used. The CGI-I was also significantly better with pramipexole treatment, with an adjusted OR of 2.4 (95% CI 1.5–4.0) for a response to treatment. A Class I parallel-group study randomized 287 patients to receive flexible dosing with pramipexole or placebo.[e28] After 6 weeks, IRLS reduction was greater with pramipexole (mean dose of 0.43 ± 0.23 mg) than with placebo (mean difference -5.1, 95% CI -7.3 to -2.9). The CGI-I responder rate was significantly higher in the pramipexole group (OR for response to treatment 3.8, 95% CI 2.2–6.6). Another Class I parallel-group study randomized 204 patients to receive flexible dosing with pramipexole (0.25–0.75 mg) or placebo. After 12 weeks, IRLS reduction was greater with pramipexole than with placebo (mean difference -3.8, 95% CI -4.0 to -3.6). The CGI-I for treatment response was also significantly better with pramipexole (OR 3.1, 95% CI 1.7–5.5).[e29]

Six Class II studies (usually Class II for a dropout rate >20%) also suggested that pramipexole was superior to placebo in the treatment of RLS over varying time frames and with varying degrees of statistical precision. A Class II parallel-group study randomized 357 patients with RLS to receive flexible dosing (mean dose of 0.42 mg) with pramipexole or placebo.[e30] After 12 weeks, IRLS reduction was greater with pramipexole (-3.8, 95% CI -3.95 to -3.65). The CGI-I responder rate was significantly higher in the pramipexole group (OR for treatment response at 12 weeks 2.9, 95% CI 1.9–4.5). An RCT of 109 patients demonstrated superiority of all 4 doses of pramipexole over placebo on the IRLS after 3 weeks of treatment (adjusted mean differences in favor of pramipexole): 0.125 mg (-5.79, 95% CI -10.11 to -1.47), 0.25 mg (-9.1, 95% CI -13.35 to -4.85), 0.5 mg (-10.93, 95% CI -13.98 to -7.88), and 0.75 mg (-9.78, 95% CI -12.90 to -6.66).[e31] The CGI-I was also superior to placebo for all pramipexole doses (data not provided), with a larger clinical response from the 3 higher doses. A parallel-group RCT of 345 patients administered flexible doses (mean of 0.35 mg) of pramipexole showed a mean difference of -6.6 (95% CI -8.6 to -4.5) on the IRLS after 6 weeks of treatment; the CGI-I responder rate was also higher in the pramipexole group (OR for treatment response 3.5, 95% CI 2.2–5.7).[e32] A 3-week RCT found that 4 doses of pramipexole (0.125 mg, $p = 0.0274$; 0.25, 0.5, 0.75 mg all $p < 0.0001$) were superior to placebo in the treatment of RLS as measured by the IRLS (adjusted mean difference can only be estimated from figure; differences in means between pramipexole and placebo range from approximately -6 points for the 0.125-mg dose to -11 points for the 0.5-mg dose).[e33] A flexible-dose (mean of 0.421 mg) RCT enrolled 402 patients with RLS and at least mild RLS-related mood disturbance and demonstrated a mean difference of -6.1 (95% CI -7.9 to -4.3) on the IRLS after 12 weeks; the OR for CGI-I response with pramipexole was 3.9 (95% CI 2.5–5.9).[e34] A fixed-dose RCT of pramipexole vs placebo and pregabalin 300 mg for 12 weeks showed a treatment advantage for the 0.5-mg pramipexole dose (-3.2, 95% CI -4.5 to -1.9) but not for the 0.25-mg dose (-0.6, 95% CI -2.0 to 0.7) vs placebo on the IRLS. Similarly, the higher pramipexole dose (OR for response 1.9, 95% CI 1.2–2.9) but not the lower dose (OR for

response 1.2, 95% CI 0.8–1.8) was associated with an increased odds of response to treatment as measured by the CGI-I.[e35]

Efficacy for sleep, mood, and QoL

One of the Class I[e28] and 4 of the Class II studies[e30,e32,e34,e35] described previously provide data on subjective sleep outcomes with pramipexole.

In the Class I study of 287 patients, the sleep satisfaction score from the RLS-6 was better with pramipexole (mean dose of 0.434 ± 0.23 mg) compared with placebo (mean difference -1.5, 95% CI -1.6 to -1.4) after 6 weeks of treatment. The intensity of daytime tiredness and sleepiness also improved more in the pramipexole group (-0.7, 95% CI -0.8 to -0.6).[e28]

A flexible-dose 12-week Class II RCT also used the RLS-6 to assess sleep outcomes. It enrolled 402 patients with RLS and moderate to severe RLS-related mood disturbance. Pramipexole (mean dose 0.421 mg) was superior to placebo for sleep satisfaction (median change -3.0, interquartile range [IQR] -6.0 to 0.0 for pramipexole and median change -1.0, IQR -3.0 to 1.0 for placebo, $p < 0.0001$). Daytime sleepiness was also improved in the pramipexole group (median change -2.0, IQR -4.0 to 0.0 for pramipexole and median change -1.0, IQR -3.0 to 0.0 for placebo, $p = 0.0007$).[e34]

In a 12-week Class II study of 369 patients, pramipexole was flexibly dosed from 0.125 to 0.75 mg, with 15.4% of patients receiving a final dose of 0.125 mg, 33.0% receiving a final dose of 0.25 mg, 26.9% receiving a final dose of 0.5 mg, and 24.7% receiving a final dose of 0.75 mg. Sleep improved in the pramipexole-treated group as measured by the MOS sleep disturbance scale (adjusted mean treatment difference -8.5, 95% CI -8.8 to -8.2) and the MOS sleep adequacy scale (median change 10.0, IQR 0.0–30.0 for placebo and median change 20.0, IQR 0.0–50.0 for pramipexole, $p = 0.0008$). However, there was no difference between the placebo and pramipexole groups on the MOS sleep quantity scale (median change 0.0 hours, IQR 0.0–1.0 for placebo and median change 0.3 hours, IQR 0.0–1.0 for pramipexole, $p = 0.0795$) or the daytime somnolence scale (median change -6.7, IQR -20.0 to 0.0 for placebo and median change -13.3, IQR -26.7 to 0.0 for pramipexole, p = not significant).[e30] A fixed-dose 12-week Class II RCT showed no statistical difference between pramipexole (0.25 mg or 0.5 mg) and placebo on the MOS sleep quality scale (mean change from baseline vs placebo 1.2, 95% CI -2.4 to 4.7 in the 0.25-mg group and 3.3, 95% CI -0.2 to 6.8 in the 0.5-mg group), self-reported WASO (mean change from baseline vs placebo -1.1 minutes, 95% CI -9.7 to 7.6 in the 0.25-mg group and -4.6 minutes, 95% CI -13.1 to 3.9 in the 0.5-mg group), self-reported number of awakenings (mean change from baseline vs placebo 0.0, 95% CI -0.1 to 0.2 in the 0.25-mg group and 0.0, 95% CI -0.2 to 0.2 in the 0.5-mg group), or self-reported TST (mean change from baseline vs placebo 0.1 hours, 95% CI -0.1 to 0.3 in the 0.25-mg group and 0.2 hours, 95% CI 0.0–0.4 in the 0.5-mg group), although some CIs included potentially clinically important effects. There was a significant reduction in self-reported sleep latency in both pramipexole groups compared with the placebo group (mean change from baseline vs placebo -8.2 minutes, 95% CI -14.3 to -2.2 in the 0.25-mg group and -13.1 minutes, 95% CI -19.0 to -7.2 in the 0.5-mg group).[e35] Another flexible-dose Class II RCT of 345 patients showed a benefit of pramipexole vs placebo on sleep at 6 weeks as measured by an IRLS item on sleep disturbance due to RLS (mean difference -0.9,

95% CI -1.25 to -0.55), an IRLS item on severity of daytime sleepiness due to RLS (mean difference -0.6, 95% CI -0.92 to -0.28), and a visual analog sleep dissatisfaction scale (mean difference -16.1, 95% CI -16.77 to -15.43).[e32]

Reductions in PLMS were seen in 3 Class II studies[e31,e33,e36] that examined polysomnographic effects of pramipexole. In a triple crossover with 4-week treatment arms, PSG was performed in patients who did not demonstrate a response in a single-blind 1-week placebo run-in. The study's primary outcome was WASO, which was not different between pramipexole and placebo arms (estimated mean difference -0.2, 95% CI -1.5 to 1.1). During the pramipexole arm, patients had a lower PLMI (estimated mean difference -29.0, 95% CI -29.8 to -28.2), greater TST (estimated mean difference 6.8 min, 95% CI 4.9–8.7), and greater sleep efficiency (estimated mean difference 1.6%, 95% CI 1.2–2.0%), though the clinical importance of these differences is uncertain.[e36] In a 3-week RCT of 107 patients with RLS, all 4 pramipexole doses (0.125, 0.25, 0.5, and 0.75 mg) were superior to placebo ($p < 0.01$) in reducing the PLMI (raw numbers not provided).[e33] Sleep latency was significantly shorter than with placebo for all pramipexole doses except 0.25 mg ($p < 0.05$, raw numbers not provided). However, only the 0.5-mg dose was superior to placebo for improving TST ($p < 0.05$, raw numbers not provided). In another 3-week RCT of 109 patients, all 4 pramipexole doses (0.125, 0.25, 0.5, and 0.75 mg) were superior to placebo in reducing the PLMI (differences in medians vs placebo by dose: 0.125 mg -49.7, $p < 0.01$; 0.25 mg -28.05, $p < 0.001$; 0.5 mg -23.55, $p < 0.001$; 0.75 mg -27.0, $p < 0.001$).[e31] Sleep latency was significantly shorter for 3 of the doses (differences in medians vs placebo by dose: 0.125 mg -7.5, $p < 0.05$; 0.25 mg -3.0, $p > 0.05$; 0.5 mg -9.75, $p < 0.01$; 0.75 mg -5.0, $p < 0.05$). None of the tested doses improved sleep efficiency (differences in medians vs placebo by dose: 0.125 mg -2.25; 0.25 mg -2.9; 0.5 mg 2.45; 0.75 mg -0.55; all $p > 0.05$), and only the 0.5-mg dose improved TST (differences in medians vs placebo by dose: 0.125 mg 31.0 minutes, $p > 0.05$; 0.25 mg 25 minutes, $p > 0.05$; 0.5 mg 41.25 minutes, $p < 0.05$; 0.75 mg 9.0 minutes, $p > 0.05$).

One Class I study[e27] and 3 Class II studies,[e30,e34,e35] all 12 weeks in duration, demonstrated improved RLS-specific QoL with pramipexole (for at least some doses) as measured by the RLSQoL, although a 26-week Class III study did not.[e15] In the Class I study,[e27] pramipexole was superior to placebo for each dose (mean differences by dose: 0.25 mg 5.7, 95% CI 5.28–6.12; 0.5 mg 7.8, 95% CI 7.36–8.24; 0.75 mg 6.0, 95% CI 5.58–6.42). The flexibly dosed Class II studies showed a difference between groups in change from baseline of 5.0 (95% CI 4.7–5.3)[e30] and 7.5 (95% CI 7.2–7.8).[e34] The fixed-dose Class II study[e35] showed a mean difference of 0.5 (95% CI -1.5 to 2.4) for pramipexole 0.25 mg and 2.1 (95% CI 0.1–4.1) for the 0.5-mg dose.

One Class II study examined the effect of pramipexole on mood in 402 patients with RLS and moderate to severe RLS-related mood disturbance using flexible dosing over 12 weeks.[e34] Pramipexole treatment was associated with a small but significant reduction in depressive symptoms as assessed by the BDI-II, with a mean adjusted difference from placebo of -1.5 (95% CI -2.7 to -0.2). A similar benefit was observed on the HADS anxiety score, with pramipexole superior to placebo as shown by a mean difference of-1.0 (95% CI -1.1 to -0.9).

Safety and tolerability

The most common AEs were nausea and somnolence/fatigue.[e15,e35] In a 1-year Class II active-comparator study comparing pregabalin to 2 doses of pramipexole, an adjudication board identified augmentation at 52 weeks in 9.0% (0.5 mg) and 6.6% (0.25 mg) of patients taking pramipexole (vs 2.1% in the pregabalin group; all patients were receiving active treatment at 52 weeks).[e35] An adjudication board identified an augmentation rate of 9.2% (vs 6.0% for placebo) in a 6-month Class III study.[e15] Augmentation rates of 22% to 42% were reported in 3 single-site Class IV studies lasting 2–8 years,[e37–e39] and an augmentation rate of 70% was reported in a Class IV study lasting 10 years.[e40] Although these numbers suggest that augmentation may increase over time, the degree of contribution from study design (e.g., short-term RCTs vs long-term open-label follow-up) cannot be determined. Tolerance was reported in 46% of patients taking pramipexole over a mean follow-up of 21 months in a Class IV study,[e37] and the median dose increased from 0.38 mg to 1.0 mg after a mean of 8 years of treatment in another.[e38]

Comparative trials: Pregabalin vs pramipexole

See section with analysis of pregabalin studies.[e35]

Pramipexole vs iron sulfate

See section with analysis of iron studies.[e41]

Conclusions

It is highly likely that pramipexole improves RLS symptoms as measured by the IRLS (3 Class I and 7 Class II studies over varying time frames). It is likely that pramipexole improves PLMS (3 Class II studies) and subjective sleep measures (1 Class I study and 3 Class II studies, with an additional Class II study lacking the precision to exclude an important effect). There is insufficient evidence to support or refute an effect of pramipexole on other polysomnographic measures (e.g., sleep latency, sleep efficiency, WASO, or TST) on the basis of results with varied statistical significance and clinical importance across 3 Class II studies with sometimes limited statistical reporting. It is likely that pramipexole improves RLS-specific QoL at 12 weeks (1 Class I study and 3 Class II studies, with one of the Class II studies showing limited improvement). It is possible that pramipexole improves depression and anxiety at 12 weeks in patients with moderate to severe RLS-related mood disturbance (1 Class II study).

Rotigotine patch

Rotigotine is a nonergot transdermally administered dopamine agonist with preferential binding to D3 receptors. Our search strategy identified 2 Class I and 3 Class II studies.

Efficacy for RLS

Two Class I[e42,e43] and 3 Class II studies (usually Class II because of excessive dropouts)[e17,e44,e45] investigated the efficacy of rotigotine for the treatment of primary moderate to severe RLS, typically at doses of 1–3 mg/24 h. A Class I parallel-group study[e42] randomized 63 patients to receive 3 doses of rotigotine or placebo. After 1 week, the IRLS reduction was greater for the

rotigotine 4.5-mg dose than for placebo (least square mean with 95% CIs from an ANCOVA model -7.7, 95% CI -13.5 to -2.0). Results were not markedly significant for the 1.125-mg (least square mean -2.5, 95% CI -8.4 to 3.5) and 2.25-mg (least square mean -4.3, 95% CI -10.6 to 2.0) doses using this statistical approach, but CIs for both included clinically important effects. Similar results were obtained with the CGI-I, in which the rotigotine 4.5-mg dose (89.5% responders, $p = 0.0119$), but not the 1.125-mg (52.9% responders) or 2.25-mg (61.6% responders) dose, was superior to placebo (42.9% responders). Another Class I study[e43] randomized 67 patients (in a 2:1 ratio) to receive flexibly dosed rotigotine (mean 2.09 ± 0.78 mg) or placebo. After 4 weeks, rotigotine was superior to placebo as measured by the change in IRLS (mean difference -6.09, 95% CI -10.71 to -1.47), but the CI included a change not reaching clinical importance. Similarly, on the Clinical Global Impression of Severity scale (CGI-S), a 7-point severity scale (with 1 being not at all ill and 7 being extremely ill), rotigotine was significantly better than placebo (mean difference -0.89, 95% CI -1.62 to -0.17), but the CI included values of unlikely clinical importance. A Class II parallel-group study randomized 284 patients to receive rotigotine 2 mg, rotigotine 3 mg, or placebo. After 13 weeks, IRLS reduction was greater with either dose of rotigotine than with placebo (least square mean, 2 mg: -2.8, 95% CI -5.3 to -0.3; 3 mg: -3.1, 95% CI -5.6 to -0.6), though CIs again included changes not reaching clinical importance. The OR for a response was significant for rotigotine 3 mg (2.1, 95% CI 1.1–3.9) but not 2 mg (1.5, 95% CI 0.8–2.7), but CIs for both doses included clinically unimportant ORs.[e44] In a 6-month Class II study,[e17] 505 patients were randomized to receive 1 of 4 doses of rotigotine (0.5, 1.0, 2.0, 3.0 mg) or placebo. There was a significant reduction in the IRLS with the 2.0-mg (-4.5, 95% CI -6.9 to -2.2) and 3.0-mg (-5.2, 95% CI -7.5 to -2.9) doses, though CIs included values not considered clinically important. Reductions were not statistically significant with the 0.5-mg (-2.2, 95% CI -4.5 to 0.2) dose or 1.0-mg (-2.3, 95% CI -4.6 to 0.0) dose, although the CIs for each of these doses included clinically important effects. Similarly, the 2 highest doses were superior to placebo on the CGI-S, with a mean treatment difference of -0.65 (95% CI -1.0 to -0.3) for 2.0 mg and -0.9 (95% CI -1.3 to -0.5) for 3.0 mg, but with CIs including values of uncertain clinical importance. In another 6-month Class II study,[e45] 458 patients were randomized to receive 1 of 3 doses of rotigotine (1.0, 2.0, 3.0 mg) (with the possibility of down titration for tolerability) or placebo. There were significant reductions on the IRLS compared with placebo at the 1.0-mg (-5.1, 95% CI -7.6 to -2.7), 2.0-mg (-7.5, 95% CI -10.0 to -5.1), and 3.0-mg (-8.2, 95% CI -10.6 to -5.7) doses. All doses were superior to placebo on the CGI-S, with a mean treatment difference of -0.76 (95% CI -1.13 to -0.38) for 1.0 mg, -1.07 (95% CI -1.44 to -0.69) for 2.0 mg, and -1.21 (95% CI -1.58 to -0.83) for 3.0 mg.

Efficacy for sleep, mood, and QoL

Rotigotine produced inconsistent benefit for subjective sleep measures compared with placebo in 2 Class I studies[e42,e43] and 3 Class II studies.[e17,e44,e45] One Class I study[e42] randomized 63 patients to receive 1 of 3 different doses of rotigotine or placebo. After 1 week, the 3 rotigotine doses (1.125, 2.25, 4.5 mg) were not superior to placebo (data not provided) for improving sleep satisfaction as measured by the RLS-6 questionnaire. Without CIs, it is unknown whether this study had sufficient precision to exclude a difference between groups. A Class I flexible-dose study[e43] found that after 4 weeks, rotigotine (mean dose 2.09 ± 0.78 mg) was not superior to placebo for improving sleep adequacy (-0.9, 95% CI -19.48 to 17.68), reducing sleep disturbance (-10.6, 95% CI -24.48 to 3.28), or increasing sleep quantity (0.7 hours, 95% CI -0.05 to 1.45) on

the MOS Sleep Scale, although CIs included potentially clinically important and unimportant effects. Two 6-month Class II RCTs[e17,e45] compared rotigotine with placebo on sleep disturbance, sleep adequacy, and sleep quantity measures from the MOS Sleep Scale. In 1 study enrolling 458 patients,[e45] rotigotine was superior to placebo for improvement in sleep adequacy with mean differences of 13.5 (95% CI 4.89–22.11) at 1 mg, 14.9 (95% CI 6.29–23.51) at 2 mg, and 12.7 (95% CI 3.94–21.46) at 3 mg. Change in sleep disturbance was not significantly different from placebo for rotigotine 1 mg (-5.0, 95% CI -11.81 to 1.81), but rotigotine was superior to placebo at doses of 2 mg (-11.7, 95% CI -18.35 to -5.05) and 3 mg (-11.8, 95% CI -18.76 to -4.84). Rotigotine was superior to placebo for sleep quantity at the 2-mg dose (0.65 hours, 95% CI 0.23–1.07) but not at the 1-mg (0 hours, 95% CI -0.69 to 0.69) or 3-mg (-0.1 hours, 95% CI -0.48 to 0.28) dose. In the Class II study that enrolled 505 patients,[e17] sleep disturbance was not improved (vs placebo) at the 0.5-mg (-3.9, 95% CI -10.62 to 2.82), 1-mg (-4.7, 95% CI -11.82 to 2.42), or 2-mg (-7.3, 95% CI -14.73 to 0.13) rotigotine doses, although CIs included potentially clinically important effects and the 3-mg dose was significantly better than placebo (-9.8, 95% CI -16.84 to -2.76). None of the rotigotine doses was superior to placebo for sleep adequacy (0.5 mg 2.1, 95% CI -5.62 to 9.82; 1 mg 4.2, 95% CI -3.79 to 12.2; 2 mg 7.1, 95% CI -0.86 to 15.06; 3 mg 5.9, 95% CI -2.19 to 14.0), although CIs again included differences that could potentially be clinically important. For sleep quantity, the 0.5-mg dose was superior to placebo (0.34 hours, 95% CI 0.02–0.66), but the 1-mg (0.28 hours, 95% CI -0.08 to 0.64), 2-mg (0.27 hours, 95% CI -0.07 to 0.61), and 3-mg (0.31 hours, 95% CI -0.03 to 0.65) doses were not, although CIs included potentially clinically important effects. In a Class II study in which the Pittsburgh Sleep Quality Index (PSQI) was used as the sleep outcome (score range 0–21, ≤5 suggests good sleep quality), there was no difference with either the 2-mg (-0.6, 95% CI -1.4 to 0.3) dose or the 3-mg (-0.7, 95% CI -1.6 to 0.2) dose vs placebo. However, a significantly greater number of patients had good sleep quality (PSQI < 5.5) at the end of the study in the rotigotine groups (2 mg 77.4%, 3 mg 74.4%) vs placebo (56.4%) (p = 0.002 and 0.01, respectively).[e44]

To address limitations in precision, the guideline panel performed fixed-effect meta-analyses separately for the studies with multiple doses[e17,e45] in order to obtain a single mean change score and standard error (SE) across doses. These results were then compared with results from placebo, and a random-effects meta-analysis was performed using the difference in mean change for the 3 studies employing the MOS Sleep Scale. The meta-analyses found that rotigotine has benefit compared with placebo for sleep adequacy (8.44, 95% CI 3.00–13.88, I^2 53.57%), sleep disturbance (-7.7, 95% CI -10.8 to -4.7, I^2 0%), and sleep quantity (0.4 hours, 95% CI 0.2–0.6, I^2 0%).

In a Class I flexible-dose study of 66 patients with RLS,[e43] the PLMI was significantly reduced with rotigotine (mean dose 2.09 ± 0.78 mg) compared with placebo (-30.35, 95% CI -44.11 to -16.58). Sleep latency (6.5 minutes, 95% CI -8.0 to 21.0), sleep efficiency (2.72%, 95% CI -3.2 to 8.63), and TST (11.7 minutes, 95% CI -17.4 to 40.8) were not superior with rotigotine compared with placebo, but CIs included potentially clinically important effects.

RLS-specific QoL was investigated in 1 Class I study[e43] and 2 Class II studies[e17,e45] with rotigotine doses of 0.5–3 mg. In a Class I flexible-dose study[e43] of 66 patients with RLS, the mean difference on the RLSQoL was not statistically significant (5.2, 95% CI -2.56 to 12.96), but the CI included a potentially clinically important effect. In a Class II study[e17] of 505 patients

with RLS, none of the 4 rotigotine doses was superior to placebo for improving RLS-specific QoL after 6 months of treatment (0.5 mg 0.4, 95% CI -2.83 to 3.63; 1 mg 1.2, 95% CI -1.83 to 4.23; 2 mg 2.8, 95% CI -0.53 to 6.12; 3 mg 2.0, 95% CI -1.12 to 5.12), but CIs included potentially important differences for at least some of the doses. Another 6-month Class II study of 458 patients[e45] demonstrated a statistically significant benefit of rotigotine vs placebo at all doses 1 mg (5.8, 95% CI 2.09–9.51), 2 mg (8.4, 95% CI 4.92–11.88), and 3 mg (10.2, 95% CI 6.66–13.74).

The guideline panel addressed limitations in precision by performing fixed-effect meta-analyses separately for the studies with multiple doses[e17,e45] in order to obtain a single mean change score and SE across doses for each study. These results were then compared with placebo results, and a random-effects meta-analysis using difference in mean change for all 3 studies was performed. The meta-analyses suggested that rotigotine has benefit vs placebo for QoL as measured by the RLSQoL (4.9, 95% CI 0.5–9.3, I^2 82.8%), but with high heterogeneity in the model and a CI which included scores of uncertain clinical importance.

Safety and tolerability

The most common acute AEs were mild skin reactions at the application site and nausea.[e45,e46] Although clinically relevant augmentation was reported in only 1.5% of patients treated with rotigotine in a Class II study lasting 6 months,[e17] a Class IV 5-year open-label extension study[e46] demonstrated augmentation in 23% of patients over a mean rotigotine exposure time of roughly 3 years at a mean rotigotine dose of 3.09 mg. Tolerance requiring an increase to the highest dose of 4 mg was observed in 22% of patients.

Conclusions

It is highly likely that the rotigotine patch improves RLS symptoms as measured by the IRLS (2 Class I and 3 Class II studies, up to 6 months in duration). It is likely that rotigotine improves PLMS (1 Class I study), but there is insufficient evidence to support or refute an effect on other objective sleep measures (1 Class I study not statistically significant but whose CIs include clinically important effects). It is likely that rotigotine improves the subjective sleep measures of sleep disturbance and sleep quantity (meta-analysis of 1 Class I study and 2 Class II studies, with 1 of the Class II studies achieving statistical significance on its own and the other Class I and Class II studies achieving statistical significance together). Rotigotine possibly improves sleep adequacy (meta-analysis of 1 Class I study and 2 Class II studies that requires all 3 studies to achieve significance). Rotigotine possibly improves RLS-specific QoL at 12 weeks (meta-analysis of 1 Class I study and 2 Class II studies using the RLSQoL that requires all 3 studies to achieve significance).

Cabergoline

Cabergoline is an ergot-related dopamine agonist with preferential binding at D2 receptors. Our search strategy identified 2 Class I studies.

Efficacy for RLS

Two Class I studies[e47,e48] investigated the efficacy of cabergoline for the treatment of primary moderate to severe RLS. In a double-blind, placebo-controlled, multicenter, 5-week dose-finding trial,[e47] 86 patients were randomized to receive cabergoline 0.5 mg, 1.0 mg, 2.0 mg, or placebo. Cabergoline was superior to placebo at all doses when considering mean differences on the IRLS (0.5 mg -9.8, 95% CI -15.3 to -4.3; 1.0 mg -10.2, 95% CI -15.8 to -4.6; 2.0 mg -16.5, 95% CI -21.4 to -11.6). In a randomized, double-blind, placebo-controlled 5-week trial of cabergoline 2.0 mg daily,[e48] 43 patients with RLS were randomized, and 40 completed the study (3 patients dropped out of the cabergoline group because of AEs). Cabergoline was superior to placebo on the IRLS (mean difference -15.8, 95% CI -22.7 to -8.9). Change in CGI-S was also better in the cabergoline group (mean difference -2.1, 95% CI -3.1 to -1.1).

Efficacy for sleep, mood, and QoL

Two Class I studies[e47,e48] investigated the efficacy of cabergoline for subjective sleep measures. On the RLS-6 sleep satisfaction subscale, cabergoline was superior to placebo at doses of 0.5 mg and 2.0 mg, but the results were not statistically significant at the 1.0-mg dose (mean differences: 0.5 mg 1.2, 95% CI 0.1–2.3; 1.0 mg 0.9, 95% CI -0.2 to 2.0; 2.0 mg 1.4, 95% CI 0.3–2.5). In the RCT using cabergoline 2.0 mg, cabergoline was superior to placebo for the RLS-6 sleep satisfaction subscale (mean difference -2.6, 95% CI -4.6 to -0.6). This study also included PSG showing improvements on the PLMI (mean difference -23.5, 95% CI -43.3 to -3.7), though the CI included values of uncertain clinical importance.[e48] Differences in sleep efficiency and TST were not statistically significant (mean differences were better with rotigotine but not significantly: sleep efficiency 2.9, 95% CI -5.1 to 10.9; TST 13.5 minutes, 95% CI -24.6 to 51.6). CIs included potentially clinically important and unimportant effects for both measures.

Only the fixed-dose study assessed QoL.[e48] Cabergoline was superior to placebo with regard to improvement on the RLSQoL (mean difference 12.3, 95% CI 2.3–22.3). No cabergoline study assessed changes in mood.

Safety and tolerability

In the dose-finding study, the most common AEs were nausea and constipation (15% and 10% greater than placebo, respectively). No serious AEs (SAEs) were noted during the 5-week dose-finding study, but 1 patient experienced psychosis in the long-term open-label follow-up. In the study of cabergoline 2.0 mg, common AEs included nausea, dizziness, and fatigue. There were no SAEs. Since 2011, FDA safety labeling for cabergoline has included a warning about fibrotic complications/cardiac valvulopathy, which has been described in the context of cabergoline use. However, prescribing information states that this SAE has generally occurred in the context of doses > 2 mg/d, as are used in Parkinson disease, but not at the lower doses used for treatment of hyperprolactinemia or RLS (cabergoline prescribing information, accessed 3/20/2015). One Class II comparative study (discussed in the levodopa section) found a 6% rate of augmentation and 14% loss of efficacy with cabergoline over 30 weeks of treatment.[e49]

Comparative trials: Levodopa vs cabergoline

See efficacy data in levodopa section.[e49] There were more dropouts due to loss of efficacy or augmentation in the levodopa group than in the cabergoline group, but nausea, constipation, and fatigue/somnolence were more common with cabergoline.

Conclusions

It is highly likely that cabergoline decreases IRLS scores at 5 weeks (2 Class I studies). It is highly likely that cabergoline improves some subjective sleep measures (2 Class I studies). It is likely that cabergoline improves the PLMI (1 Class I study), but there is insufficient evidence to support or refute an effect of cabergoline on other objective sleep outcomes (1 Class I study that did not reach statistical significance and whose CIs included potentially important and unimportant effects). It is likely that cabergoline improves RLS-specific QoL at 5 weeks (1 Class I study). Cabergoline is possibly more effective than levodopa for treating patients with RLS who do not have a placebo response (1 Class II study).

Levodopa

Levodopa (combined with a dopa decarboxylase inhibitor [benserazide or carbidopa] to prevent peripheral effects) is a dopaminergic agent with preferential binding to dopamine D1 and D2 receptors. Our literature search identified 5 Class III studies assessing the efficacy of levodopa in RLS for more than a single night.

Efficacy for RLS

Four Class III studies examined the efficacy of levodopa vs placebo for primary RLS, 3 using regular-release levodopa and 1 using sustained-release levodopa. In a crossover trial of 4 weeks per treatment,[e50] 35 patients (4 of whom had RLS secondary to ESRD) were administered flexibly dosed levodopa/benserazide (mean 159 mg/40 mg), which produced a higher score on the investigator-developed global severity scale (rated 1–7, with 7 being most improved) than placebo (5.2 [1.2] vs 3.6 [1.2], mean difference 1.6, 95% CI 0.5–2.7). Treatment with levodopa also resulted in less patient-reported burden caused by symptoms (levodopa 18.8 ± 6.7, placebo 21.8 ± 5.0, mean difference -3.0, 95% CI -0.9 to -0.2, rated on a 50-point scale). In a similar 4-week crossover trial,[e51] 17 patients with idiopathic RLS had slightly less severe RLS as rated by the clinician (where 8 = severe) after flexibly dosed levodopa/benserazide (mean 146 mg levodopa) than after placebo (6.2 vs 6.4, mean difference -0.2, estimated 95% CI -0.6 to 0.2), but this was not statistically significant. For the patient-reported measure of RLS severity overnight (on a 0–10 scale, where 10 is most severe), patients had a better score after levodopa treatment than after placebo (3.6 [2.5] vs 5.5 [3.1], mean difference -1.9, estimated 95% CI -3.5 to -0.3). In a crossover trial of 6 patients with primary RLS receiving 2 weeks of placebo and 2 weeks of levodopa 100 mg/benserazide 25 mg administered twice nightly (1 hour before and 3 hours after bedtime), patients reported less "pain or paresthesias in the legs" (mean difference -1.0, 95% CI -2.0 to 0) and fewer "arm and leg movements at bedtime" (mean difference -0.9, 95% CI -1.9 to 0.1) after levodopa, as assessed on a scale from 1–4 (1 = not present, 4 = considerable), but these findings were not statistically significant.[e52] Sample size limited statistical precision in many of these assessments, resulting in CIs which included potentially clinically important and unimportant effects. In a 3-arm crossover trial comparing sustained-release levodopa (200 mg

with 50 mg benserazide), slow-release valproate (600 mg), and placebo for 3 weeks each in 20 patients with RLS,[e53] the difference in RLS intensity score (a 0–10 visual analog scale) was not statistically different between sustained-release levodopa and placebo (4.4 ± 2.5 vs 5.5 ± 1.7, mean difference -1.1, estimated 95% CI -2.4 to 0.2, which includes potentially clinically important and unimportant effects).

Because many of these studies were limited by insufficient statistical precision, the guideline panel performed a random-effects meta-analysis of the patient-reported outcome measures relating to symptom severity (described previously) using standardized mean differences. When all 4 studies were combined, levodopa treatment was associated with a statistically significant improvement vs placebo (-0.5, 95% CI -0.7 to -0.3, I^2 0%). When only the 2 studies failing to achieve statistical significance on their own were considered with regard to patient-reported measures,[e52,e53] levodopa was also superior (-0.4, 95% CI -0.8 to -0.04, I^2 0%), but with a CI including values of uncertain clinical importance.

Efficacy for sleep, mood, and QoL

In 1 of the crossover studies,[e50] in the 32 patients finishing the study, levodopa/benserazide resulted in better self-reported sleep quality on a scale of 1–5 than placebo (3.0 [0.7] vs 2.3 [0.7], mean difference 0.7, estimated 95% CI 0.3–1.1). Similarly, sleep latency and TST by sleep diary were better after treatment with levodopa than after placebo (sleep latency mean difference -25.2 minutes, estimated 95% CI -37.9 to -12.5; TST 0.9 hours, estimated 95% CI 0.4–1.4). In the crossover trial enrolling 17 patients with idiopathic RLS,[e51] self-reported sleep quality (as assessed on a 0–10 scale, with 10 being good) was higher after levodopa treatment (4.8 ± 1.9) than after placebo (3.1 ± 2.4) (mean difference 1.7, estimated 95% CI 0.2–3.2). Frequency of awakenings was not statistically significant when levodopa and placebo were compared (mean difference -0.5, estimated 95% CI -1.2 to 0.2), but the CI included a potentially clinically important effect. In the 6-patient crossover study,[e52] patients described shorter sleep latency with levodopa than with placebo (mean difference -13.0 minutes, estimated 95% CI -24.7 to -1.3) but no difference in TST (mean difference 49 minutes, 95% CI -14.4 to 112.4), although the CI included potentially clinically important effects. Finally, in an early double-blind crossover study enrolling 16 patients with RLS and insomnia, 13 patients were treated with levodopa 200 mg plus benserazide 50 mg during a 2-week treatment period, and results were compared with placebo (3 other patients were treated with other therapies).[e54] When results were combined for moderate and severe patients in a fixed-effect meta-analysis, there was a reduction both in the number of times patients woke (-2.1, 95% CI -2.2 to -2.0) and in the hours they were awake overnight (-2.1 hours, 95% CI -2.5 to -1.8) during levodopa treatment vs placebo.

In 1 of the crossover trials, flexibly dosed levodopa/benserazide resulted in a lower PLMI as measured by actigraphy (mean difference -26.8, estimated 95% CI -40.3 to -13.3).[e50] In another crossover trial, the difference in PLMI between levodopa and placebo treatment was not statistically significant for 17 patients with idiopathic RLS[e51] (mean difference -12.0, 95% CI -28.3 to 4.2), though the CI included a potentially clinically important difference. The 6-patient crossover study[e52] demonstrated a lower PLMI with levodopa (dosed 1 hour before and 3 hours after bedtime) (estimated mean difference -26.6, 95% CI -41.0 to -12.2). Similarly, there was a reduction in polysomnographically recorded sleep latency (estimated mean difference -5.5

minutes, 95% CI -10.7 to -0.3). Differences in sleep efficiency, nocturnal awakenings, and TST were not significant between groups, but interpretation is limited by the small sample size and limited precision. In the 3-arm crossover trial comparing sustained-release levodopa, slow-release valproate (600 mg), and placebo for 3 weeks each,[e53] sustained-release levodopa resulted in a lower PLMI than placebo (mean difference -23.3, estimated 95% CI -39.6 to -7.0). There was no benefit of sustained-release levodopa vs placebo for other PSG parameters, but sample size limited statistical precision. A random-effects meta-analysis of the PLMI using the 4 studies resulted in a mean difference of -22.9 (95% CI -30.3 to -15.4, I^2 0%) in favor of levodopa.

QoL was evaluated in 2 of the Class III studies.[e50,e51] In the first,[e50] levodopa/benserazide resulted in higher life satisfaction (levodopa 26.6 ± 5.5, placebo 23.8 ± 4.7, $p = 0.0039$) as rated on a 50-point scale. In the second,[e51] differences between levodopa and placebo were not statistically significant for life satisfaction (levodopa 27.5 ± 6.7, placebo 24.1 ± 4.4, estimated difference in means 3.4, 95% CI -0.4 to 7.2) and "negative feelings and complaints" (with 50 being high) (levodopa 17.8 ± 6.9, placebo 22.3 ± 8.7, estimated difference in means -4.5, 95% CI -15.6 to 6.6), but the CIs included potentially clinically important effects of levodopa. Mood was not studied in levodopa trials.

Comparative trials: Regular-release levodopa vs regular-release levodopa plus sustained-release levodopa

A Class III crossover study[e55] with 4-week treatment periods randomized patients with RLS and a response to regular-release levodopa but with recurrence of RLS symptoms in the second half of the night (as assessed by awakenings and the PLMI by PSG at screening) to receive regular-release levodopa (100–200 mg) plus either placebo or sustained-release levodopa (100 mg plus benserazide 25 mg). Thirty-seven patients were randomized, and 30 completed the study and were analyzed. Although there was no difference in clinician-rated RLS severity (on a scale from 2–8, with 8 being severe) between the addition of sustained-release levodopa (6.17 ± 0.53) and placebo (6.07 ± 0.52) ($p = 0.403$), the addition of sustained-release levodopa was significantly better than placebo for clinician-rated improvement in RLS symptoms (4.34 ± 1.01 vs 6.37 ± 0.85, $p = 0.0036$). Sleep measures were also improved with the combination of immediate- and sustained-release levodopa, with a reduction in nighttime wake time ($p < 0.005$) and the PLMI (22.4 ± 28.9 vs 42.3 ± 38.9, $p < 0.0001$). Life satisfaction was not different between groups, but numbers were not provided.

Levodopa vs cabergoline

In a Class II RCT lasting 30 weeks,[e49] 361 patients with RLS who passed a 1-week placebo run-in phase were randomized to receive cabergoline (2 mg) or levodopa (200 mg) with flexible dosing. Patients receiving cabergoline had a greater reduction in IRLS score at 6–8 weeks (depending on need for dose adjustment) than those receiving levodopa (difference in baseline-adjusted least square mean -6.6, 95% CI -8.6 to -4.7). At 30 weeks, cabergoline was also superior (-7.0, 95% CI -9.1 to -4.9).

Levodopa vs pergolide

A Class III crossover study of 11 patients compared levodopa/carbidopa (250 mg) to pergolide (0.125 mg) 1–3 hours before sleep.[e56] Each medication was administered over a 14-day period. Only 1 patient reported complete resolution of nighttime RLS symptoms while taking levodopa, whereas 9 patients reported complete resolution and 2 reported partial resolution during the pergolide arm. Details regarding this assessment were not provided. PLMS "cluster time" (in minutes) was lower in the pergolide arm (35.37 ± 35.81) than in the levodopa arm (90.6 ± 72.3) ($p < 0.01$). Patients in the pergolide arm also had a significant increase in TST and time in bed ($p < 0.05$) vs levodopa. Of note, pergolide was withdrawn from the US market in 2007 because of its link to valvular heart disease; thus, studies looking at pergolide alone are not included in this practice guideline.

Sustained-release levodopa vs valproic acid

In the Class III 3-arm crossover trial comparing sustained-release levodopa, slow-release valproate (600 mg), and placebo for 3 weeks,[e53] there was no difference in the mean (± SD) RLS intensity score (using a 0–10 visual analog scale) between valproic acid and sustained-release levodopa (2.5 ± 3.8 vs 4.4 ± 2.5, estimated mean difference -0.6, 95% CI -2.2 to 1.0), although the CI included a potentially clinically important difference. The PLMI was significantly lower after the sustained-release levodopa arm (19.9 ± 23.2) than after valproate (38.0 ± 32.3); the estimated difference was large, at 18.1 (95% CI 0.7–35.5), but the CI includes values of uncertain clinical importance. Other parameters such as TST did not differ between groups, but assessment was limited by statistical precision.

Safety and tolerability

The most common AE in the 3- to 6-week studies was nausea, which was generally mild. In the 30-week Class II study, 45.5% of patients receiving levodopa withdrew prematurely (vs 41.6% in the cabergoline group); various numbers were provided for how many withdrew because of AEs. Augmentation was the most common AE in this study (present in 17.5% of the patients treated with levodopa vs 6.2% of those treated with cabergoline; OR for augmentation with levodopa vs cabergoline 3.2, 95% CI 1.6–6.6).[e49] The augmentation rate was 60% to 67% in two 6- to 12-month Class IV studies of levodopa (50–500 mg)[e57,e58] and in one 12-month study of levodopa controlled-release (100–300 mg).[e59] Loss of efficacy was present in 25% of those on levodopa at 30 weeks.[e49]

Conclusions

Levodopa (100–200 mg) possibly improves patient-reported RLS symptom severity (4 Class III studies, 2 of which show a benefit alone and 2 of which show a benefit when combined in a meta-analysis to increase statistical precision). Levodopa possibly improves subjective sleep measures (4 Class III studies with improvements in at least some subjective sleep measures) and the PLMI (3 Class III studies with sufficient precision and 1 Class III study with insufficient precision; meta-analysis showed significant effect). There is insufficient evidence to support or refute the effect of levodopa on QoL in RLS (2 Class III studies, only 1 with sufficient precision). There is insufficient evidence to support or refute the addition of sustained-release levodopa to regular-release levodopa in individuals with a response to regular-release levodopa

but recurrence of symptoms in the second half of the night (1 Class III study). Cabergoline is possibly more effective than levodopa in treating patients with RLS who do not have a placebo response (1 Class II study). There is insufficient evidence to support or refute the efficacy of levodopa compared with pergolide or valproic acid (1 Class III study each).

α2δ ligands

Gabapentin

Gabapentin is a γ-aminobutyric acid analog that modulates α2δ calcium channels and is used to treat epilepsy and neuropathic pain.

Efficacy for RLS

One Class III study randomized 24 patients with primary moderate to severe RLS to receive flexibly dosed gabapentin (600–2,400 mg/d, with a mean of 1,855 mg/d in 2 divided doses) or placebo in a randomized, double-blind, crossover study with each treatment period lasting 6 weeks.[e60] Patients had a lower IRLS mean total score at 6 weeks during the gabapentin treatment arm than during the placebo arm (mean difference -8.4, 95% CI -12.1 to -4.7).

Efficacy for sleep, mood, and QoL

The same Class III study[e60] assessed sleep using the PSQI and PSG. At 6 weeks, gabapentin was superior to placebo as measured by the PSQI (mean difference -3.3, 95% CI -4.5 to -2.1). The PLMI was also lower at the end of gabapentin treatment vs placebo (mean difference -9.7, 95% CI -19.1 to -0.3), though the CI included a difference of uncertain clinical importance. Compared with placebo, gabapentin resulted in increased TST ($p = 0.01$), sleep efficiency ($p < 0.0001$), and slow-wave sleep ($p < 0.05$) (additional details not provided).

Safety and tolerability

In this Class III study, the most common AEs were mild to moderate malaise (26.1%) and somnolence (8.7%).[e60]

Conclusion

There are insufficient data to support or refute a benefit of immediate-release gabapentin on RLS severity or sleep outcomes (1 Class III study).

Gabapentin enacarbil

Gabapentin enacarbil is a slow-release prodrug of gabapentin that modulates α2δ calcium channels and is absorbed via high-capacity nutrient transporters.[e61]

Efficacy for RLS

Four Class I studies,[e62–e65] 2 Class II studies,[e61,e66] and 2 Class III studies[e67,e68] investigated gabapentin enacarbil for treating moderate to severe primary RLS in time periods ranging from 2–24 weeks. Because there are several Class I studies available for analysis of efficacy, studies with lesser ratings are not discussed. Two Class I studies examined the effect of gabapentin enacarbil at 14 days. In a double-blind, placebo-controlled, crossover study of gabapentin enacarbil 1,800 mg/d vs placebo with 14-day treatment arms in 38 patients with RLS, gabapentin enacarbil was superior to placebo treatment (mean difference in change from baseline IRLS score at day 14: -10.2, 95% CI -13.3 to -7.1).[e62] Both investigator (CGI-I) and patient (Patient Global Impression of Improvement [PGI-I]) ratings of improvement were better at day 14 in patients treated with gabapentin enacarbil (responder rates): 79.5% vs 14.7% (adjusted $p < 0.006$) for investigators and 85.3% vs 14.7% (adjusted $p < 0.006$) for patients. A separate RCT randomized 95 patients to receive gabapentin enacarbil 1,200 mg/d, gabapentin enacarbil 600 mg/d, or placebo. Gabapentin enacarbil 1,200 mg/d was superior to placebo (adjustment mean treatment difference -7.2, 95% CI -11.1 to -3.4), but gabapentin enacarbil 600 mg/d was not (-0.2, 95% CI -3.7 to 3.3, though the CI included a clinically important difference).[e63] Both investigators and patients reported a higher response rate with gabapentin enacarbil 1,200 mg/d than with placebo (CGI-I 81.3% vs 48.5%, adjusted $p < 0.001$; PGI-I 81.3% vs 45.5%, adjusted $p < 0.001$). Response rates in the 600-mg/d group were described as similar to those in the placebo group.

Two Class I studies examined the effects of gabapentin enacarbil at 12 weeks. In an RCT randomizing patients with moderate to severe RLS to receive either gabapentin enacarbil 1,200 mg/d (n = 114) or placebo (n = 108), gabapentin enacarbil was superior to placebo on the IRLS (adjusted mean treatment difference -4.0, 95% CI -6.2 to -1.9), although the CI included values not considered clinical important. Gabapentin enacarbil was also superior to placebo on the CGI-I at 12 weeks (adjusted OR 5.1, 95% CI 2.8–9.2).[e64] In an RCT randomizing 325 patients to receive gabapentin enacarbil 1,200 mg/d, 600 mg/d, or placebo, gabapentin enacarbil resulted in improved mean treatment difference on the IRLS at 12 weeks vs placebo (adjusted mean treatment difference: 1,200 mg/d -3.5, 95% CI -5.6 to -1.3; 600 mg/d -4.3, 95% CI -6.4 to -2.3), but CIs included some values not considered clinically important.[e65] More patients treated with gabapentin enacarbil were rated as responders on the CGI-I (1,200 mg/d adjusted OR 4.3, 95% CI 2.34–7.86; 600 mg/d adjusted OR 3.3, 95% CI 1.84–5.99).

Efficacy for sleep, mood, and QoL

All identified studies reported subjective sleep outcomes. In the crossover study enrolling 38 patients, sleep quality (as assessed by the Post Sleep Questionnaire [PSQ]) improved at day 14 in the gabapentin enacarbil group (adjusted $p < 0.05$ *at day 14* [i.e., not clearly reflecting change score] for overall sleep quality, number of nights with RLS symptoms, number of awakenings during the night because of RLS symptoms, and number of hours awake per night because of RLS symptoms; adjusted $p = 0.43$ for ability to function).[e62] In the 14-day parallel-group RCT, sleep quality, as assessed by the PSQ, improved at day 14 with the 1,200-mg/d dose (adjusted $p < 0.05$ at day 14 [i.e., not calculated for change score] for overall sleep quality, number of nights with RLS symptoms, number of awakenings during the night because of RLS symptoms, and number of hours awake per night because of RLS symptoms; $p > 0.999$ for ability to function). Responses in the 600-mg/d group were similar to those in the placebo group.[e63]

In the 12-week Class I studies, various subjective sleep measures also generally improved in response to gabapentin enacarbil treatment. The RCT randomizing patients with moderate to severe RLS to receive either gabapentin enacarbil 1,200 mg/d (n = 114) or placebo (n =108) used both the MOS Sleep Scale and the PSQ.[e64] All MOS Sleep Scale subscales improved with gabapentin enacarbil at week 12 compared with placebo: daytime somnolence (mean difference -7.8, 95% CI -13.0 to -2.6), sleep quantity (0.4 hours, 95% CI 0.03–0.77), sleep adequacy (15.3, 95% CI 7.1–23.5), and sleep disturbance (-13.6, 95% CI -20.1 to -7.1), though the CI for sleep quantity in particular included values of uncertain clinical importance. All PSQ sleep outcomes also significantly improved with gabapentin enacarbil. In the RCT randomizing patients to receive gabapentin enacarbil 1,200 mg/d, 600 mg/d, or placebo, sleep outcomes were measured using the MOS Sleep Scale and the Pittsburgh Sleep Diary. Gabapentin enacarbil 1,200 mg significantly improved all MOS Sleep Scale subscales vs placebo at week 12: daytime somnolence (-6.4, 95% CI -11.8 to -1.0), sleep quantity (0.5 hours, 95% CI 0.1–0.9), sleep adequacy (14.1, 95% CI 6.6–21.6), and sleep disturbance (-13.7, 95% CI -20.1 to -7.4), though some CIs included values of uncertain clinical importance. MOS Sleep Scale results for the 600-mg dose were significant for sleep adequacy (15.5, 95% CI 8.0–23.0) and sleep disturbance (-12.5, 95% CI -18.5 to -6.5) but not for sleep quantity (0.3 hours, 95% CI -0.03 to 0.6) or daytime somnolence (-0.1, 95% CI -5.62 to 5.42). PSQ and Pittsburgh Sleep Diary items also significantly improved with both gabapentin enacarbil doses at 12 weeks.[e65]

PSG results were reported in 2 studies, 1 Class I study and 1 Class III study. In a 12-week Class I crossover trial (discussed earlier), gabapentin enacarbil treatment significantly improved TST (mean difference 25.2 minutes, 95% CI 2.2–48.2), sleep efficiency (5.2%, 95% CI 0.5–9.9), wake time after persistent sleep onset (-28.2 minutes, 95% CI -44.8 to -11.6), wake time during sleep (-25.6 minutes, 95% CI -41.0 to -10.2), and number of awakenings (-2.5, 95% CI -4.0 to -1.0), though some CIs included values of uncertain clinical importance. The PLMI also improved during the gabapentin enacarbil phase, but this did not reach statistical significance, with the CI including potentially clinically important and unimportant effects (mean difference -9.4, estimated 95% CI -21.7 to 2.9).[e62] In a 4-week Class III crossover study of gabapentin enacarbil 1,200 mg/d vs placebo,[e67] gabapentin enacarbil significantly improved the PLMI (mean difference -8.1, 95% CI -12.4 to -3.7), wake time during sleep (adjusted mean difference -26.0, 95% CI -35.6 to -16.4), WASO (mean difference -24.5, 95% CI -12.4 to -3.7), and number of awakenings (adjusted mean difference -2.49, 95% CI -3.33 to -1.65) compared with placebo. One Class I study assessed RLS-related QoL. In a 12-week RCT randomizing patients to receive gabapentin enacarbil 1,200 mg/d or placebo, gabapentin enacarbil treatment resulted in a significant improvement in RLSQoL vs placebo (7.3, 95% CI 2.41–12.19).[e64]

Mood was assessed in 1 Class I study and 1 Class III study. In the Class I RCT,[e63] patients completed a mood assessment questionnaire on day 14, rating overall change in mood since the start of the study using a 7-point scale (1 = very much improved, 7 = very much worse). Patients treated with gabapentin enacarbil 1,200 mg/d rated themselves as "much improved" or "very much improved" significantly more often than those taking placebo (53.1% vs 21.2%, adjusted p = 0.045). The difference was not seen in patients receiving 600 mg/d vs placebo (27.6% vs 21.2%, p value not provided). In a 12-week Class III study randomizing patients to receive gabapentin enacarbil 600 mg (n = 48), gabapentin enacarbil 1,200 mg (n = 45), gabapentin enacarbil 1,800 mg (n = 38), gabapentin enacarbil 2,400 mg (n = 45), or placebo (n = 41), the

Mood Assessment was used to measure global change in overall mood. More patients treated with gabapentin enacarbil reported that their mood was ‘‘very much improved’’ or ‘‘much improved’’ in all dose groups (600 mg 30.3%; 1,200 mg 48.1%; 1,800 mg 45.2%; 2,400 mg 35.5%) compared with placebo (21.4%), but measures of statistical significance were not provided.[e68]

Safety and tolerability

The most commonly reported AEs were mild to moderate somnolence and dizziness, which were usually dose related.[e62,e64,e67,e68] Only 2 studies of gabapentin enacarbil specifically mentioned monitoring for augmentation. No cases of augmentation occurred in either 12-week study.[e66,e68]

Conclusions

It is highly likely that gabapentin enacarbil decreases IRLS scores (4 Class I studies with different study durations). It is highly likely that gabapentin enacarbil improves subjective sleep measures (4 Class I studies) and likely that it improves at least some objective sleep measures other than the PLMI (1 Class I study and 1 Class III study). Because results of the Class I study were not statistically significant and CIs included both potentially clinically important and unimportant effects, there is insufficient evidence to support or refute the effect of gabapentin enacarbil on the PLMI. It is likely that gabapentin enacarbil improves RLS-specific QoL (1 Class I study) and mood (1 Class I study and 1 Class III study with limited statistics) at doses of 1,200 mg/d.

Pregabalin

Pregabalin, a drug that modulates α2δ calcium channels, is used as an adjunct medication to treat partial seizures with or without secondary generalization in adults and to treat neuropathic pain.

Efficacy for RLS

One Class I study and 3 Class II studies investigated pregabalin for the treatment of moderate to severe primary RLS as measured by the IRLS. A randomized, double-blind, dose-ranging Class I study assigned 137 patients with moderate to severe RLS to receive placebo or pregabalin doses of 50, 100, 150, 300, or 450 mg/d for 6 weeks after a placebo run-in. There was a difference in mean change on the IRLS vs placebo for the 150-mg/d (-8.3, 95% CI -13.4 to -3.2), 300-mg/d (-5.2, 95% CI -10.0 to -0.4), and 450-mg/d (-8.6, 95% CI -13.6 to -3.6) doses, though the CI for the 300-mg/d dose included changes not considered clinically relevant. There was no significant difference between the 50-mg/d (-4.1, 95% CI -9.1 to 0.9) dose or 100-mg/d (-4.1, 95% CI -8.9 to 0.7) dose vs placebo, but CIs include both clinically important and unimportant effects.[e69] In a Class II double-blind placebo-controlled RCT of 58 placebo-unresponsive patients with RLS, pregabalin (mean dose 322.5 mg/d) was superior to placebo on the IRLS (mean difference -4.92, 95% CI -9.1 to -0.7) at 12 weeks, but the CI included clinically unimportant effects.[e70] In a Class II study comparing pregabalin and pramipexole, 731 participants were randomized to pregabalin 300 mg/d, pramipexole 0.25 or 0.5 mg/d, or placebo for 12 weeks. Pregabalin was superior to placebo on the IRLS (mean difference -4.5, 95% CI -5.9 to -3.2). The CGI-I responder rate was

also significantly higher for pregabalin than for placebo (OR for treatment response 2.8, 95% CI 1.8–4.4).[e35] Another Class II study randomized 85 patients to a three-way crossover with pregabalin 300 mg, pramipexole 0.5 mg, and placebo arms. After 4 weeks of each treatment, IRLS reduction was greater with pregabalin than with placebo (-6.1, 95% CI -8.1 to -4.1). A higher proportion of participants were CGI-I treatment responders with pregabalin (61.2%) compared with placebo (33.3%).[e36]

Efficacy for sleep, mood, and QoL

In the dose-finding Class I study with placebo run-in described earlier, improvements on the MOS Sleep Scale with pregabalin vs placebo were significant only for sleep disturbance with the 450-mg/d dose, sleep quantity with the 150-mg/d and 300-mg/d doses, sleep adequacy with the 50-mg/d dose, and somnolence with the 50-mg/d dose as shown by the study-reported mixed-model analyses. Raw mean differences in mean change scores vs placebo were as follows: sleep disturbance (50 mg -9.9, 95% CI -24.2 to 4.35; 100 mg -6.0, 95% CI -19.8 to 7.8; 150 mg -14.1, 95% CI -28.8 to 0.57; 300 mg -12.1, 95% CI -26.1 to 1.9; 450 mg -20.9, 95% CI -35.0 to -6.8), sleep quantity (50 mg 0.3 hours, 95% CI -0.3 to 0.9; 100 mg 0.1 hours, 95% CI -0.47 to 0.67; 150 mg 0.7 hours, 95% CI 0.13–1.27; 300 mg 0.1 hours, 95% CI -0.5 to 0.7; 450 mg 0.6 hours, 95% CI 0.48–0.72), sleep adequacy (50 mg 17.8, 95% CI 1.5–34.1; 100 mg 11.2, 95% CI -4.3 to 26.7; 150 mg 10.0, 95% CI -6.7 to 26.7; 300 mg 2.4, 95% CI -13.3 to 18.1; 450 mg 14.3, 95% CI -1.8 to 30.4), and somnolence (50 mg -14.6, 95% CI -26.7 to -2.5; 100 mg -3.1, 95% CI -14.8 to 8.6; 150 mg -10.0, 95% CI -22.4 to 2.4; 300 mg -1.7, 95% CI -13.4 to 10.0; 450 mg -2.2, 95% CI -14.2 to 9.8).[e69] In the flexible-dose Class II study, pregabalin was better than placebo for sleep satisfaction ($p < 0.001$) from the RLS-6.[e70] Pregabalin also improved MOS Sleep Scale scores for sleep disturbance ($p < 0.001$), sleep adequacy ($p = 0.001$), and sleep quantity ($p < 0.001$) (subscale scores not provided). In the trial randomizing patients to receive pregabalin, pramipexole, or placebo, patients receiving pregabalin vs placebo had less time awake at night after persistent sleep (-17.2 minutes, 95% CI -25.8 to -8.7), better sleep quality (10.6, 95% CI 7.1–14.2), fewer awakenings (-0.6, 95% CI -0.8 to -0.4), and greater TST (0.4 hours, 95% CI 0.3–0.6), but the time to sleep onset was not significantly different (-5.5 minutes, 95% CI -11.4 to 0.5).[e35] In the Class II 4-week crossover study, patients reported having significantly less WASO (-25.3 minutes, 95% CI -35.8 to -14.8), fewer awakenings per night (-0.8, 95% CI -1.2 to -0.5), greater TST (30.8 minutes, 95% 16.1–45.5), and a shorter time to fall asleep (-7.6 minutes, 95% CI -14.0 to -1.1) on the Subjective Sleep Questionnaire while taking pregabalin, though some CIs included values of uncertain clinical importance. In addition, pregabalin improved MOS Sleep Scale scores for sleep disturbance (-14.6, 95% CI -20.9 to -8.2) and sleep adequacy (14.2, 95% CI 6.3–22.1) but not sleep quantity (0.5, 95% CI -0.2 to 1.1), though the CI included a potentially clinically important difference.[e36]

With regard to objective measures, in the flexible-dose Class I trial with placebo run-in, at-home actigraphy measures suggested that TST was improved with pregabalin doses of 150–450 mg/d vs placebo as indicated by the study-reported mixed-model analysis (raw mean differences: 50 mg 35.9, 95% CI 27.1–44.7; 100 mg 23.8, 95% CI 15.0–32.6; 150 mg 70.0, 95% CI 60.9–79.1; 300 mg 66.0, 95% CI 57.0–75.0; 450 mg 59.2, 95% CI 50.7–67.7). Sleep efficiency was better than placebo in only the 300-mg/d and 450-mg/d groups as shown by the study-reported mixed-model analysis (raw mean differences: 50 mg 3.7, 95% CI 2.4–5.0; 100 mg 5.4, 95% CI 4.0–6.8;

150 mg 6.5, 95% CI 5.1–7.9; 300 mg 6.8, 95% CI 5.4–8.2; 450 mg 6.6, 95% CI 5.3–7.9).[e69] On PSG in 1 Class II study, pregabalin significantly improved WASO (mean difference -18.74 minutes, 95% CI -33.0 to -4.5), sleep efficiency (mean difference 5.2%, 95% CI 1.6–8.9), and the PLMI (-27.2, 95% CI -43.4 to -11.0), but not sleep latency (mean difference -14.3 minutes, 95% CI -33.9 to 5.2) or TST (mean difference 32.8 minutes, 95% CI -25.5 to 91.1) (CIs include both potentially clinically important and unimportant effects).[e70] In the crossover Class II study using PSG, pregabalin significantly improved WASO (mean difference -27.1 minutes, 95% CI -35.8 to -18.4), sleep efficiency (mean difference 6.8%, 95% CI 4.6–9.0), TST (mean difference 32.7, 95% CI 22.0–43.4), and PLMI (mean difference, -14.5, 95% CI -20.8 to -8.2), but not sleep latency (mean difference -7.7, 95% CI -17.1 to 1.6) compared with placebo.[e36]

In the dose-finding Class I study with placebo run-in, there were no significant differences between pregabalin and placebo on the RLSQoL (data not shown).[e69] In the crossover Class II study, pregabalin produced significantly greater improvement on the RLSQoL than placebo (5.3, 95% CI 2.0–8.6).[e36] In the flexible-dose Class II study also with placebo run-in, no significant differences on the State Trait Anxiety Inventory were identified between the treatment and placebo groups (adjusted absolute difference -3.82, 95% CI -8.4 to 0.7),[e70] although the CI included both potentially clinically important and unimportant effects.

Safety and tolerability

The most common AEs in the pregabalin group were unsteadiness and daytime sleepiness.[e70]

Comparative trials: Pregabalin vs pramipexole

Efficacy for RLS

Two Class II studies compare use of pregabalin and pramipexole. In the 12-week Class II study with placebo run-in mentioned previously,[e35] a noninferiority assessment demonstrated a greater reduction in the IRLS at 12 weeks with pregabalin treatment than with either pramipexole dose (0.25 mg least squares mean difference -4.0, upper limit of the 97.5% CI -2.8; 0.5 mg least squares mean difference -1.7, upper limit of the 97.5% CI -0.5), though the upper bounds of the CIs for both included differences not considered clinically meaningful. In a post hoc analysis, CGI-I responder rate was also better with pregabalin at 12 weeks vs pramipexole 0.25 mg (OR for response 2.4, 95% CI 1.5–3.7) but not pramipexole 0.5 mg (OR for response 1.6, 95% CI 1.0–2.5), though the CI included a potentially clinically important difference. In the Class II 3-arm crossover study randomizing 85 patients to pregabalin 300 mg, pramipexole 0.5 mg, and placebo arms, IRLS reduction was greater with pregabalin than pramipexole (-3.1; 95% CI -5.1 to -1.1) after 4 weeks in each arm, though the CI included a difference that is not clinically meaningful. A higher proportion of participants were CGI-I treatment responders with pregabalin (61.2%) than with pramipexole (50.0%), though statistics were not performed.[e36] Whereas both studies showed a greater improvement in IRLS during pregabalin treatment vs pramipexole treatment, CIs in both studies included changes not considered clinically meaningful. A random-effects meta-analysis was performed by calculating effect sizes and variances for each study using a 2-tailed approach, as either medication could be superior. After calculating effect sizes and CIs for pregabalin and the 0.5-mg pramipexole doses, the random-effects meta-analysis

demonstrated a reduction in IRLS with pregabalin vs pramipexole 0.5 mg that was statistically significant but for which the point estimate was not clinically important (mean difference -2.0, 95% CI -3.6 to -0.34, I^2 49%). The CI included the possibility of a clinically important improvement with pregabalin vs pramipexole.

Efficacy for sleep, mood, and QoL

Both Class II studies reported subjective sleep outcomes. In the 12-week Class II study with placebo run-in, outcomes on subjective sleep questionnaires were superior for pregabalin vs pramipexole 0.5 mg for sleep quality (mean difference 7.30, 95% CI 3.77–10.83), number of awakenings (-0.6, 95% CI -0.8 to -0.4), TST (0.2 hours, 95% CI 0.02–0.38), and time to sleep onset (-18.6 min, 95% CI -24.5 to -12.7), though some of the CIs included differences of uncertain clinical importance.[e35] In the crossover study,[e36] pregabalin produced better patient-reported sleep than pramipexole, with significantly less WASO (-28.5, 95% CI -38.9 to -18.0), fewer awakenings per night (-1.0, 95% CI -1.3 to -0.6), and greater TST (26.8 minutes, 95% 12.3–41.3), but not a shorter time to fall asleep (-1.9 minutes, 95% CI -4.5 to 8.3) in patients receiving pregabalin. Compared with pramipexole, pregabalin also improved MOS Sleep Scale scores for sleep adequacy (11.1, 95% CI 3.2–18.9) but not for sleep disturbance (-6.1, 95% CI -12.4 to 0.2) or sleep quantity (-0.1, 95% CI -0.7 to 0.6), though CIs for both included potentially clinically meaningful differences.[e36]

PSG was performed only in the Class II crossover trial.[e36] PLMI was lower during the pramipexole arms compared with the pregabalin arms (-14.4 favoring pramipexole, 95% CI -20.7 to -8.2). In contrast, pregabalin improved sleep more than pramipexole for WASO (-26.9 minutes, 95% CI -35.5 to -18.3), sleep efficiency (5.2%, 95% CI 3.0–7.5), and TST (25.9 minutes, 95% CI 15.2–36.5) but not for sleep latency (-0.4 minutes, 95% CI -9.7 to 8.9), though CIs included a potentially clinically important values.

In the 12-week Class II study with placebo run-in,[e35] there was no statistically significant difference between pregabalin and pramipexole 0.5 mg on the RLSQoL (pregabalin vs pramipexole mean difference 1.80, 95% CI -0.18 to 3.78). In the crossover trial,[e36] there was also no significant advantage of pregabalin over pramipexole on the RLSQoL (3.3, 95% CI -0.01 to 6.5). When data for the 2 medications were combined in a random-effects meta-analysis, pregabalin was superior to pramipexole 0.5 mg for improving QoL (2.2, 95% CI 0.5–3.9, I^2 0%), though the CI included values of uncertain clinical importance.

Safety and tolerability

In the Class II trial[e35] comparing pregabalin 300 mg daily vs pramipexole at doses of 0.25 mg or 0.5 mg and placebo, participants were randomized to 12 weeks of one of the four parallel arms, after which patients in the placebo arm were randomly assigned to one of the three active treatment arms for the 40 additional weeks of the study (which lasted 52 weeks in total); augmentation was determined by a blinded adjudication panel. No difference was seen in the odds of augmentation with pregabalin treatment vs pramipexole in the group receiving treatment for 40 weeks (OR vs pramipexole 0.25 mg 2.0, 95% CI 0.2–22.7; OR vs pramipexole 0.5 mg 1.0, 95% CI 0.1–7.1), but the CIs included potentially clinically important differences in both

directions. The odds of augmentation were lower with pregabalin for patients treated for 52 weeks (OR vs pramipexole 0.25 mg 0.2, 95% CI 0.07–0.9; OR vs pramipexole 0.5 mg 0.2, 95% CI 0.05–0.6). Overall, augmentation occurred in 2.1% of patients receiving pregabalin, 5.3% of patients receiving pramipexole 0.25 mg, and 7.7% of patients receiving pramipexole 0.5 mg.

Conclusions

Pregabalin likely improves IRLS scores at doses of at least 150 mg/d (1 Class I study and 3 Class II studies; insufficient evidence to support or refute doses of 50–100 mg/d because analyses did not reach statistical significance but CIs included important effects in 1 Class I study). Pregabalin likely improves the PLMI (2 Class II studies) and likely improves at least some other objective sleep measures (1 Class I study and 2 Class II studies with results varying by dose and measure). Pregabalin likely improves subjective sleep outcomes (1 Class I study and 3 Class II studies, 1 of which had insufficient precision at many doses). Pregabalin 300 mg possibly improves RLS-related QoL (1 Class II study; 1 Class I study reported no difference but did not provide data to assess). There is insufficient evidence to support or refute the use of pregabalin for mood in RLS.

There is insufficient evidence to support or refute the superiority of pregabalin over pramipexole for treating IRLS symptoms (meta-analysis of 2 Class II studies where the mean difference point estimate is not clinically important but the CI includes a potentially important benefit of pregabalin compared with pramipexole). Pregabalin likely improves subjective sleep outcomes more than pramipexole (2 Class II studies). Pramipexole possibly improves PLMI more than pregabalin (1 Class II study), whereas pregabalin possibly improves other objective sleep outcomes more than pramipexole (1 Class II study). Pregabalin possibly improves QoL more than pramipexole (meta-analysis of 2 Class II studies, each with insufficient precision to drive a recommendation on its own). Pregabalin possibly has a decreased odds of augmentation at 52 weeks compared with pramipexole (1 Class II study), but there is insufficient evidence to support or refute a difference at 40 weeks (1 Class II study with CIs including potentially important differences in both directions).

Iron treatments

Multiple studies[e71] have documented reductions in CNS iron measures in patients with RLS. For this reason, oral and IV iron treatments have been investigated for the treatment of RLS. Because oral iron is absorbed only in the context of low iron levels, for the purposes of this practice guideline oral iron studies were considered for inclusion only if the population studied had at least some indication of iron deficiency. On the other hand, as IV iron absorption is not limited by serum iron status, IV iron studies in populations without iron deficiency were also evaluated for inclusion. IV iron formulations are each considered separately because they differ considerably in terms of delivery of iron to various body tissues.

Oral iron treatment: Ferrous sulfate

One Class I study investigated the efficacy of oral ferrous sulfate in the treatment of patients with moderate to severe RLS and iron deficiency.

Efficacy for RLS

A Class I parallel-group study[e72] randomized 18 patients with RLS and serum ferritin ≤ 75 μg/L to receive iron sulfate 325 mg or placebo over 12 weeks, both taken orally twice daily with 100 mg vitamin C. Iron was superior to placebo for reducing IRLS scores after 12 weeks of treatment (mean difference 95% CI -16.12 to -2.2), though the CI included a difference that is not clinically important.

Efficacy for sleep, mood, and QoL

The same Class I study demonstrated no improvement in QoL (as assessed by a single dichotomized question) with oral iron 325 mg received twice daily compared with placebo (OR for improvement with iron 8.75, 95% CI 0.74–103.8), but the CI included a clinically important effect. No identified studies included sleep or mood outcomes.

Safety and tolerability

The most common AEs were constipation and nausea.[e72] In order to ensure iron overload (e.g., transferrin saturation > 50%) does not develop, it is necessary to screen for hemochromatosis with regular blood tests (2–6 months after starting iron and yearly after that). Neither this study[e72] nor a comparative trial (described next[e41]) evaluated augmentation.

Comparative trial: iron sulfate vs pramipexole

A Class III parallel-group study[e41] randomized 30 patients with RLS and serum ferritin ≤ 50 μg/L to receive iron sulfate 325 mg BID or flexibly dosed pramipexole (mean = 0.32 mg +/-0.17 mg) for 12 weeks of treatment. IRLS improved with treatment in both groups (iron: mean reduction -9.1, SD 7.07; pramipexole mean reduction -8.7, SD 8.31) with no significant difference between the two (difference in mean treatment -0.4 favoring iron, 95% CI -5.9 to 5.1), though the CI included a clinically important effect in both directions (i.e., the CI included the possibility for either treatment to be clinically superior).

Conclusions

It is likely that ferrous sulfate 325 mg with vitamin C 200 mg taken twice daily improves RLS symptoms as measured by the IRLS in patients with serum ferritin ≤ 75 μg/L (1 Class I study). There is insufficient evidence to support or refute the preferential use of iron vs pramipexole in patients with RLS and ferritin levels ≤ 50 μg/L (1 Class III study).

IV iron

One Class I study of ferric carboxymaltose (FCM) and 2 Class II studies of iron sucrose assessed efficacy for the treatment of moderate to severe RLS. One of the Class II iron sucrose studies required serum ferritin ≤45 μg/L,[e73] but the other studies included patients with RLS regardless of their serum iron status.

Efficacy for RLS

A Class I parallel-group study[e74] randomized 46 patients with moderate to severe primary RLS to receive 2 doses of IV FCM 500 mg or IV placebo 5 days apart. FCM resulted in a -4.9 (95% CI -9.59 to -0.21) greater reduction in IRLS score 28 days after the initial IV treatment compared with placebo, though the CI included a change that is not clinically important. In analysis of treatment response, including 2 additional patients receiving placebo who were not included in the IRLS analysis, the OR for a treatment response was 5.08 (95% CI 1.18–21.9).

Two Class II studies investigated efficacy of iron sucrose in the treatment of moderate to severe primary RLS. A parallel-group study rated Class II because of dropout rate (9 of 30 patients receiving iron sucrose and 21 of 30 receiving placebo, with most dropouts ascribed to lack of efficacy)[e73] failed to show benefit of IV iron sucrose (1,000 mg in 5 divided doses of 200 mg given over 21 days) compared with placebo in 60 patients with moderate to severe RLS and serum ferritin ≤ 45 μg/L. At the predetermined primary assessment (11 weeks), using an intention-to-treat analysis with the last observation carried forward, the difference in change on the IRLS between groups was not statistically significant (-2.3, 95% CI -7.6 to 3.0), though the CI included clinically important differences in both directions. Another parallel-group RCT[e75] using IV iron sucrose 500 mg on consecutive days also found no difference in the mean change in IRLS score (1.9 [placebo was superior by point estimate], 95% CI -6.42 to 10.22), but the CI again included clinically important differences in both directions. A random-effects meta-analysis of these 2 studies also results in insufficient precision to support or exclude an important effect of iron sucrose (-1.09, 95% CI -5.55 to 3.36).

Efficacy for sleep, mood, and QoL

In the Class I FCM study of 46 patients,[e74] the change in MOS Sleep Scale total score was not significantly different between groups (40.7, 95% CI -7.27 to 88.67). The CI included both potentially clinically important and unimportant effects. There was also limited precision to detect a difference between FCM and placebo with regard to change in the PLMI (right leg -1.9, 95% CI -10.83 to 7.03; left leg -3.0, 95% CI -6.3 to 12.3), with CIs that included potentially important effects in both directions. FCM produced a clinically and statistically significant improvement in QoL, as assessed by the RLSQoL (37.0, 95% CI 5.83–68.17).

Only 1 iron sucrose study assessed sleep outcomes.[e75] Iron sucrose did not improve sleep efficiency (5.9, 95% CI -90.83 to 102.63) or the PLMI (-13.1, 95% CI -88.43 to 62.23) compared with placebo, but CIs included potentially clinically important differences in both directions. No iron sucrose studies assessed QoL, and no IV iron studies assessed mood.

Safety and tolerability

No significant AEs were noted with FCM and iron sucrose IV formulations. FCM did produce a transient decrease in blood phosphorous that has no known clinical significance.[e74] IV iron products are associated with a risk of potentially life-threatening allergic reactions and have

associated FDA warnings and prescribing instructions. Augmentation was not assessed in the reported studies.

Conclusions

IV FCM 500 mg given twice 5 days apart likely improves RLS symptoms in patients with moderate to severe RLS regardless of ferritin level (1 Class I study). In this population, IV FCM likely improves RLS-specific QoL at 28 days after initial treatment (1 Class I study). There is insufficient evidence to support or refute an effect of IV FCM on subjective sleep measures or PLMI (1 Class I study without statistical significance but with CIs including potentially clinically important effects). Studies investigating iron sucrose use in RLS had insufficient precision to support or refute a treatment effect (2 Class II studies did not reach statistical significance but had CIs including clinically important effects).

Opioid agonists

One Class II study and 1 Class III study evaluated the effect of opioid agonists in treating RLS.

Efficacy for RLS

A Class II parallel-group study[e76] randomized 306 patients with moderate to severe RLS and previous unsuccessful treatment to receive flexibly dosed prolonged-release oxycodone/naloxone or placebo. After 12 weeks, oxycodone/naloxone resulted in a greater IRLS reduction than placebo (-8.15, 95% CI -10.85 to -5.46) (mean dose of oxycodone 21.9 ± 15.0 mg, naloxone 11.0 ± 7.5 mg). For the 276 patients with CGI-I measurements, the CGI-I responder rate was significantly higher in the oxycodone/naloxone group (67%) than in the placebo group (35%) (OR 3.76, 95% CI 2.28–6.19).

A Class III double-blind crossover study randomized 11 patients with moderate to severe RLS to receive oxycodone in divided doses (2 hours before and at bedtime) or placebo. On self-rated 0–4 scales, oxycodone (mean dose of 15.9 mg/d) improved RLS symptoms of motor restlessness (mean posttreatment difference 1.37, 95% CI 0.29–2.35) and leg paresthesia (mean posttreatment difference 1.32, 95% CI–2.31) compared with placebo.[e77]

Efficacy for sleep, mood, and QoL

In the Class II study of 306 patients mentioned previously,[e76] sleep improved more in the oxycodone/naloxone group than in the placebo group as measured by the MOS sleep adequacy subscale (mean difference between groups 0.68, estimated 95% CI 0.34–1.02). Similarly, sleep quantity derived from the MOS Sleep Scale improved more in the oxycodone/naloxone group than in the placebo group (mean difference between groups 0.39 hours, estimated 95% CI 0.19–0.59), although the clinical importance of the values at the lower end of the CI is uncertain. Daytime somnolence was not different between groups (mean difference between groups 0.24, estimated 95% CI -1.20 to 1.69).

In the Class III study on this topic,[e77] daytime drowsiness (rated on a 0–4 scale) improved more in the oxycodone arm than in the placebo arm (mean posttreatment difference 0.68, estimated 95% CI 0.07–1.29), though the clinical importance of the values at the lower end of the CI is uncertain. In addition, mean PLMI was lower with oxycodone than with placebo (mean posttreatment difference -44.5, estimated 95% CI -74.8 to -14.2), and sleep efficiency was higher (mean posttreatment difference 24.7%, estimated 95% CI 7.1–42.3).

The Class II study[e76] demonstrated improved RLS-specific QoL with oxycodone/naloxone compared with placebo (mean difference between groups -0.76, estimated 95% CI -1.14 to -0.38).

Safety and tolerability

The most common AEs of opioid therapy were constipation, nausea, sedation, and depression. Drug withdrawal symptoms occurred in three patients: one after the 12-week RCT and two after the 40 weeks of open-label follow-up. No augmentation was observed.[e76]

Conclusions

It is possible that prolonged-release oxycodone/naloxone improves RLS symptoms, sleep adequacy, sleep quantity, and RLS-specific QoL in patients with RLS who have not responded to other treatments (1 Class II study). It is possible that prolonged-release oxycodone/naloxone does not improve daytime somnolence (1 Class II study). There is insufficient evidence to support or refute the use of oxycodone in RLS (1 Class III study). Benefits of opioid use must be weighed against risks such as potential abuse.

Other medications

A number of other medications have been evaluated for RLS treatment, addressed briefly in the following sections. Additional analyses (e.g., to determine CIs) were not performed, as most Class III studies are unable to drive conclusions or recommendations.

Clonazepam

Two small Class III studies evaluated the effect of the benzodiazepine clonazepam in treating RLS.[e78,e79] One crossover study randomized 6 patients to receive 1.0 mg of clonazepam or placebo for 1 week each; patients were also treated with vibratory stimulation for an additional week. Patients judged symptoms on a 4-point scale over the week of treatment, with clonazepam improving sleep quality and leg dysesthesia ($p < 0.05$ for both).[e78] The other study was also a crossover trial of 6 patients but with 4-week crossover arms. Treatment was started with clonazepam 0.5 mg before bedtime and increased by 1 tablet weekly until it was dosed 4 times per day. Patients rated their symptoms on a 5-point scale (0 = no symptoms, 5 = extreme symptoms). The difference between the clonazepam and placebo arms was not statistically significant (mean score 1.46 during clonazepam arm and 2.55 during placebo arm, difference in means -1.09, estimated 95% CI -2.46 to 0.28), though the CI included potentially clinically important differences.[e79]

Bupropion

Bupropion is an antidepressant that inhibits dopamine and norepinephrine reuptake. A Class II double-blind, placebo-controlled, parallel study randomized 60 patients with primary moderate to severe RLS to receive daytime sustained-release bupropion 150 mg or placebo 2 hours before bedtime. Mean change in IRLS score was better in the bupropion group at 3 weeks (-4.8, 95% CI -9.1 to -0.5, where the CI included a difference not considered clinically important) but not at the planned primary outcome assessment at 6 weeks (-2.8, 95% CI -7.2 to 1.6, where the CI included a difference that is clinically important).[e80] BDI-II scores were not different between groups at 6 weeks (mean difference 3.5, 95% CI -2.6 to 9.6). AEs were not reported.

Clonidine

A Class III flexibly dosed, double-blind, 4-week crossover trial of the α2 blocker clonidine (mean dose of 0.5 mg) given before bedtime in primary RLS[e81] reported that when rating subjective symptoms on a 4-point scale, patients described less paresthesia (-1.4, 95% CI -2.6 to -0.2), motor restlessness (-1.3, 95% CI -2.1 to -0.5), and daytime fatigue (-1.1, 95% CI -2.0 to -0.2) during the clonidine treatment arm than when taking placebo. There was no difference in the PLMI between groups (mean difference 12.2, 95% CI -60.1 to 84.5), but the CI included potentially clinically important effects in both directions. Reduction in sleep latency, but no change in TST, was observed on PSG. The most common AEs were hypotension, decreased cognition, dry mouth, and sleepiness.

Botulinum neurotoxin

A Class III 6-patient placebo-controlled trial of botulinum neurotoxin injections into the legs showed no benefit for RLS symptoms, but there was a prominent placebo response and the study was inadequately powered to detect a modest response.[e82]

Rifaximin

A Class III randomized placebo-controlled trial (Class III for lack of equivalence at baseline and absence of a primary outcome) of the antibiotic rifaximin (1,650 mg/d for 10 days in 30 patients with RLS and small intestinal bowel overgrowth) reported improvement on the IRLS in the rifaximin group vs placebo at assessment on days 11 and 18 but not day 25, with maximum improvement at day 18. On calculation of the mean difference, however, the CI at day 18 was not statistically significant and included clinically important and unimportant effects (mean difference -3.9, 95% CI -9.6 to 1.8).[e83]

Valproic acid

In a Class III 3-arm crossover trial comparing sustained-release levodopa (200 mg with 50 mg benserazide), slow-release valproate (600 mg), and placebo for 3 weeks each in 20 patients with RLS,[e53] the RLS intensity score (0–10 visual analog scale) was significantly better after treatment with valproate vs placebo (3.8 ± 2.5 vs 5.5 ± 1.7, $p = 0.022$). There was no difference

in the PLMI between the 2 groups (38.0 ± 32.2 vs 43.2 ± 36.9, estimated difference -5.2, 95% CI -26.7 to 16.3), but the CI included potentially clinically important effects in both directions.

Carbamazepine

A Class III study randomized 181 patients with RLS to receive carbamazepine (100–300 mg/d, mean 236 mg) or placebo for 5 weeks. Patients receiving carbamazepine reported fewer "attacks" of RLS at weeks 3 ($p = 0.04$) and 5 ($p = 0.03$) and a greater improvement as measured by 15-cm visual analog scale ($p < 0.01$, exact numbers not provided).[e84]

Conclusion

For patients with moderate to severe RLS, there is insufficient evidence to support or refute the effectiveness of clonazepam, bupropion, clonidine, botulinum neurotoxin, rifaximin, valproic acid, and carbamazepine.

Nutraceuticals

Valerian

A Class II placebo-controlled parallel study randomized 48 patients with primary moderate to severe RLS to receive valerian 800 mg or placebo at bedtime. In the 37 patients who completed the study, there was no significant difference in the change on the IRLS between valerian and placebo at 8 weeks (mean difference -1.3, 95% CI -7.7 to 5.1), but the CI included clinically important differences in both directions. Similarly, there were no differences between the valerian and placebo groups on multiple subjective measures of sleep. The most common AEs were gastrointestinal distress and fatigue.[e85]

Selenium

A Class III placebo-controlled crossover study[e86] assigned 68 patients with primary moderate to severe RLS to receive selenium 50 μg, 200 μg, or placebo in varying order with a 1-month washout between arms. Both doses of selenium were superior to placebo for reduction of RLS symptoms as assessed by the IRLS (mean reduction 6.09 for the placebo arm, 12.86 for the 50-μg arm, and 14.03 for the 200-μg arm, $p < 0.001$). The higher selenium dose was superior to the lower selenium dose ($p = 0.007$). No AEs were reported with selenium.

Conclusions

For patients with moderate to severe RLS, there is insufficient evidence to support or refute the effectiveness of selenium or valerian, because of either insufficient precision or reliance on a single Class III study.

Physical measures

Near-infrared spectroscopy

Two Class II studies used near-infrared spectroscopy (NIRS) for the treatment of primary moderate to severe RLS. A Class II sham-controlled study of NIRS[e87] randomized 34 patients to receive twelve 30-minute NIRS treatments with the Anodyne device over 4 weeks or sham treatment. There was a greater reduction in the IRLS score at 4 weeks with NIRS (mean difference between groups -8.3, 95% CI -12.3 to -4.3). Another Class II study[e88] randomized 25 patients to receive NIRS on 1 of 2 devices (Anodyne or HealthLight) for 4 weeks. Mean change in IRLS score from baseline to week 4 was -10.5 (± 9.5) in the Anodyne group and -8.9 (± 7.9) in the HealthLight group, with no between-group differences ($p = 0.75$). No AEs were reported with NIRS.

Pneumatic compression

One Class I study[e89] randomized 35 patients to receive at least 1 hour of pneumatic compression of the leg daily at 40 cm of H_2O of air pressure before usual symptom onset or sham pneumatic compression at 3 to 4 cm of H_2O. The study excluded patients who had previously received pneumatic compression treatments in order to prevent unblinding. The active device resulted in a lower IRLS score at 4 weeks (mean difference -5.7, 95% CI -8.2 to -3.2). Similarly, QoL at 4 weeks favored active treatment on all RLSQoL subscales: social function (16.0, 95% CI 10.2–21.8), daytime function (14.2, 95% CI 8.2–20.2), sleep quality (15.5, 95% CI 6.1–24.9), and emotional well-being (18.5, 95% CI 9.7–27.3). No AEs were reported.

Transcranial direct current stimulation

One Class I crossover study[e90] randomized 33 women with RLS who were drug-naïve to receive 5 daily sessions of cathodal, anodal, or sham transcranial direct current stimulation (tDCS) over the bilateral medial aspect of the primary motor cortex. There was no difference in mean IRLS change between the active and placebo groups either 3 days (cathodal vs placebo: -1.4, 95% CI -3.4 to 0.6; anodal vs placebo 3.2, 95% CI 1.1–5.3) or 13 days (cathodal vs placebo 1.0, 95% CI -1.7 to 3.7; anodal vs placebo 2.0, 95% CI -0.6 to 4.6) after the final session[e90] except when anodal stimulation was compared with placebo at 3 days, where change scores were significantly better in the placebo group. The only CI that included a clinically important value was in the cathodal vs placebo group at 3 days, where the lower bound of the CI was -3.4. There were also no differences in change scores on mood and subjective sleep measures between groups (data not provided).

Repetitive transcranial magnetic stimulation

A Class II study randomized 19 patients with RLS to 10 sessions of repetitive 5-Hz transcranial magnetic stimulation (rTMS), each spaced 3 days apart. There was an unequal sex distribution between the 2 groups, as the real stimulation group consisted of all women (11/11) and the sham group was mostly men (2/8 were women). Mean posttreatment IRLS scores were significantly lower in the therapeutic stimulation group vs the sham group after 5 sessions (-9.5, 95% CI -12.7 to -6.3) and after 10 sessions (-15.9, -19.9 to -11.9) (change scores with 95% CIs not calculable).[e91]

Vibrating pads

Two Class II studies described together in a pooled analysis[e92] and a meta-analysis[e93] investigate the use of vibratory stimulation pads vs sham pads (a sound-producing sham pad in one study and a light-emitting sham pad in the other). The studies enrolled a combined total of 158 patients with IRLS scores ≥15. There was no difference in mean change in IRLS score between vibration and sham groups at 4 weeks (-0.29, 95% CI -2.66 to 2.08). When mean change in total MOS-II scores was considered, difference between vibratory stimulation and sham pads was statistically significant in one study ($p = 0.023$) but not the other study ($p = 0.302$). When combined data were presented, mean change was greater in the vibration groups than in the sham groups (-7.09, 95% -12.92 to -0.27), though the clinical importance of the upper bound of the 95% CI is uncertain. RLSQoL scores were not statistically different between groups (4.13, 95% CI -1.33 to 9.59), but the CI includes a potentially clinically important effect of the vibration.

Acupuncture

One 6-week Class III single-blind study randomized 38 patients with primary RLS to either traditional acupuncture individualized for the patient's RLS discomfort or randomized placement of acupuncture needles, each occurring 3 times per week.[e94] Only the 31 patients completing the study were included in the analysis. The study reported significant differences between treatment and sham completers on the IRLS scores (standard acupuncture superior at 4 and 6 weeks), the Epworth Sleepiness Scale (ESS; a self-reported 8-item questionnaire addressing daytime sleepiness in different situations) (standard acupuncture superior at 4 and 6 weeks), mean activity of sleep (standard acupuncture superior at 4 and 6 weeks), and mean activity of early sleep (standard acupuncture superior at 6 weeks) (scores provided in figures only; differences not estimated because of Class III classification and inability to drive conclusions).[e94]

Conclusions

Pneumatic compression is likely effective in the treatment of patients with primary moderate to severe RLS (1 Class I study). NIRS is possibly effective in the treatment of primary moderate to severe RLS (1 Class II study vs sham and 1 Class II study showing no difference between 2 devices). rTMS is possibly effective in the treatment of primary moderate to severe RLS (1 Class II study). Vibrating pads are possibly ineffective in treating RLS symptoms (meta-analysis of 2 Class II studies excluding a clinically important benefit) but possibly effective in treating subjective sleep outcomes (meta-analysis of 2 Class II studies where only one was sufficient to drive recommendations on its own). There is insufficient evidence to support or refute an effect of vibrating pads on QoL in RLS (meta-analysis of 2 Class II studies that is not statistically significant but where the CI includes a potentially clinically important effect). Both cathodal and anodal types of tDCS are probably ineffective for improving RLS symptoms in women with RLS who are drug-naïve (one negative Class I study), though a small benefit of cathodal stimulation at 3 days (but not 13 days) cannot be completely excluded. There is insufficient evidence to support or refute use of acupuncture in RLS (single Class III study).

Treatment of secondary RLS

There are many causes of secondary RLS. However, adequate evidence is available only for treatment of secondary RLS in patients with ESRD who are on hemodialysis (HD). Evidence to

support conclusions and recommendations in other forms of secondary RLS, such as pregnancy, was not identified.

Ropinirole

One study[e95] randomized 32 patients with RLS and ESRD on HD to exercise training (discussed later), ropinirole 0.25 mg, or placebo for 6 months. This study was rated Class II for the ropinirole analysis. The ropinirole-treated group had a greater reduction in IRLS scores than the placebo group (difference in mean change -11.4, 95% CI -18.8 to -4.0), despite the fact that the ropinirole dose used was much lower than the mean dose in other studies. Depression also improved in both the exercise and ropinirole groups, but this was confounded by worse baseline depression in those groups than in the placebo group. There were no differences in the ESS between groups (mean difference -2.14, 95% CI -7.19 to 2.91), but the CI included a potentially clinically important difference. Mean change in a sleep diary measure combining different features of sleep disturbance was improved in the ropinirole-treated group compared with the placebo group (-4.84, 95% CI -7.89 to -1.80). No AEs were reported.

Levodopa

Two Class III studies investigated levodopa use in patients with RLS and ESRD on HD. A 4-week Class III crossover study[e51] evaluated the effect of levodopa/benserazide 100–200 mg on RLS associated with ESRD on HD in 11 patients referred from dialysis centers (in addition to patients with idiopathic RLS, discussed previously). On the 8-point CGI-S (where higher scores indicate more severe symptoms), there was no significant difference between groups with levodopa vs placebo (6.3 vs 6.5, mean difference -0.2, estimated 95% CI -0.7 to 0.3), though the CI included a potentially clinically important effect. The PLMI was significantly lower after levodopa treatment (mean difference -28.0, estimated 95% CI -48.1 to -7.9). On 50-point QoL measures, life satisfaction was greater after levodopa treatment (24.2 vs 17.4, mean difference 6.8, estimated 95% CI 0.8–12.8, which includes values of uncertain clinical importance), but there was no difference with regard to change in negative feelings (21.6 vs 24.3, estimated mean difference -2.7, 95% CI -7.9 to 2.6, which includes values that could potentially be clinically important). A separate Class III crossover study[e96] randomized patients with RLS and ESRD on HD to receive levodopa/carbidopa 100/25 mg nightly or placebo in 1-week crossover arms. No difference in subjective RLS symptom reports was identified (details not provided), but the PLMI decreased with levodopa treatment (PLMI mean difference -40.0, estimated 95% CI -68.5 to -11.5).

Comparative trials: Levodopa controlled-release vs gabapentin

See discussion that follows.

Gabapentin

One randomized, double-blind, placebo-controlled crossover Class III study used gabapentin in 16 patients with RLS and ESRD on HD in 6-week blocks.[e97] Gabapentin 300 mg was administered 3 times weekly (following dialysis because of its renal excretion and potential

toxicity in those with renal failure). With use of a modified 8-point RLS scale, mean score at completion was 5.8 ± 2.3 after placebo (n = 14) and 3.0 ± 2.2 after gabapentin (n = 13) (mean posttreatment difference -2.8, 95% CI -5.5 to -1.1). The OR for a response rate was 38.3 with a continuity correction (95% CI 4.3–338.1). The main AE was somnolence.

Comparative trials: Gabapentin vs levodopa controlled release

One Class III study randomized 87 patients with RLS with ESRD on HD to 4 weeks of either gabapentin 200 mg or levodopa controlled release 110 mg. Interpretation of the results is limited by the study's use of a nonvalidated method of diagnosing RLS (by questionnaire), invalid completion of the IRLS (by the patients), and assessment of completers rather than use of an intention-to-treat approach (2 patients receiving gabapentin and 3 patients receiving levodopa dropped out and were not included in the analysis). Gabapentin produced a greater reduction in IRLS at 4 weeks (baseline: 27.8 ± 4.6; posttreatment: 10.4 ± 5.7) than levodopa (baseline: 27.6 ± 4.4; posttreatment: 14.2 ± 7.6) ($p = 0.016$ per study). Gabapentin was also described as significantly superior to levodopa with regard to posttreatment scores for sleep latency ($p = 0.001$), sleep disturbance ($p < 0.0001$), sleep quality ($p < 0.0001$), and daytime sleepiness ($p < 0.0001$) but not for sleep duration ($p = 0.326$) or ESS ($p = 0.116$).[e98]

Vitamins C and E

One randomized, double-blind, placebo-controlled Class I study examined vitamin C and vitamin E alone and in combination in patients with RLS and ESRD on HD.[e99] This study assigned 60 patients with moderate to severe RLS to receive placebo, vitamin C (200 mg), vitamin E (400 mg), or the combination of vitamin C and vitamin E for 8 weeks. The difference in mean IRLS score change vs placebo was significant for all 3 treatment groups: vitamins C and E (-7.2, 95% CI -10.3 to -4.1), vitamin C and placebo (-6.9, 95% CI -9.2 to -4.6), and vitamin E and placebo (-7.0, 95% CI 10.4 to -3.6). There was no significant difference between treatment groups. Nausea and dyspepsia were the most common AEs in the vitamin C and vitamin E groups.

IV iron

One randomized, double-blind, placebo-controlled Class III study (rated Class III for lack of description of allocation concealment or primary outcome) used IV iron dextran in patients with RLS and ESRD on HD.[e100] IV iron dextran (1,000 mg) or placebo was administered in a double-blind fashion in 25 patients with ESRD on HD and RLS symptoms assessed by the IRLS. Median decrease in IRLS score favored iron dextran at 1 week (2 [IQR -6 to -1] vs 0.5 [IQR -1.25 to 0], $p = 0.03$) and 2 weeks (3 [IQR 5–2] vs 0 [IQR -1 to 0], $p = 0.01$) but not 4 weeks (data not provided), when both groups showed a 25% worsening of IRLS scores. Nausea, vomiting, and headaches were the most commonly reported AEs with IV iron dextran. Parenteral administration of iron dextran has an FDA black box warning regarding a risk of anaphylactic-type reactions.

Exercise

Four studies (1 Class II and 3 Class III) examined the effects of exercise in RLS with ESRD/HD.[e95,e101–e103] The Class II study[e101] randomized 24 patients with RLS and ESRD on HD to 45 minutes of cycling 3 times per week on a recumbent ergometer with either progressive exercise (increasing resistance adjusted monthly) or no-resistance exercise for 6 months. The progressive exercise group had a greater reduction in IRLS score (difference in mean change -11.1, 95% CI -19.1 to -3.1) at 6 months, although results are confounded by the fact that they had worse IRLS scores at baseline. Depression as measured by the Zung Depression Scale also improved more in the progressive resistance exercise group (difference in mean change -9.9, 95% CI -17.3 to -2.5). Change scores on a sleep diary measure and the ESS were not different between groups.

One Class III study of 14 patients with RLS who were on HD allowed patients to choose to participate in an exercise group (n = 7) or a control group (n = 7).[e102] Patients who chose to exercise were younger and had better functional status at baseline than those who chose to be in the control group. Change in IRLS score was greater in the exercise group (mean difference -12, 95% CI -22 to -1.9), but the CI included changes not considered clinically important. Another Class III study[e95] randomized 32 patients with RLS and ESRD to 1 of 3 groups for 6 months: exercise training 3 times per week on a recumbent ergometer with monthly increases in intensity, ropinirole 0.25 mg, or placebo (ropinirole discussed earlier). This study was rated Class III for the comparison of exercise with placebo because the exercise group was not blinded but the study had independent outcome assessments. The exercise group had greater reduction in IRLS score than the placebo group (difference in mean change -12.0, 95% CI -19.6 to -4.4). Depression also improved in the exercise group, but this was confounded by worse baseline depression in this group vs placebo. Sleep measures did not change in the exercise group vs placebo. No AEs were reported.

The other Class III study[e103] randomized 26 patients with RLS and ESRD on HD to aerobic exercise (bicycling) 3 times per week or to no intervention for 16 weeks. Study limitations included lack of information regarding baseline characteristics of the 2 groups, the randomization procedure, allocation concealment, and the number of dropouts. The mean change in the IRLS was greater in the exercise group vs controls (-5.0, 95% CI -7.9 to -2.0), though the upper limit of the CI includes a clinically unimportant effect.

Conclusions

Ropinirole 0.25 mg daily is possibly effective in the treatment of RLS symptoms associated with ESRD/HD (1 Class II study). Levodopa is possibly effective in treating PLMS associated with RLS (2 Class III studies), but there is insufficient evidence to support or refute an effect of levodopa on RLS severity (2 Class III studies with insufficient precision/details). Vitamins C and E alone and in combination are likely effective in the treatment of RLS symptoms associated with ESRD/HD (1 Class I study). Exercise is possibly effective in the treatment of RLS symptoms associated with ESRD/HD (1 Class II study compared with nonresistance exercise, 1 Class III study compared with placebo pill, and 1 Class III study with an undefined control group, with an additional Class III study lacking precision to detect an important effect). There is insufficient evidence to support or refute the efficacy of gabapentin or IV iron dextran in RLS associated with ESRD/HD (1 Class III study each). There is also insufficient evidence to support

or refute using levodopa or gabapentin preferentially over the other in this population (1 Class III study).

PRACTICE RECOMMENDATIONS

1. In moderate to severe primary RLS, clinicians should consider prescribing a pharmacologic agent to reduce RLS symptoms. There is strong evidence to support the use of pramipexole, rotigotine, cabergoline, and gabapentin enacarbil (Level A); moderate evidence to support the use of ropinirole, pregabalin, and IV FCM (Level B); and weak evidence to support the use of levodopa (Level C). There are few head-to-head comparisons of these agents to suggest that one should be used preferentially, though in practice clinicians often decide on the basis of comorbidities or potential side effects such as augmentation with dopaminergic agents. When considering efficacy alone, clinicians may consider choosing cabergoline instead of levodopa (Level C). However, cabergoline is rarely used in clinical practice for RLS because of a risk of cardiac valvulopathy at higher doses. There is insufficient evidence to support or refute the preferential use of pregabalin instead of pramipexole (Level U).

2. For patients with primary RLS for whom clinicians want to target sleep, clinicians should consider prescribing a pharmacologic agent that improves objective or subjective sleep parameters (or both). Evidence supports agents to different extents for subjective and objective outcomes.
    a. When targeting PLMS, specifically the PLMI as measured by PSG, there is strong evidence to support the use of ropinirole (Level A); moderate evidence to support the use of pramipexole, rotigotine, cabergoline, and pregabalin (Level B); and weak evidence to support the use of levodopa (Level C). There is insufficient evidence to support or refute the use of gabapentin enacarbil, FCM, or iron sucrose for PLMS (Level U). There is weak evidence (Level C) for using pramipexole in preference to pregabalin with regard to PLMI alone.
    b. With regard to other objective sleep measures (e.g., TST, sleep efficiency, sleep latency, and WASO), there is moderate evidence to support the use of ropinirole, gabapentin enacarbil, and pregabalin for at least some objective sleep measures (Level B). There is insufficient evidence to support or refute the use of pramipexole, rotigotine, cabergoline, or levodopa for these measures (Level U). There is weak evidence (Level C) for using pregabalin in preference to pramipexole with regard to objective sleep measures other than PLMI.
    c. With regard to subjective sleep measures, there is strong evidence to support the use of cabergoline and gabapentin enacarbil (Level A); moderate evidence to support the use of ropinirole, pramipexole, and pregabalin (Level B); weak to moderate evidence to support the use of rotigotine (Levels B and C); and weak evidence to support the use of levodopa (Level C), with the strength of evidence varying by measure and, sometimes, dose. There is insufficient evidence to support or refute the use of FCM for subjective sleep measures (Level U). There is moderate evidence to support the use of pregabalin instead of pramipexole with regard to subjective sleep outcomes (Level B).

3. For patients with RLS for whom clinicians want to target concomitant psychiatric symptoms, clinicians should consider ropinirole in the context of anxiety (Level B) and may consider ropinirole in the context of depression (Level C). In the context of moderate to severe RLS-related mood disturbance, clinicians may consider prescribing pramipexole for depression and anxiety (Level C). For overall mood, clinicians should consider prescribing gabapentin enacarbil (Level B).

4. For patients with RLS for whom clinicians want to select an agent that improves QoL, clinicians should consider prescribing ropinirole, pramipexole, cabergoline, gabapentin enacarbil, or IV FCM (Level B) and may consider prescribing rotigotine or pregabalin (Level C). There is insufficient evidence to support or refute the use of levodopa for improving QoL in RLS (Level U).

5. When avoidance of augmentation is a deciding factor, clinicians may consider prescribing pregabalin rather than pramipexole when considering 52-week treatment in light of lower augmentation rates with pregabalin (Level C). Clinicians may also consider prescribing cabergoline rather than levodopa when considering 30-week treatment in light of lower augmentation rates with cabergoline (Level C); however, this needs to be weighed against the risk of cardiac valvulopathy with high doses of cabergoline. There is insufficient evidence to support or refute which dopaminergic agents cause the least augmentation because augmentation rates are most commonly reported in long-term open-label Class IV studies (Level U). Results of these studies are summarized in this practice guideline but cannot support formal recommendations.

6. For patients with RLS who have not responded to other treatments, clinicians may consider prescribing prolonged-release oxycodone/naloxone (where available) for RLS symptoms, subjective sleep symptoms, and QoL (Level C), but potential benefits need to be weighed against known opioid risks.

7. There is insufficient evidence to support or refute the use of gabapentin, iron sucrose, oxycodone, clonazepam, bupropion, clonidine, selenium, rifaximin, botulinum neurotoxin, valproic acid, carbamazepine, or valerian in the treatment of RLS (Level U).

8. For patients or clinicians wanting to use nonpharmacologic approaches to treat RLS, clinicians should consider prescribing pneumatic compression before usual symptom onset (Level B) and may consider prescribing NIRS or rTMS (where available) (Level C). Clinicians may consider prescribing vibrating pads for subjective sleep concerns (Level C) but not for RLS symptoms (Level C against). Clinicians may also choose not to consider tDCS for RLS symptoms (Level C against). There is insufficient evidence to support or refute use of acupuncture in RLS (Level U).

9. In patients with RLS and serum ferritin $\leq$ 75 μg/L, clinicians should consider prescribing ferrous sulfate 325 mg with vitamin C 200 mg twice daily for improvement of RLS symptoms (Level B).

10. In patients with secondary RLS associated with ESRD on HD, clinicians should consider prescribing vitamin C and E supplementation (alone or in combination) (Level B) and may consider prescribing ropinirole, levodopa, or exercise (Level C). There is insufficient evidence to support or refute the use of gabapentin or IV iron dextran in RLS associated with ESRD/HD (Level U). There is also insufficient evidence to support or refute the use of gabapentin or levodopa preferentially over the other in this population (Level U).

CLINICAL CONTEXT

When addressing RLS, clinicians and patients must first determine whether symptoms require treatment, the setting in which this practice guideline is relevant. Treatment should be considered if RLS symptoms interfere with sleep or daytime function to an important degree. Before determining the best treatment, it is important to first ensure there are no contributing factors to RLS symptoms (e.g., iron deficiency or serotonergic antidepressants). Because iron deficiency is a known contributor to RLS, can result in other complications, and may respond to iron supplementation, it is reasonable for clinicians to check iron studies in patients with RLS with new or worsening symptoms and treat the iron deficiency first if indicated.

There are important limitations in the evidence regarding RLS treatments. The clinical significance of some outcomes used in RLS trials, such as PLMI, is uncertain; thus conclusions drawn regarding these outcomes are of unknown clinical relevance. Additionally, apart from the IRLS, clinically important differences for the measures used in RLS trials are unknown, forcing clinicians to use clinical judgment in interpreting study results using these measures/outcomes. Most of the studies are short-term treatment trials, often 12 or fewer weeks, whereas clinical treatment of RLS is ongoing over years. Conclusions regarding long-term efficacy and risks are difficult to develop because of the open-label nature of many of the longer duration studies. Short-term trials are less able to inform risks associated with prolonged medication exposure, such as augmentation occurring with dopaminergic medications. Augmentation is a major concern for clinicians and patients with RLS and an important consideration when choosing a treatment approach. Long-term risks with other treatment approaches, such as opioid use, are also important to consider.

FDA dosing guidelines are presented in table e-1. Most treatments have been investigated only for daily use, and the value of PRN medications for those with intermittent or situation-specific symptoms is unknown, though a substantial number of patients have RLS symptoms on an intermittent basis and may thus need treatment only intermittently.[e2] Additionally, there are no data to guide the approach to cases where monotherapy is not adequately effective or clinicians want to use multiple agents to minimize doses of dopaminergic agents, though one study found that more than 50% of patients in the community are treated with polypharmacy for their RLS.[e104] Clinical trials of RLS medications generally exclude patients with common comorbid conditions such as mood and anxiety disorders and peripheral neuropathy, so the generalizability of these studies to populations with those disorders is uncertain.[e105] Certain populations with secondary RLS, such as pregnant women, are also under-studied. In the circumstance where treatment of secondary RLS has the most evidence—patients with ESRD on HD—the presence of evidence specific to this population does not preclude consideration of agents shown helpful for idiopathic RLS but that are to date unstudied in ESRD.

In patients with RLS symptoms requiring treatment, choosing the most appropriate intervention requires an individualized approach including regard for patient factors, such as the most prominent symptoms (e.g., presence of sleep disturbance, because of varying strength of evidence by outcome), comorbidities relating to RLS (e.g., mood), other comorbidities (such that an agent may be used preferentially to treat more than one indication or avoided because of a presumed higher risk of side effects), age (as this could change side effect risks), side effect profile, augmentation risks, and patient preferences (e.g., pharmacologic or nonpharmacologic approaches). Although this practice guideline describes the AEs commonly reported in the treatment trials—in addition to the risk of augmentation for dopaminergic agents—it is now recognized that some agents for RLS have less common but important risks. These risks include not only cardiac valvulopathy with cabergoline, as discussed earlier, but also side effects such as impulse control disorders with the dopamine agonists. RLS is a chronic condition for many patients. Thus, the relative risks and benefits of long-term medication use are relevant—particularly the appearance of augmentation with the use of dopaminergic agents. Unfortunately, there are insufficient data to guide clinicians in the decision-making process,[e106] as only a few standardized, adjudicated studies of augmentation exist, and the longest comparative or blinded study is only 1 year in length. Nevertheless, for patients on dopaminergic agents, careful reassessment of changes in the time of RLS symptom onset and its anatomical distribution, total medication dose, and medication timing are indicated at least yearly. In the absence of evidence, it is reasonable to consider discontinuing a patient's current dopaminergic medication in the setting of clinically important augmentation and switching to a nondopaminergic agent or a longer-acting dopaminergic medication.

RECOMMENDATIONS FOR FUTURE RESEARCH

Although major strides have been made in the identification and treatment of patients with RLS, a number of important issues remain. Augmentation is a substantial problem complicating RLS treatment, and a number of related matters require further study:

1. Is the rate of augmentation genuinely reduced by the use of long-acting dopaminergics, or do these agents simply delay the appearance of this complication by masking the earlier advance of symptoms?

2. Can clinicians predict, on the basis of clinical, biochemical, or genetic factors, the appearance of (or, conversely, protection from) this complication?

3. In patients who develop augmentation, what are the relative benefits of earlier dosing, increased doses, switches to longer-acting agents or to agents from other classes, or use of polypharmacy for symptomatic treatment while possibly limiting dose-dependent side effects?

Additionally, the following nonaugmentation topics merit further consideration for research:

1. Inclusion of patients with primary RLS with medical and psychiatric comorbidities (especially depression, anxiety, somatoform disorders, and chronic pain) in clinical trials[e105] in order to better guide treatment of patients with RLS who are commonly managed.

2. Investigation of treatment options for RLS symptoms occurring on an intermittent basis.

3. Additional studies of treatments for individuals with secondary RLS, both temporary (e.g., in pregnancy) and ongoing (e.g., in peripheral neuropathy, peripheral vascular disease, and ESRD).

4. Investigation of combination treatments after unsuccessful monotherapy, which are urgently needed, including both pharmacologic and nonpharmacologic approaches.

Table e-1. Summary of interventions evaluated in idiopathic restless legs syndrome, with Level A–C recommendations

Intervention	FDA guidelines for starting dose, therapeutic dose (mg/d)	Level of evidence to support use				Augmentation risk?[b]	Other common or important adverse events
		RLS symptoms	PLMI	Subjective sleep measures[a]	Psychiatric symptoms		
Ropinirole	0.25, 0.25–4.0	Level B	Level A	Level B	Depression: Level C Anxiety: Level B	Yes	Dopamine agonist AEs include nausea, somnolence, impulse control disorders
Pramipexole	0.125, 0.25–0.5	Level A	Level B	Level B	Depression: Level C Anxiety: Level C	Yes	(See ropinirole)
Rotigotine patch (worn 24 h/d)	1.0, 1.0–3.0	Level A	Level B	Level B		Yes	(See ropinirole) Drug-specific: skin reactions
Cabergoline	Not FDA-approved for RLS	Level A	Level B	Level A		Yes	(See ropinirole) Drug-specific: cardiac valvulopathy
Levodopa	Not FDA-approved for RLS	Level C	Level C	Level C		Yes	Nausea
Gabapentin enacarbil	600, 600	Level A	Level U	Level A	Global mood: Level A	Unknown[c]	Somnolence, dizziness
Pregabalin	Not FDA-approved for RLS	Level B	Level B	Level B	Level U	No	Unsteadiness, somnolence
Oral iron[d]	Not FDA-approved for RLS	Level B				Unknown	Constipation, nausea
Ferric carboxymaltose	Not FDA-approved for RLS	Level B	Level U	Level U		Unknown	IV iron is associated with potentially life-
Iron sucrose	Not FDA-approved	Level U		Level U		Unknown	

	for RLS						threatening allergic reactions
Prolonged-release oxycodone/ naloxone	Not FDA-approved for RLS (approved in European Union)	Level C (in patients who have failed other treatments)		Level C		Unknown[c]	Constipation, nausea, sedation, depression; drug withdrawal
NIRS	N/A	Level C				Unknown	
Pneumatic compression	N/A	Level B				Unknown	
rTMS	N/A	Level C				Unknown[c]	
Vibratory stimulation	N/A	Level C Against		Level C		No	
tDCS	N/A	Level C Against				Unknown	

Abbreviations: AEs = adverse events; FDA = US Food and Drug Administration; NA = not applicable; NIRS = near-infrared spectroscopy; PLMI = Periodic Limb Movement Index; RLS = restless legs syndrome; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.

[a]Level of evidence cited is the highest level of evidence identified for at least one subjective sleep rating; subjective sleep ratings are considered individually in the guideline text, with sometimes differing levels of evidence by measure. Please refer to full guideline for details on different subjective measures.

[b]Augmentation marked as yes if present in >2.4% at any time point in available studies (many of which are Class IV open-label long-term follow-up); the 2.4% cutoff was determined by averaging placebo augmentation responses from 3 studies (see text).

[c]Augmentation listed as unknown because studies describing augmentation were 12 weeks or less in duration and thus cannot reliably inform augmentation risks (augmentation typically develops after at least 6 months of treatment).

[d]Oral studies were included only if patients had evidence of iron deficiency.

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2015–2017

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.
Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD; (Co-Vice-Chair); Eric J. Ashman, MD; Stephen Ashwal, MD; Brian Callaghan, MD; Jane Chan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Gary S. Gronseth, MD (Senior evidence-based medicine methodology expert); Jeffrey Fletcher, MD; Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jacqueline French, MD (Guideline Process Historian)

Appendix e-3. Complete search strategy

Original Search

While the staff of HealthSearch makes every effort to ensure that the information gathered is accurate and up-to-date, HealthSearch disclaims any warranties regarding the accuracy or completeness of the information or its fitness for a particular purpose. HealthSearch provides information from public sources both in electronic and print formats and does not guarantee its accuracy, completeness or reliability. The information provided is only for the use of the Client and no liability is accepted by HealthSearch to third parties.

Database: EMBASE <1980 to 2007 Week 43>

Search Strategy:

---

1 Restless Legs Syndrome/ (1976)

2 nocturnal myoclonus.tw. (81)

3 sleep myoclonus.tw. (38)

4 sleep myoclonus/ (23)

5 restless leg$1 syndrome.mp. (2038)

6 ekbom$2 syndrome.mp. (39)

7 periodic limb movement$1 of sleep.mp. (23)

8 periodic limb movement$1 in sleep.mp. (100)

9 periodic limb movement$1 during sleep.mp. (50)

10 periodic leg movement$1 of sleep.mp. (18)

11 periodic leg movement$1 in sleep.mp. (73)

12 periodic leg movement$1 during sleep.mp. (66)

13 periodic leg movement$1 while awake.mp. (3)

14 periodic limb movement$1 while awake.mp. (2)

15 rls.tw. (982)

16 (right-to-left shunt or recursive least square or reference limits or resonance light scattering or required for latent stp or record linkage system or Rayleigh light scattering technique or Refact Laboratory standard or resistant lymphoma).ab. (1456)

17 15 not 16 (880)

18 plmw.tw. (15)

19 periodic leg movement$1 during wake:.mp. (2)

20 periodic leg movement$1 of wake:.mp. (2)

21 plm.tw. (461)

22 (proteolytic enzyme plasmin or phospholemman or polariz$5 light microscop$1 or permeation liquid membrane or plums or pseudoknot local motif or post launch monitoring or plasmepsin or protein-like material or probe-level model or posturo-locomotion-manual or Png-Lv-Mixture or preop lymphatic mapping or permeation liquid membrane$1).ab. (863)

23 21 not 22 (338)

24 or/1-14,17-20,23 (2737)

25 Clonidine/ or clonidine.mp. (27402)

26 exp benzodiazepine derivative/ (91367)

27 (benzodiazepine$1 or clonazepam or temazepam or flurazepam or diazepam or oxazepam).mp. (85288)

28 Zolpidem/ (2796)

29 Zaleplon/ (670)

30 Zopiclone/ (1907)

31 Anticonvulsive Agent/ (28923)

32 Valproate Semisodium/ (2685)

33 Valproic Acid/ (25372)

34 Carbamazepine/ (32083)

35 Gabapentin/ (9692)

36 Etiracetam/ (2497)

37 Levodopa/ (19799)

38 exp Dopamine Receptor Stimulating Agent/ (93231)

39 Carbidopa Plus Levodopa/ (2653)

40 (Zolpidem or Zaleplon or Zopiclone or Anticonvulsant$1 or depakote or valproate or Carbamazepine or oxycarbamezepine or gabapentin or levetiracetam or levodopa or l dopa or dopamine agonist$1 or sinemet).mp. (81526)

41 Pramipexole/ (2128)

42 Ropinirole/ (1775)

43 Rotigotine/ (376)

44 Apomorphine/ (11346)

45 Lisuride/ (2127)

46 Terguride/ (332)

47 Piribedil/ (847)

48 (Pramipexole or Ropinirole or Rotigotine or Apomorphine or Lisuride or Terguride or Piribedil).mp. (16659)

49 Pergolide/ (2930)

50 Cabergoline/ (1875)

51 Bromocriptine/ (13453)

52 Opiate/ (27708)

53 Oxycodone/ (4157)

54 Dextropropoxyphene/ (4178)

55 (Pergolide or Cabergoline or Bromocriptine or Opiate$1 or opioid$1 or Oxycodone or propoxyphene).mp. (91500)

56 Methadone/ (12704)

57 Tramadol/ (5560)

58 Hydrocodone/ (1388)

59 Baclofen/ (8580)

60 Folic Acid/ (17833)

61 Sclerotherapy/ (4224)

62 Iron/ (41607)

63 antidepressant agent/ or serotonin uptake inhibitor/ or citalopram/ or escitalopram/ or fluoxetine/ or paroxetine/ or sertraline/ or trazodone/ (67181)

64 Venlafaxine/ (7626)

65 Amfebutamone/ (7058)

66 (Methadone or Tramadol or Hydrocodone or Baclofen or Folic Acid or Sclerotherapy or Iron or ssri$1 or antidepressant$1 or citalopram or escitalopram or fluoxetine or paroxetine or sertraline or trazodone or Venlafaxine or bupropion).mp. (219017)

67 exp exercise/ (78893)

68 Ferrous Sulfate/ (3482)

69 transcutaneous nerve stimulation/ (2516)

70 leg compression/ (1263)

71 Alpha Tocopherol/ (30800)

72 (exercise or transcutaneous electric$2 nerve stimulation or leg compression or vitamin E).mp. (146199)

73 or/25-72 (659296)

74 and/24,73 (1412)

75 longitudinal study/ or prospective study/ or retrospective study/ or case control study/ or clinical trial/ or controlled clinical trial/ or randomized controlled trial/ (633463)

76 cohort analysis/ (45090)

77 case study/ (5141)

78 n=1:.ab. (39918)

79 and/77-78 (14)

80 "review"/ or meta analysis/ or "systematic review"/ (867011)

81 (metanalys?s or meta analys?s or metaanalys?s or review: or cohort: or case series or case control: or random:).mp. (1664487)

82 or/75-76,79-81 (1945690)

83 and/74,82 (704)

84 limit 83 to human (695)

85 limit 74 to (human and "treatment (2 or more terms min difference)") (232)

86 limit 74 to (human and (article or "review")) (995)

87 or/84-86 (1094)

88 limit 87 to (human and (book or conference paper or editorial or erratum or letter or note or proceeding or report or short survey)) (93)

89 87 not 88 (1001)

Updated search

1. **Clinical Questions**
   Please note that the current clinical questions were modified slightly. The original clinical questions can be found in the project plan, attached to the updated lit search request email.

   1) What are safe and effective therapies, including both medication and non-medication approaches, for the symptoms and clinical consequences (disturbed sleep, PLMS, depression/anxiety, and quality of life) of restless legs syndrome in non-cognitively impaired adults?

2. **Dates:** March 2013 to present

3. **Databases to search:** PubMed, Web of Science, EMBASE, Cochrane

4. **Inclusion and Exclusion Criteria/ Filters**

   a) Languages: All
   b) Study population
      a. Human studies: Include
      b. Animal Studies: Exclude
      c. Children: Exclude
   c) Additional diseases to include: None
   d) Interventions to be:
      i) Included: Pharmacologic, surgical, injection, alternative
      ii) Excluded: None
   e) Outcomes to be:
      i) Included: None
      ii) Excluded: None
   f) Types of studies to be:
      i) Included: RCT, Cohort, Case Control,
      ii) Excluded: Review papers, meta-analyses, case-reports
   g) Standard exclusion criteria:
      i) Not relevant to the clinical question
      ii) Unrelated disease
      iii) Outside of study population
      iii) Articles not peer reviewed

5. Keywords

a) Key Text words and Index words for the condition or closely related conditions, if appropriate (linked by the word "OR"):
Restless Legs Syndrome
Nocturnal Myoclonus Syndrome
Willis-Ekbom Syndrome
Wittmaack Ekbom Syndrome

b) Key Text words and Index words for the intervention
Data on each of the major therapeutic approaches for primary RLS will be addressed in turn: dopamine agonists, alpha two delta α2δ ligands agents, levodopa, iron treatments, opioids, miscellaneous treatments, followed by therapeutic trials for secondary RLS.
drug therapy or pharmacologic therapy or therapy or medication therapy or medication

Opiods
levodopa
Clonidine/ or clonidine
benzodiazepine
clonazepam
temazepam
zolpidem
flurazepam
diazepam
triazolam
oxazepam
zaleplon
zoplicone
Anticonvulsants
valerates or valproic acid or depakote or valproate
oxycarbamazepine or Carbamazepine
dihydroxyphenylalanine or levodopa
dopamine agents or agonists
dihydroxyphenylalanine/ or Apomorphine
Ergolines or lisuride
piperazines or piribedil
sinemet or pramipexole or ropinirole or rotigotine or Apomorphine or lisuride or terguride or piribedil
Pergolide or l-dopa
Bromocriptine
Analgesics, Opioid
Oxycodone
Propoxyphene
cabergoline or Bromocriptine or opioids
Propoxyphene
Methadone
Tramadol
Hydrocodone
Baclofen
Iron
Folic Acid
Sclerotherapy
serotonin uptake inhibitors
Sclerosing Solutions/ (3734)
Antidepressive Agents/ (23214)
exercise/ or exercise therapy/ (56565)
Exertion/ (48646)
electric stimulation therapy/ or transcutaneous electric nerve stimulation
leg compression
Vitamin E

Appendix e-4. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:
a. concealed allocation
b. primary outcome(s) clearly defined
c. exclusion/inclusion criteria clearly defined
d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.

Class II

A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV

Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.
*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e.5. Classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the CI is > 2).

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews, and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. The AAN provides this information on an "as is" basis and makes no warranty, expressed or implied, regarding the information. The AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. The AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[e18]

E-REFERENCES

e1. Allen RP, Picchietti DL, Garcia-Borreguero D, et al.; for the International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. Sleep Med 2014;15:860–873.
e2. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–1292.
e3. Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996;47:1435–1441.
e4. Zucconi M, Ferri R, Allen R, et al.; for the International Restless Legs Syndrome Study Group. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Med 2006;7:175–183.
e5. Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. Sleep 2009;32:772–778.
e6. Hornyak M. Depressive disorders in restless legs syndrome: epidemiology, pathophysiology and management. CNS Drugs 2010;24:89–98.
e7. Reinhold T, Müller-Riemenschneider F, Willich SN, Brüggenjürgen B. Economic and human costs of restless legs syndrome. PharmacoEconomics 2009;27:267–279.
e8. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Mov Disord 2011;26:114–120.
e9. Walters AS, LeBrocq C, Dhar A, et al.; for the International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121–132.
e10. Allen RP. Minimal clinically significant change for the International Restless Legs Syndrome Study Group rating scale in clinical trials is a score of 3. Sleep Med 2013;14:1229.
e11. Kohnen R, Oertel WH, Stiany-Kolster K, Benes H, Trenkwalder C. Severity rating of restless legs syndrome: validation of the RLS-6 scales. Sleep 2004;27(Suppl):A304.
e12. Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. Sleep Med Rev 2010;14:339–346.
e13. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J; for the International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101–119.
e14. Garcia-Borreguero D, Allen RP, Benes H, et al. Augmentation as a treatment complication of restless legs syndrome: concept and management. Mov Disord 2007;22 Suppl 18:S476–S484.
e15. Hőgl B, Garcia-Borreguero D, Trenkwalder C, et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. Sleep Med 2011;12:351–360.
e16. Garcia-Borreguero D, Hőgl B, Ferini-Strambi L, et al. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis-Ekbom disease): results from a prospective, multicenter study over 66 weeks. Mov Disord 2012;27:277–283.

e17. Hening WA, Allen RP, Ondo WG, et al.; for the SP792 Study Group. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010;25:1675–1683.
e18. American Academy of Neurology. *Clinical Practice Guideline Process Manual,* 2004 ed. St Paul, MN: The American Academy of Neurology; 2004:1–57.
e19. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY; for the TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc 2006;81:17–27.
e20. Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep 2004;27:907–914.
e21. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al.; for the Therapy with Ropinirole; Efficacy and Tolerability in RLS 1 Study Group. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004;75:92–97.
e22. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K; for the TREAT RLS 2 (Therapy with Ropinirole: Efficacy And Tolerability in RLS 2) Study Group. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord 2004;19:1414–1423.
e23. Kushida CA, Geyer J,Tolson JM, Asgharian A. Patient- and physician-rated measures demonstrate the effectiveness of ropinirole in the treatment of restless legs syndrome. Clin Neuropharmacol 2008;31:281–286.
e24. Benes H, Mattern W, Peglau I, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. J Neurol 2011;258:1046–1054.
e25. Giorgi L, Asgharian A, Hunter B. Ropinirole in patients with restless legs syndrome and baseline IRLS total scores ≥ 24: efficacy and tolerability in a 26-week, double-blind, parallel-group, placebo-controlled study followed by a 40-week open-label extension. Clin Ther 2013;35:1321–1336.
e26. RRL106721. GSK Clinical Study Registry [database online]. A multicenter 3:1-randomized placebo-controlled double-blind Phase IIIb study on the effects of Ropinirole on mood/(subclinical) depression in the therapy of patients with moderate to severe idiopathic RLS in Germany; 2009. http://www.gsk-clinicalstudyregister.com/study/RRL106721#ps. Updated May 31, 2012.
e27. Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006;67:1034–1039.
e28. Ma JF, Wan Q, Hu XY, et al. Efficacy and safety of pramipexole in chinese patients with restless legs syndrome: results from a multi-center, randomized, double-blind, placebo-controlled trial. Sleep Med 2012;13:58–63.
e29. Zhang J, Liu B, Zheng Y, Chu T, Yang Z. Pramipexole for Chinese people with primary restless legs syndrome: a 12-week multicenter, randomized, double-blind study. Sleep Med 2015;16:181–185.
e30. Ferini-Strambi L, Aarskog D, Partinen M, et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. Sleep Med 2008;9:874–881.
e31. Partinen M, Hirvonen K, Jama L, et al. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: a polysomnographic dose-finding study—the PRELUDE study. Sleep Med 2006;7:407–417.

e32. Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al.; for the Pramipexole RLS Study Group. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord 2007;22:213–219.
e33. Jama L, Hirvonen K, Partinen M, et al. A dose-ranging study of pramipexole for the symptomatic treatment of restless legs syndrome: polysomnographic evaluation of periodic leg movements and sleep disturbance. Sleep Med 2009;10:630–636.
e34. Montagna P, Hornyak M, Ulfberg J, et al. Randomized trial of pramipexole for patients with restless legs syndrome (RLS) and RLS-related impairment of mood. Sleep Med 2011;12:34–40.
e35. Allen RP, Chen C, Garcia-Borreguero D, et al. Pregabalin versus pramipexole for restless legs syndrome. N Engl J Med 2014;370:621–631.
e36. Garcia-Borreguero D, Patrick J, DuBrava S, et al. Pregabalin versus pramipexole: effects on sleep disturbance in restless legs syndrome. Sleep 2014;37:635–643.
e37. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med 2004;5:9–14.
e38. Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med 2012;13:1280–1285.
e39. Montplaisir J, Fantini ML, Desautels A, Michaud M, Petit D, Filipini D. Long-term treatment with pramipexole in restless legs syndrome. Eur J Neurol 2006;13:1306–1311.
e40. Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011;12:440–444.
e41. Lee CS, Lee SD, Kang SH, Park HY, Yoon IY. Comparison of the efficacies of oral iron and pramipexole for the treatment of restless legs syndrome patients with low serum ferritin. Eur J Neurol 2014;21:260–266.
e42. Stiasny-Kolster K, Kohnen R, Schollmayer E, Mőller JC, Oertel WH; for the Rotigotine Sp 666 Study Group. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. Mov Disord 2004;19:1432–1438.
e43. Oertel WH, Benes H, Garcia-Borreguero D, et al. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. Sleep Med 2010;11:848–856.
e44. Inoue Y, Shimizu T, Hirata K, et al.; for Rotigotine Trial Group. Efficacy and safety of rotigotine in Japanese patients with restless legs syndrome: a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group study. Sleep Med 2013;14:1085–1091.
e45. Trenkwalder C, Benes H, Poewe W, et al.; for the SP790 Study Group. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2008;7:595–604.
e46. Oertel W, Trenkwalder C, Benes H, et al.; for the SP710 study group. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol 2011;10:710–720.
e47. Stiasny-Kolster K, Benes H, Peglau I, et al. Effective cabergoline treatment in idiopathic restless legs syndrome. Neurology 2004;63:2272–2279.
e48. Oertel WH, Benes H, Bodenschatz R, et al. Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). Neurology 2006;67:1040–1046.

e49. Trenkwalder C, Benes H, Grote L, et al.; for the CALDIR Study Group. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord 2007;22:696–703.
e50. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep 1999;22:1073–1081.
e51. Trenkwalder C, Stiasny K, Pollmächer T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. Sleep 1995;18:681–688.
e52. Brodeur C, Montplaisir J, Godbout R, Marinier R. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. Neurology 1988;38:1845–1848.
e53. Eisensehr I, Ehrenberg BL, Rogge Solti S, Noachtar S. Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid. J Neurol 2004;251:579–583.
e54. Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. Clin Neuropharmacol 1987;10:69–79.
e55. Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. Neurology 1999;52:285–290.
e56. Staedt J, Wassmuth F, Ziemann U, Hajak G, Rüuther E, Stoppe G. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa. J Neural Transm (Vienna) 1997;104:461–468.
e57. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996;19:205–213.
e58. Hőgl B, Garcia-Borreguero D, Kohnen R, et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. J Neurol 2010;257:230–237.
e59. Trenkwalder C, Collado Seidel V, Kazenwadel J, et al. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? Mov Disord 2003;18:1184–1189.
e60. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002;59:1573–1579.
e61. Bogan RK, Bornemann MA, Kushida CA, Trân PV, Barrett RW; for the XP060 Study Group. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. Mayo Clin Proc 2010;85:512–521.
e62. Kushida CA, Walters AS, Becker P, et al.; for the XP021 Study Group. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. Sleep 2009;32:159–168.
e63. Walters AS, Ondo WG, Kushida CA, et al.; for the XP045 Study Group. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol 2009;32:311–320.
e64. Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, Barrett RW; for the XP052 Study Group. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. Neurology 2009;72:439–446.

e65. Lee DO, Ziman RB, Perkins AT, Poceta JS, Walters AS, Barrett RW; for the XP053 Study Group. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J Clin Sleep Med 2011;7:282–292.
e66. Inoue Y, Hirata K, Uchimura N, Kuroda K, Hattori N, Takeuchi M. Gabapentin enacarbil in Japanese patients with restless legs syndrome: a 12-week, randomized, double-blind, placebo-controlled, parallel-group study. Curr Med Res Opin 2013;29:13–21.
e67. Winkelman JW, Bogan RK, Schmidt MH, Hudson JD, DeRossett SE, Hill-Zabala CE. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. Mov Disord 2011;26:2065–2072.
e68. Lal R, Ellenbogen A, Chen D, et al. A randomized, double-blind, placebo-controlled, dose-response study to assess the pharmacokinetics, efficacy, and safety of gabapentin enacarbil in subjects with restless legs syndrome. Clin Neuropharmacol 2012;35:165–173.
e69. Allen R, Chen C, Soaita A, et al. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. Sleep Med 2010;11:512–519.
e70. Garcia-Borreguero D, Larrosa O, Williams AM, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. Neurology 2010;74:1897–1904.
e71. Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. Sleep Med 2005;6:301–305.
e72. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. Sleep Med 2009;10:973–975.
e73. Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. Mov Disord 2009;24:1445–1452.
e74. Allen RP, Adler CH, Du W, Butcher A, Bregman DB, Earley CJ. Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: a multi-centred, placebo-controlled preliminary clinical trial. Sleep Med 2011;12:906–913.
e75. Earley CJ, Horská A, Mohamed MA, Barker PB, Beard JL, Allen RP. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. Sleep Med 2009;10:206–211.
e76. Trenkwalder C, Beneš H, Grote L, et al.; for the RELOXYN Study Group. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol 2013;12:1141–1150.
e77. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep 1993;16:327–332.
e78. Montagna P, Sassoli de Bianchi L, Zucconi M, Cirignotta F, Lugaresi E. Clonazepam and vibration in restless legs syndrome. Acta Neurol Scand 1984;69:428–430.
e79. Boghen D, Lamothe L, Elie R, Godbout R, Montplaisir J. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. Can J Neurol Sci 1986;13:245–247.
e80. Bayard M, Bailey B, Acharya D, et al. Bupropion and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med 2011;24:422–428.

e81. Wagner ML, Walters AS, Coleman RG, Hening WA, Grasing K, Chokroverty S. Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. Sleep 1996;19:52–58.
e82. Nahab FB, Peckham EL, Hallett M. Double-blind, placebo-controlled, pilot trial of botulinum toxin A in restless legs syndrome. Neurology 2008;71:950–951.
e83. Weinstock LB, Zeiss S. Rifaximin antibiotic treatment for restless legs syndrome: a double-blind, placebo-controlled study. Sleep Biolog Rhythms 2012;10:145–153.
e84. Telstad W, Sørensen O, Larsen S, Lillevold PE, Stensrud P, Nyberg-Hansen R. Treatment of the restless legs syndrome with carbamazepine: a double blind study. Br Med J (Clin Res Ed) 1984;288:444–446.
e85. Cuellar NG, Ratcliffe SJ. Does valerian improve sleepiness and symptom severity in people with restless legs syndrome? Altern Ther Health Med 2009;15:22–28.
e86. Rahimdel AG, Ayatollahi P, Zeinali A, Mehrabanian N, Mellat-Ardekani A. The effect of selenium administration on restless leg syndrome treatment. Iran Red Crescent Med J 2012;14:14–19.
e87. Mitchell UH, Myrer JW, Johnson AW, Hilton SC. Restless legs syndrome and near-infrared light: An alternative treatment option. Physiother Theory Pract 2011;27:345–351.
e88. Mitchell UH, Johnson AW, Myrer JW. Comparison of two infrared devices in their effectiveness in reducing symptoms associated with RLS. Physiother Theory Pract 2011;27:352–359.
e89. Lettieri CJ, Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. Chest 2009;135:74–80.
e90. Koo YS, Kim SM, Lee C, et al. Transcranial direct current stimulation on primary sensorimotor area has no effect in patients with drug-naïve restless legs syndrome: a proof-of-concept clinical trial. Sleep Med 2015;16:280–287.
e91. Altunrende B, Yildiz S, Cevik A, Yildiz N. Repetitive transcranial magnetic stimulation in restless legs syndrome: preliminary results. Neurol Sci 2014;35:1083–1088.
e92. Burbank F, Buchfuhrer MJ, Kopjar B. Sleep improvement for restless legs syndrome patients. Part I: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms. J Parkinsonism Restless Legs Syndr 2013;3:1–10.
e93. Burbank F, Buchfuhrer M, Kopjar B. Improving sleep for patients with restless legs syndrome. Part II: meta-analysis of vibration therapy and drugs approved by the FDA for treatment of restless legs syndrome. J Parkinsonism Restless Legs Syndr 2013;3:11–22.
e94. Pan W, Wang M, Li M, Wang Q, Kwak S, Jiang W, Yamamoto Y. Actigraph evaluation of acupuncture for treating restless legs syndrome. Evid Based Complement Alternat Med 2015;2015:343201. doi: 10.1155/2015/343201. Epub 2015 Feb 11.
e95. Giannaki CD, Sakkas GK, Karatzaferi C, et al. Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. BMC Nephrol 2013;14:194.
e96. Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. Sleep 1996;19:214–218.
e97. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. Am J Kidney Dis 2001;38:104–108.

e98. Razazian N, Azimi H, Heidarnejadian J, Afshari D, Ghadami MR. Gabapentin versus levodopa-c for the treatment of restless legs syndrome in hemodialysis patients: a randomized clinical trial. Saudi J Kidney Dis Transpl 2015;26:271–278.
e99. Sagheb MM, Dormanesh B, Fallahzadeh MK, et al. Efficacy of vitamins C, E, and their combination for treatment of restless legs syndrome in hemodialysis patients: a randomized, double-blind, placebo-controlled trial. Sleep Med 2012;13:542–545.
e100. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. Am J Kidney Dis 2004;43:663–670.
e101. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, et al. A single-blind randomized controlled trial to evaluate the effect of 6 months of progressive aerobic exercise training in patients with uraemic restless legs syndrome. Nephrol Dial Transplant 2013;28:2834–2840.
e102. Sakkas GK, Hadjigeorgiou GM, Karatzaferi C, et al. Intradialytic aerobic exercise training ameliorates symptoms of restless legs syndrome and improves functional capacity in patients on hemodialysis: a pilot study. ASAIO J 2008;54:185–190.
e103. Mortazavi M, Vahdatpour B, Ghasempour A, et al. Aerobic exercise improves signs of restless leg syndrome in end stage renal disease patients suffering chronic hemodialysis. ScientificWorldJournal 2013. Epub 2013 Nov 6.
e104. Tzonova D, Larrosa O, Calvo E, et al. Breakthrough symptoms during the daytime in patients with restless legs syndrome (Willis-Ekbom disease). Sleep Med 2012;13:151–155.
e105. Godau J, Spinnler N, Wevers AK, Trenkwalder C, Berg D. Poor effect of guideline based treatment of restless legs syndrome in clinical practice. J Neurol Neurosurg Psychiatry 2010;81:1390–1395.
e106. Mackie SE, Winkelman JW. Long-term treatment of RLS: An approach to management of worsening symptoms, loss of efficacy, and augmentation. CNS Drugs 2015;29:351–357.