R E V I E W

Treatment of Restless Legs Syndrome: Evidence-Based Review and Implications for Clinical Practice (Revised 2017)[§]

Juliane Winkelmann, MD,[1,2,3][†][*] Richard P. Allen, PhD,[4,5] Birgit Högl, MD,[6] Yuichi Inoue, MD,[7,8] Wolfgang Oertel, MD,[9] Aaro V. Salminen, PhD,[1,9] John W. Winkelman, MD,[10,11] Claudia Trenkwalder, MD,[12,13] and Cristina Sampaio, MD[14][‡]

[1]Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany
[2]Department of Neurology and Department of Human Genetics, Klinikum rechts der Isar, Technical University, Munich, Germany
[3]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[4]Sleep Disorders Center, Johns Hopkins Bayview Medical Center, Baltimore, Maryland, USA
[5]Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA
[6]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria
[7]Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan
[8]Department of Somnology, Tokyo Medical University, Tokyo, Japan
[9]Department of Neurology, Philipps-Universität Marburg, Marburg, Germany
[10]Harvard Medical School, Boston, Massachusetts, USA
[11]Departments of Psychiatry and Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA
[12]Department of Neurosurgery, University Medical Center, Goettingen, Germany
[13]Paracelsus-Elena Hospital, Kassel, Germany
[14]CHDI Foundation, Princeton, Princeton, NJ, USA, and the Instituto de Medicina Molecular, University of Lisbon, Lisbon, Portugal

ABSTRACT: The objective of the current review was to update the previous evidence-based medicine review of treatments for restless legs syndrome published in 2008. All randomized, controlled trials (level I) with a high quality score published between January 2007 and January 2017 were reviewed. Forty new studies qualified for efficacy review. Pregabalin, gabapentin enacarbil, and oxycodone/naloxone, which did not appear in the previous review, have accrued data to be considered efficacious. Likewise, new data enable the modification of the level of efficacy for rotigotine from likely efficacious to efficacious. Intravenous ferric carboxymaltose and pneumatic compression devices are considered likely efficacious in idiopathic restless legs syndrome. Bupropion and clonidine were reviewed, but the lack of data determined a rating of insufficient evidence for efficacy. The following interventions continue to be considered efficacious as in 2008: levodopa, ropinirole, pramipexole, cabergoline, pergolide, and gabapentin. Bromocriptine, oxycodone, carbamazepine, and valproic acid are considered likely efficacious. Oral iron is non-efficacious in iron-sufficient subjects, but its benefit for patients with low peripheral iron status has not been adequately evaluated. Restless legs syndrome augmentation has been identified as a significant long-term treatment complication for pramipexole more than pregabalin and possibly for all dopaminergic agents more than α2δ ligands. Therefore, special monitoring for augmentation is required for all dopaminergic medications as well as tramadol. Other drugs also require special safety monitoring: cabergoline, pergolide, oxycodone, methadone, tramadol, carbamazepine, and valproic acid. Finally, we also highlighted gaps and needs for future clinical research and studies of restless legs syndrome. © 2018 International Parkinson and Movement Disorder Society

Key Words: restless legs syndrome (RLS); evidence-based medicine; guidelines; MDS recommendations; therapy; treatment; augmentation

---

For almost 25 years patients with restless legs syndrome (RLS) have been examined in controlled trials. It is evident that the most common treatment side effect encountered in RLS, "augmentation," is related to dopaminergic treatment. Augmentation emerges as an adverse effect with the longer-term use of these medications. Dopaminergic drugs were approved for RLS treatment between 2004 and 2008. Nondopaminergic substances, such as α2δ ligands and opioids, have been investigated in recent research programs. They appear to be as effective as dopaminergic treatment, can be used according to clinical needs, and provide alternative initial treatments for RLS. At this time, the use of these drugs is somewhat less frequent worldwide than dopaminergic medications, as only gabapentin enacarbil has received approval for the treatment of RLS in the United States and Japan. Clinical experience with very long-term use of nondopaminergic drugs in RLS has generally not been published. However, some agents have been evaluated in trials lasting 1 year and, unlike dopaminergic medications, have not been shown to cause augmentation. Gaps remain between current treatment trials and clinical practice, as treatment studies have failed to address certain issues, such as the use of combinations of drugs and divided doses over the day, as well as the optimal management of augmentation under dopaminergic treatment. Independently, many case studies of various interventions have been reported. Still, there is no new class of pharmacological substance available for patients, and aside from iron replacement, only symptomatic treatment strategies are used.

To assess the current state of treatment for RLS and its implications for clinical practice and to ascertain which gaps in the knowledge need to be bridged, it was necessary to perform an update of the previous International Parkinson and Movement Disorder Society (MDS) evidence-based review of the literature. Consequently, the MDS commissioned a task force to perform an evidence-based review of current treatment strategies in RLS.[1] The members of this MDS-appointed task force, who are also the authors of the present article, are movement disorder and/or sleep specialists with extensive experience in treating RLS from Europe, Asia, and North America.

Strategic Options

In this review, the task force evaluates the therapeutic efficacy of each drug, and reports on implications for clinical practice and research using the methodology standardized by the MDS Committee for Evidence-Based Medicine and used in the previous review (2008).[2] The task force has also chosen to include a section on augmentation but decided not to address the effect of medication on associated conditions such as depression, sleep, and periodic leg movements. Single treatments are reviewed independently rather than as part of a management strategy. As in the previous review, combination therapies have not yet been investigated in level I RLS trials and therefore could not be reviewed. The task force's recommendations for practical use are given in the Implications for Clinical Practice sections after the conclusions for each drug or class of drugs. These recommendations cannot take into account country-specific regulations, and therefore the task force is only able to provide a general summary, including recommendations for clinical practice, but does not provide guidelines for RLS treatment.

Efficacy was determined through the evaluation of level I studies; lower-quality studies were not reviewed (see Table 1 for levels of evidence). All conclusions were agreed on by the members of the task force. Definitions for specific recommendations are given in Table 2. This evidence-based review does not include quantitative summaries (no meta-analyses were conducted) of the different data sets. The qualitative approach, such as the one undertaken here, is an important contribution to highlight the evidence available and facilitates the inclusion of some subjectivity and expert opinion. This is explicitly limited to the 2 sections within each paragraph titled: (1) Implications for Clinical Practice and (2) Implications for Clinical Research.

Methodological limitations of this review have been identified. Although publications in some non-English languages were not reviewed, the literature search included English and several non-English languages (Italian, French, German, and Portuguese). This language bias may have inflated positive results.[3-5] Another methodological limitation is caused by the primary sources of evidence being electronic databases, which provide incomplete lists of articles.[6]

Aims and Goals

The aims of this evidence-based review were to evaluate the evidence on therapeutic interventions for RLS. The current review includes articles published between January 2007 until January 2017. The clinical efficacy, safety, and RLS-specific safety problems of these interventions are evaluated. In addition, the implications of this evidence for clinical practice are considered.

Similarly to the previous review, the specific goals of the current review were to:

1. Review the literature and identify the clinical evidence that supports specific pharmacological and nonpharmacological treatments for RLS;
2. Determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice;

TABLE 1. Levels of evidence

Level of evidence	Definition
Level I studies	Randomized, controlled trials
Level II studies	Controlled clinical trials or observational controlled studies such as cohort or case-control studies
Level III studies	Noncontrolled studies like case series

Adapted from the American Academy of Neurology classifications of evidence (appendix E-1, the Neurology web ite at www.neurology.org).

3. Identify where specific evidence is lacking, so future research efforts may be directed toward addressing these specific areas of need; and

4. Separately identify the RLS-specific side effect, which is augmentation.

Methods

The methodological approach taken was that defined by the MDS Committee of Evidence-Based Medicine with specific adjustments for RLS (see supplementary material for details of methods and Supplementary Evidence Tables e-1 and e-2 for an overview of studies reviewed) and included a literature search of articles published between January 2007 and January 2017.

Evidence-Based Conclusions

Following a review of the literature, the EBM task force members determined the quality of evidence provided by the studies (see table 3) and reached a consensus on the efficacy and safety of each therapeutic intervention (Table 4), as well as implications for clinical practice and research. For those therapeutic agents for which data were lacking, the task force was unable to make a relevant recommendation pertaining to efficacy. Where no evidence was available, this was clearly stated. The criteria for specific recommendations are summarized in Table 2. No treatment recommendations according to the quality of evidence were made.

Results

General Remarks

All new studies included in the current review include patients with moderate to severe RLS symptoms and normal ferritin levels. The conclusions are presented and compared with the previous treatment guidelines[2] in Table 4, with new conclusions appearing in bold typeface.

TABLE 2. Definitions for specific recommendations

Efficacy conclusions	Definition	Required evidence
Efficacious	Evidence shows that the intervention has a positive effect on studied outcomes	Supported by data from at least 1 high-quality (score > 75%) randomized, controlled trial without conflicting level I data
Likely efficacious	Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes	Supported by data from any level I trial without conflicting level I data
Investigational	Evidence suggests that the intervention does not have a positive effect on outcomes	Supported by data from any level I trial without conflicting level I data
Insufficient evidence	Evidence shows that the intervention does not have a positive effect on studied outcomes	Supported by data from at least I high-quality (score > 75%) randomized, controlled trial without conflicting level I data
Nonefficacious	There is not enough evidence either for or against efficacy of the intervention in the treatment of restless legs syndrome	All the circumstances not covered by the previous statements

Safety conclusions
Acceptable risk without special monitoring
Acceptable risk, with special monitoring
Unacceptable risk
Insufficient evidence to make conclusions on the safety of the intervention

Implications for clinical practice	
Clinically useful	For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit
Possibly useful	For a given situation, evidence available suggests but is insufficient to conclude that the intervention provides clinical benefit
Investigational	Available evidence is insufficient to support the use of the intervention in clinical practice, but further study is warranted
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit
Efficacy unlikely	Evidence suggests that the intervention does not have a positive effect on studied outcomes; supported by data from any level I trial without conflicting level I data

TABLE 3. Rating scale for quality of evidence

Rating scale: efficacy	
Results	
Item 1	Is an estimate of the treatment effect given?
Item 2	Is the reported treatment effect of clinical importance?
Item 3	Is the estimate of treatment effect sufficiently precise?
Validity: selection	
Item 4	Was the spectrum of patients well defined?
Item 5	Was the diagnosis of RLS well defined?
Item 6	Were the eligibility criteria used suitable for the study?
Measurement	
Item 7	Was assignment to treatments stated to be random?
Item 8	If yes, was the method of randomization explained?
Item 9	Were all patients accounted for after randomization?
Item 10	Were losses to follow-up low (<10%)?
Item 11	Were the treatment groups similar in important factors at the start of the trial?
Item 12	Were all patients otherwise treated alike?
Item 13	Were patients, health care workers, and investigators blinded to treatment?
Item 14	Was the assessment of outcome blind?
Item 15	Was the occurrence of side effects explicitly looked for?
Item 16	If yes, were estimates of their frequency and severity given?
Statistical analysis	
Item 17	Was the main analysis on "intention to treat"?
Item 18	If no, was a sensitivity analysis performed?
Item 19	Were additional clinically relevant factors allowed for?
Item 20	Were appropriate statistical methods used?
Item 21	If subgroup analyses were done, were they explicitly presented as such?
Utility	
Item 22	Do the results help me choose a treatment?
Scoring criteria	
Yes	2
Unclear/possibly	1
No	0
Not applicable	N/A
Final scores	
Total	Total points that the paper received
Score 1	Percentage of the points from the maximum score from all items
Score 2	Percentage of the points from the maximum score from the items applicable to this paper

Dopaminergic Agents
Levodopa: No New Conclusions

Since 2007 no further studies have been published that qualify for inclusion in this review. Previously, 9 randomized, controlled trials[7-15] (level I) qualified for inclusion. Of these, only 2[14,15] meet the current inclusion criteria (see supplementary material).

Conclusions. Levodopa is considered efficacious for the treatment of idiopathic RLS as well as in patients with RLS undergoing hemodialysis.

Safety. Levodopa is considered to pose an acceptable risk but requires special monitoring for augmentation.

Implications for Clinical Practice. Levodopa is considered clinically useful for RLS treatment. However, augmentation has been reported to develop at all dosages with continued daily use, but more commonly at doses ≥ 200 mg.

Implications for Clinical Research. Long-term trials of intermittent use, either as monotherapy or add-on therapy, a common context in which levodopa is used, would be valuable to determine the risk of these schedules of use of levodopa for RLS.

Nonergot-Derived Dopamine Agonists
Rotigotine: 5 New Studies[16-20];
New Conclusion: Efficacious

One randomized, controlled trial (level I) qualified for inclusion in the previous review[21]; 5 more-recent studies qualify for inclusion in the present review (see supplementary material).[16-20]

TABLE 4. Summary of recommendations (new conclusions in bold)

Intervention	Efficacy in 2008	Efficacy in 2017	Safety
Levodopa	Efficacious for the treatment of RLS	Efficacious for the treatment of idiopathic and uremic RLS	Acceptable risk with special monitoring for augmentation
Ropinirole	Efficacious for the treatment of idiopathic RLS at a dose of 0.25-4 mg	Efficacious for the treatment of idiopathic RLS at a dose of 0.78-4.6 mg	Acceptable risk with special monitoring for augmentation
Rotigotine	Likely efficacious for the treatment of RLS	**Efficacious for the treatment of idiopathic RLS at a dose of 2-3 mg**	Acceptable risk with special monitoring for local site reactions and augmentation
Pramipexole	Efficacious for the treatment of idiopathic RLS at a dose of 0.75 mg	Efficacious for the treatment of idiopathic RLS at doses of 0.25, 0.50, and 0.75 mg	Acceptable risk with special monitoring for augmentation
Cabergoline	Efficacious for the treatment of RLS	Efficacious for the treatment of RLS at a dose of 2-3 mg	Acceptable risk with cardiopulmonary monitoring for fibrosis, as well as special monitoring for augmentation; contraindicated in patients with a history of cardiac, pulmonary, or retroperitoneal fibrosis or signs of cardiac valve abnormalities
Pregabalin	N/A	**Efficacious for the treatment of RLS at a dose of 150-450 mg**	Acceptable risk without special monitoring
Gabapentin enacarbil	N/A	**Efficacious for the treatment of RLS at a dose of 1200 mg; insufficient evidence to conclude on the efficacy at a dose of 600 mg**	Acceptable risk without special monitoring
Gabapentin	Efficacious for the treatment of RLS	Efficacious for the treatment of idiopathic RLS at a dose of 800 mg and uremic RLS at a dose of 200 mg	Acceptable risk without special monitoring
Oxycodone/naloxone	N/A	**Efficacious in patients with severe treatment-resistant RLS**	Acceptable risk with special monitoring in those with addictive tendencies. Possible sleep-related respiratory problems should be monitored
Oxycodone	Likely efficacious for the relief of the symptoms of RLS in those with significant daily symptoms	Likely efficacious for the relief of the symptoms of RLS in those with significant daily symptoms	Acceptable risk with special monitoring in those with addictive tendencies. Possible sleep-related respiratory problems should be monitored
Bupropion	N/A	**Insufficient evidence to conclude on efficacy**	Insufficient evidence to conclude on safety
Clonidine	Efficacious for the treatment of RLS	**Investigational**	Insufficient evidence to conclude on safety
Oral iron preparations	Not efficacious for the treatment of iron-sufficient RLS patients; investigational in the treatment of iron-deficient RLS patients	**Insufficient evidence to conclude on efficacy**	Acceptable risk without special monitoring
Intravenous ferric carboxymaltose	N/A	**Likely efficacious for the treatment of RLS**	Acceptable risk without special monitoring
Intravenous iron sucrose	N/A	**Insufficient evidence to conclude on efficacy**	Acceptable risk without special monitoring
Intravenous high-molecular-weight iron dextran	Likely efficacious for the treatment of uremic RLS; investigational in the treatment of idiopathic RLS	Likely efficacious for the treatment of uremic RLS	Unacceptable risk
Vitamins C and E	N/A	**Likely efficacious for the treatment of uremic RLS**	Acceptable risk without special monitoring
Exercise	Investigational	**Likely efficacious for the treatment of uremic RLS**	Acceptable risk without special monitoring
Pneumatic compression devices	N/A	**Likely efficacious for the treatment of RLS**	Acceptable risk without special monitoring

Conclusions. The new level I studies reported here enable the efficacy conclusion for transdermal rotigotine to be changed from likely efficacious to efficacious at doses of 2-3 mg. There is insufficient evidence for the 1-mg dose, and 0.5 mg is considered nonefficacious.

Safety. Acceptable risk with special monitoring for local site reactions and augmentation.

Implications for Clinical Practice. There is sufficient evidence to conclude that rotigotine transdermal patch is clinically useful for the management of RLS in patients with moderate to severe clinical symptomology. Special concerns about "sleep attacks" have not been raised, whereas application-site reactions have been relatively frequent.

Implications for Clinical Research. Long-term trials with rotigotine need to be undertaken to monitor local site reactions and augmentation, and dose and treatment duration dependence need to be taken into consideration. Similarly to pramipexole and ropinirole, further study is needed exploring the biology of augmentation and possible methods to reduce the risk and severity of its occurrence.

Ropinirole: 2 New Studies[22,23]; No New Conclusions

Seven level I trials were included in the previous review.[24-30] These studies, varying in duration from 4 to 26 weeks, found ropinirole at mean doses between 0.78 and 4.6 mg to be effective in reducing RLS symptoms and improving quality of life and sleep parameters. Two more-recent studies qualify for inclusion in the current review (see supplementary material).[22,23]

Conclusions. Ropinirole (0.78 to 4.6 mg) is considered efficacious for treating RLS.

Safety. Ropinirole is considered to pose an acceptable risk, with special monitoring for augmentation. Only 1 study evaluated augmentation prospectively, reporting an incidence of 4% at 26 weeks.[23]

From the available published clinical trials, there is no evidence that the incidence of adverse reactions is lower or higher than with any other available dopamine agonist, and there are no specific concerns about hypersomnolence in RLS patients. There has been no specific monitoring for dopamine dysregulation syndrome. The majority of level I studies of ropinirole last 12 weeks, whereas the more recent long-term study included in this current review followed patients for a total of 66 weeks (26 weeks double-blind and 40 weeks open-label). This recent study[23] is also the first to prospectively evaluate the incidence of augmentation with ropinirole, finding an incidence of 4% at 26 weeks.

Implications for Clinical Practice. There is sufficient evidence to conclude that ropinirole is clinically useful for both RLS symptoms and improving sleep in patients with moderate to severe clinical symptomatology. One trial comparing ropinirole with gabapentin found that they were equally efficient in treating RLS, but this study only included 16 patients who were treated for 4 weeks.[24]

Implications for Clinical Research. Given the high rate of augmentation for ropinirole, further study is needed exploring the biology of augmentation and possible methods to reduce the risk and severity of its occurrence.

Pramipexole: 6 New Studies[31-36]; No New Conclusions

Five level I trials were included in the previous review[37-41]; these studies, varying in duration from 3 to 12 weeks, found pramipexole at doses of 0.25, 0.50, and 0.75 mg to be effective in reducing RLS symptoms and improving quality of life. Six more-recent studies qualify for inclusion in the present review,[31-34,36] including 1 comparative trial.[35] These new studies range in duration from 6 to 56 weeks (see supplementary material).

Conclusions. Pramipexole (at doses of 0.25, 0.50, and 0.75 mg) is considered efficacious for the treatment of RLS.

Safety. Acceptable risk with special monitoring for augmentation.

Implications for Clinical Practice. There is sufficient evidence to conclude that pramipexole is clinically useful for the management of RLS in patients with moderate to severe clinical symptomology. Subjective reports of sleep, general RLS severity, and depressive and anxiety symptoms improved. Special concerns about "sleep attacks" have not been raised.

Implications for Clinical Research. Given the high rate of augmentation for pramipexole, further study is needed exploring the biology of augmentation and possible methods to reduce the risk and severity of its occurrence.

Ergot-Derived Dopamine Agonists

Since the previous review, no further study with an ergot-derived dopamine agonist in RLS has been published.

Cabergoline: No New Studies; No New Conclusions

Three randomized, controlled trials (level I) were included in the earlier review,[15,42,43] but only one of

these, the abovementioned comparative study by Trenkwalder et al,[15] meets the current inclusion criteria. This study reported a statistically significant improvement in RLS symptoms with cabergoline (2-3 mg) compared with levodopa/benserazide (300/75 mg).

Conclusions. Cabergoline (2-3 mg) is considered efficacious for the treatment of RLS, but special monitoring is necessary.

Safety. Cabergoline is contraindicated in patients with a history of cardiac, pulmonary, or retroperitoneal fibrosis or signs of cardiac valve abnormalities; therefore, the task force concludes that cabergoline is considered to pose an acceptable risk, with cardiopulmonary monitoring for fibrosis as well as special monitoring for augmentation.

Implications for Clinical Practice (unchanged from previous review)[2]. There is sufficient evidence to conclude that cabergoline is efficacious for the management of RLS in patients with moderate to severe RLS including patients with daytime RLS. Sleep, and RLS severity, considerably improved. Cabergoline is the only dopamine agonist to be compared with levodopa in a large-scale controlled trial and has been shown to be superior to the latter.

It is important to note that in the United States, where the U.S. Food and Drug Administration has withdrawn the ergot-dopamine agonist pergolide from the market, cabergoline has only been approved for hyperprolactinemic disorders.

Implications for Clinical Research (unchanged from previous review)[2]. Long-term trials with cabergoline need to be undertaken with better monitoring of the potential side effects such as fibrosis (especially heart valve fibrosis), augmentation, and compulsive behaviors.

α2δ Ligands

Pregabalin
Review of Clinical Studies: 3 New Studies[35,44,45]; New Conclusion: Efficacious

Pregabalin is a new drug to appear in this review. Since the previous review, 3 randomized, controlled trials (level I), which examined the efficacy of pregabalin in more than 900 RLS patients over 6-52 weeks, have been published that qualify for inclusion.[35,44,45] No new side effects were observed compared with those already known from registration trials for the indications "seizure/epilepsy" and "neuropathic pain." The most frequently reported AEs were dizziness, somnolence, fatigue, and headache (see supplementary

material). See the Augmentation section for details on augmentation.

Conclusions. Pregabalin is efficacious for the treatment of moderate to severe idiopathic RLS when given at doses between 150 and 450 mg/day, 1-3 hours before bedtime.

Safety. Acceptable risk without special monitoring.

Implications for Clinical Practice. Pregabalin is considered clinically useful and has been shown to be noninferior to pramipexole. Given that pregabalin is metabolized renally, lower doses may be necessary in older populations, who may also experience dizziness and somnolence. Side effects may be dose dependent. Pregabalin has been shown to improve sleep architecture. There have been suggestions that pregabalin may be preferentially effective in patients who describe their sensory discomforts as pain; however, the evidence for this is lacking.

Implications for Clinical Research. Although the evidence establishes pregabalin as clinically useful, long-term studies, studies in those with renal impairment, and data on withdrawal are lacking. Further studies are also needed to determine whether low doses may be efficacious in certain patients—dose effect using regression showed the greatest efficacy at doses of ≥150 mg.

Gabapentin Enacarbil: 7 New Studies[46-52]; New Conclusion: Efficacious

Trials on gabapentin enacarbil were not available at the time of the previous review. Since 2008, 7 randomized, controlled trials (level I), which examined the efficacy of gabapentin enacarbil in RLS, have been published that qualify for inclusion.[46-52] These 7 high-quality studies,[46-52] ranging in duration from 2 to 12 weeks, indicate that gabapentin enacarbil is efficacious up to 12 weeks at a dose of 1200 mg. A high rate of dropouts compared with placebo is striking in several studies (see supplementary material).[46-49]

Conclusions. Gabapentin enacarbil is efficacious at a dose of 1200 mg. There is insufficient evidence to make a conclusion about the efficacy of the 600-mg dose, with 1 study showing efficacy at 600 mg[49] and 2 studies that did not.[46,50]

Safety. Acceptable risk without special monitoring.

Implications for Clinical Practice. There are no major safety concerns with gabapentin enacarbil. Adverse effects are fairly common and include dizziness and somnolence, which should be specifically

monitored in older patients. Side effects may be dose dependent. Gabapentin enacarbil has not been used in divided doses in the abovementioned trials. No long-term studies > 12 weeks are available, and long-term efficacy needs to be studied.

Implications for Clinical Research. The available evidence establishes the usefulness of gabapentin enacarbil in RLS over the short term and as a potential initial treatment for RLS. As with all α2δ ligands, there is a clinical suggestion that gabapentin enacarbil may be preferentially effective in patients whose RLS symptomatology is focused on sensory discomforts, and the sedative aspect of the drug might be especially helpful in those with RLS emergent primarily at sleep onset or with an additional insomnia problem. Long-term studies on both efficacy and safety are needed.

Gabapentin: No New Studies; No New Conclusions

Four level I trials were included in the previous review[14,24,53,54]; these studies varied in duration from 4 to 12 weeks. Gabapentin has been studied in comparison with other agents: a dopamine agonist[24] in the treatment of idiopathic RLS and a levodopa preparation in the treatment of patients with RLS and renal failure on dialysis.[14] In patients with normal kidney function, effective doses were within the range typically used for seizure or pain control.[54] However, much lower doses were used in the dialysis samples because gabapentin is eliminated renally.

Conclusions. Gabapentin is efficacious for the treatment of RLS at a dose of 800 mg, and at 200 mg for patients undergoing hemodialysis.

Safety. Acceptable risk without special monitoring.

Implications for Clinical Practice. Gabapentin is used off-label in RLS patients in several countries. A combination treatment of gabapentin together with other medications is used, but has not been investigated. There are no major safety concerns with gabapentin. Side effects are fairly common, and older patients may experience dizziness, somnolence, and peripheral edema. Side effects may be dose dependent. Unlike dopaminergic agents, gabapentin has been used in divided doses in trials.

Implications for Clinical Research. Although the evidence establishes the usefulness of gabapentin in RLS, there have not yet been the large multicenter studies that can provide a better estimate of the range of benefits and safety issues. There is a clinical suggestion that gabapentin may be a useful supplementary medication for those on dopaminergic therapy in RLS, and

this combination modality should be explored further. There has also been a suggestion in some reports that gabapentin may be preferentially effective in patients who describe their sensory discomforts as pain and that more severe RLS may not respond to gabapentin; however, the evidence for these limitations is not conclusive. Another issue is whether the sedative aspect of the drug might be especially helpful in those with RLS emergent primarily immediately before or during sleep.

α2δ Ligands: General Implications for Clinical Research

This group of medications is an attractive therapeutic alternative to dopaminergics, particularly for initial treatment. They have been found to have more or equivalent efficacy to therapeutic doses of the dopamine agonists, and they do not have the dopaminergic problems of augmentation, compulsive behaviors, or profound daytime sleepiness. Gabapentin has been used for many years for pain without showing any unexpected long-term complications, but similar experience is not available for RLS. The other 2 α2δ ligands, gabapentin enacarbil and pregabalin, are relatively new, so clinical experience for more than 2-4 years is limited, but so far there have been no reports of the emergence of unexpected adverse effects with longer-term use. The α2δ ligands have an advantage of improved sleep and no significant augmentation, but they are limited by the adverse effect of dizziness, which may be a problem for older patients. In addition, daytime sleepiness may be a problem. It would be useful to provide a clinical case series of long-term use of these drugs and to have long-term clinical trials comparing these with the longer-acting dopaminergic agents. Finally, in RLS patients consuming alcohol or taking other classes of drugs for comorbidity, the interaction and additive effects of anticonvulsants have to be taken into account.

Opioids
Oxycodone-Naloxone: One New Study[55]; New Conclusion: Efficacious for Treatment-Resistant RLS

One level I study in 304 subjects qualified for inclusion in the present review.[55] This was a 12-week study that sought to assess the efficacy and safety of a fixed-dose combination of prolonged-release oxycodone-naloxone (5.0/2.5 mg twice daily uptitrated to a maximum dose of 40/20 mg twice daily) in patients with severe RLS (see supplementary material).

Conclusions. Based on this high-quality level I study, oxycodone-naloxone (mean dose, 21.9 mg) is

considered efficacious in patients with severe treatment-resistant RLS.

Safety. Acceptable risk with special monitoring in those with addictive tendencies. Possible sleep-related respiratory problems should be monitored.

Implications for Clinical Practice. This high-quality study has demonstrated that oxycodone-naloxone is efficacious and well tolerated in patients with severe RLS—the mean International RLS Study Group Rating Scale (IRLS) total score at baseline was 28.6 in the above study—and in those who are resistant to treatment with other drugs.

Implications for Clinical Research. See Opioids: General Implications for Clinical Research, below.

Oxycodone: No New Studies; No New Conclusions

One level I study[56] was included in the previous review. No further studies of oxycodone alone (see above for oxycodone-naloxone) have been published, and therefore the previous conclusions remain unchanged.

Conclusions. Based on 1 controlled study,[56] oxycodone is likely efficacious for the relief of the symptoms of RLS in those with significant daily symptoms and is widely used in various countries for pain syndromes. For pain relief, oxycodone is usually prescribed in combination with other nonopioid analgesics. It is also available in an extended-release formulation. It has been subject to abuse in its immediate-release form or when the extended-release formulation is used improperly.

Safety. Acceptable risk with special monitoring in those with addictive tendencies. Possible sleep-related respiratory problems should be monitored.

Implications for Clinical Practice. See Opioids: General Implications for Clinical Practice, below.

Implications for Clinical Research. See Opioids: General Implications For Clinical Research, below.

Opioids: General Conclusions

As stated in the previous review,[2] opioids when taken at a sufficient analgesic dose cause a series of minor and major adverse effects. Dizziness, nausea, vomiting, urinary retention, and constipation can all occur with recommended doses. Respiratory depression is a major concern, especially at higher doses or with the more potent agents. This was addressed in 1 long-term case series that did not qualify for inclusion in the efficacy part of this review, but reported respiratory depression

in RLS patients under opioid medication.[57] This is of greater concern in those with preexisting respiratory compromise. When treating patients with opioids, it is necessary to be aware of the addiction potential, especially in those with preexisting addictive tendencies or a known history of addiction. In clinical practice opioid-opioid interactions should be a caveat in patients cotreated by several doctors or for those with RLS and other pain conditions.

Opioids: General Implications for Clinical Practice

Oxycodone combined with naloxone is considered clinically useful for the treatment of severe treatment-resistant RLS at a mean dose of $21.9/11.0 \pm 7.5$ mg up to 12 weeks. Oxycodone alone is likely efficacious, as concluded from the single controlled study available. Many patients are treated with opioids, either as a monotherapy or in combination with dopaminergic drugs, although trials of combination therapy are not available. It is noted, however, that other opioids such as tramadol are often used to treat RLS. Little is known about the long-term efficacy in RLS. Special monitoring is required to avoid addiction in those with addictive tendencies, and possible sleep-related respiratory problems need to be monitored.

Opioids: General Implications for Clinical Research

The major issue with opioids is the small number of controlled studies. The single randomized, controlled trial of oxycodone-naloxone[55] covers only one of the drugs that is commonly used in the clinical setting to treat RLS. Two major issues in the studies of these medications have been the reluctance of the manufacturers to extend the range of opioid indications and the problems of dependence and the related controlled status of opioids. Additional controlled and comparative studies would be very beneficial, especially if they focused on methadone and tramadol, which were excluded from this review due to lack of new published studies, as well as combinatory therapies with dopaminergics.

Antidepressants
Bupropion: 1 New Study; New Conclusion[58]: Investigational

Bupropion, a dopamine-enhancing substance, did not appear in the previous review. Since then, 1 randomized, controlled study (level I)[58] in patients with idiopathic RLS has been published that qualified for inclusion in the current review (see supplementary material).

Conclusions. This 1 small, underpowered study provides insufficient evidence to make a conclusion about the efficacy of bupropion for the treatment of RLS.

Safety. There is insufficient evidence to make a conclusion on the safety of bupropion in RLS.

Implications for Clinical Practice. Bupropion is considered investigational for the treatment of RLS.

Implications for Clinical Research. Sufficiently powered studies are needed to establish the efficacy of bupropion in RLS and to investigate whether adding bupropion to a selective serotonin reuptake inhibitor (SSRI) would improve SSRI-induced symptoms of RLS.

Clonidine: Review of Clinical Studies; No New Studies; Previous Conclusion Revised According to Current Criteria

One level I study[59] was included in the previous review. No further studies have been published, and therefore the previous was revised from efficacious to investigational in accordance with the current criteria.

Conclusions. Clonidine is investigational in RLS for those patients who are primarily bothered by symptoms at bedtime.

Safety. The major side effects of clonidine are xerostomia and sedation, with some patients having mental changes and headache.

Implications for Clinical Practice. Clonidine is considered investigational for the treatment of RLS.

Implications for Clinical Research. The ability of clonidine to benefit RLS patients or a subcategory of bedtime-onset RLS patients needs to be better established by larger, well-designed controlled trials. It remains open to discussion whether clonidine should be considered for future RLS trials with respect to its side-effect profile.

Minerals and Vitamins
Oral Iron Preparations (Oral Ferrous Sulfate): 1 New Study[60]; No New Conclusions

One randomized, controlled study[61] (level I) in patients with idiopathic and secondary RLS qualified for inclusion in the previous review, and a case series[62] (level III) examining the efficacy of oral iron in idiopathic RLS and not RLS secondary to iron deficiency was also included. One new study has been published in patients with idiopathic RLS.[60] As an exception to the inclusion criteria, this study is presented in the supplementary material despite a low quality score to demonstrate the level of evidence available for oral iron therapy in RLS. The 2 level I studies available have conflicting conclusions. A previous study by Davis et al[61] reported unlikely therapeutic benefit from oral iron to patients with adequate iron body stores. The study by Wang et al.[61] on the other hand, reported a possible benefit to patients with low-normal serum ferritin (see supplementary material). So far, no level I studies have been published in iron-deficient RLS patient groups.

Conclusions. There is insufficient evidence to make a conclusion about the efficacy of oral ferrous sulfate.

Safety. Oral ferrous sulfate is considered to have an acceptable risk without the need for special monitoring.

Implications for Clinical Practice (unchanged from previous review)[2]. Oral ferrous sulfate is considered possibly useful in clinical practice.

There is a possibility of iron overload in those with tendencies toward iron retention, especially hemochromatosis. Therefore, iron status needs to be monitored before and periodically during treatment. The major adverse effects involve gastrointestinal discomfort, especially constipation, but also include nausea, reflux, abdominal pain, and diarrhea.

Implications for Clinical Research (unchanged from previous review)[2]. The efficacy and safety of oral iron treatment, especially in those with low iron indices, need to be further established by well-designed, well-controlled trials. It may be useful to examine different oral formulations beyond ferrous sulfate, such as ferrous fumarate or ferrous gluconate.

Intravenous Ferric Carboxymaltose
Review of Clinical Studies: 2 New Studies[63,64]; New Conclusion: Likely Efficacious

Intravenous ferric carboxymaltose appears for the first time in this review, as no studies were available at the time of the previous review. Since then 2 randomized, controlled trials have been published.[63,64] These studies assessed the efficacy of ferric carboxymaltose (either as 2×500-mg infusions[63] or 1×1000-mg infusion[64] at 4-week[63] and 6-week[64] end points (see supplementary material).

Conclusions. Intravenous ferric carboxymaltose (1000 mg) is considered to be likely efficacious for the treatment of RLS.

Safety. Intravenous ferric carboxymaltose is considered to present an acceptable risk without special monitoring. Some regions require intravenous iron formulations to be administered in a facility with cardiac resuscitation.

Implications for Clinical Practice. Intravenous ferric carboxymaltose is considered possibly useful in clinical practice.

Implications for Clinical Research. More data are required to confirm the efficacy of intravenous ferric carboxymaltose; in particular, larger studies are needed.

Intravenous Iron Sucrose
Review of Clinical Studies: 2 New Studies[65,66]; New Conclusion: Insufficient Evidence

Intravenous iron sucrose is a new drug to appear in this review, as no studies were available at the time of the previous review. Since then 2 randomized, controlled trials[65,66] have been published that examined the efficacy of iron sucrose in RLS, but only one of these, an 11-week study of 1000 mg iron sucrose,[66] qualifies for inclusion (see supplementary material).

Conclusions. There is insufficient evidence to make a conclusion about the efficacy of intravenous iron sucrose.

Safety. Intravenous iron sucrose is considered to have an acceptable risk without the need for special monitoring. There is a possibility of iron overload in those with tendencies toward iron retention, especially hemochromatosis. Therefore, iron status needs to be monitored before and periodically during treatment.

Implications for Clinical Practice. Intravenous iron sucrose is considered investigational for clinical practice.

Implications for Clinical Research. More randomized, controlled studies are needed to examine the efficacy of intravenous iron sucrose in RLS, both with and without iron deficiency. In addition, long-term studies of intravenous iron sucrose are needed with special emphasis on the possibilities of iron overload and respective adverse events.

Intravenous High-Molecular-Weight Iron Dextran (note that this formulation has been removed from the market in most of the world and is only listed here for exhaustivity)
Review of Clinical Studies: No New Studies, No New Conclusions

One randomized, controlled study[67] and 2 level III studies were included in the previous review. No further studies have been published, and therefore the previous conclusions remain.

Conclusions (unchanged from previous review)[2]. One level I study has shown intravenous high-molecular-weight (HMW) iron dextran to likely be efficacious for the treatment of RLS secondary to end-stage renal disease. However, the waning of effectiveness at 4 weeks indicates that this treatment may need to be repeated, if that is tolerable. Two level III trials of intravenous HMW iron in RLS without renal failure were positive, but because of the lack of controlled trials, intravenous HMW iron must remain investigational for those RLS patients with normal renal function with special monitoring.

Safety. Because of concerns about anaphylactic reactions, HMW iron dextran is considered to present an unacceptable risk.

General Conclusions on Iron

It needs to be stressed that the iron formulations differ in bioavailability, mode of action, and route of application (oral versus intravenous). Therefore, they are treated separately as different medications. The only formulations for which sufficient evidence enables a conclusion to be drawn are intravenous ferric carboxymaltose, which is considered likely to be efficacious for the treatment of RLS, and HMW dextran, which is considered likely to be efficacious for treatment of RLS secondary to end-stage renal disease. For all other formulations, both oral and intravenous, there is insufficient evidence to make any conclusions. Further controlled trials in larger cohorts are warranted with all iron formulations.

All intravenous iron formulations, similarly to oral iron formulations, require long-term monitoring for the development of iron overload and/or toxicity, with careful attention to the possibility that patients may have a tendency toward hemochromatosis.

Implications for Clinical Practice — Oral Versus Intravenous Iron Administration (unchanged from previous review)[2]

The gastrointestinal side effects so prominent with oral iron do not occur with intravenous iron therapy. However, there is the same, if not greater concern about a toxic iron overload. In addition, with the HMW dextran formulation, the risk of an anaphylactic reaction has been reported. The risk is higher in those with preexisting autoimmune or rheumatoid disorders and can occur in as many as 3% of those given this formulation. Fortunately, this formulation has been taken off the market. Anaphylactic reactions are very rare for low-molecular-weight iron dextran and other nondextran intravenous iron formulations.

Implications for Clinical Research

The efficacy and safety of intravenous iron need to be established with larger, well-designed controlled trials. A particular issue is how long the treatment effects last

and whether repeated doses will lead to adverse effects of iron accumulation. Intravenous iron formulations that do not contain polymerized dextran, for example, ferric carboxymaltose, sodium ferric gluconate, and iron sucrose, to date have not been associated with anaphylaxis. Moreover, it may be important to note the relative lack of efficacy of the intravenous iron formulations that release iron rapidly into the blood (eg, iron sucrose) compared with those that release the iron very slowly over many hours (eg, ferric carboxymaltose). This may reflect the issues of iron management and transport to the brain. It will be important to investigate these matters further. In general, we need to know more about how iron is handled in RLS, which may be a primary abnormality in many patients, and the causal role of iron deficiency for some RLS patients. Moreover, as RLS is a heterogeneous disorder, there may be subgroups of patients who tend to respond differently to iron, and they need to be identified.

Vitamins C and E
Review of Clinical Studies; 1 New Study[68];
New Conclusion: Likely Efficacious for the
Treatment of RLS in Uremic Patients

Vitamins C and E did not appear in the previous review. Since then 1 randomized, controlled study in uremic RLS has been published, which meets the current inclusion criteria.[68] This single-center trial reported the efficacy of vitamins C and E in improving RLS symptoms over the short term in uremic patients (see supplementary material).

Conclusions. Vitamins C (200 mg) and E (400 mg) treatment are likely efficacious in uremic patients.

Safety. Vitamins C and E pose an acceptable risk without special monitoring.

Implications for Clinical Practice. Vitamins C and E are considered possibly useful for the treatment of RLS in patients undergoing hemodialysis.

Implications for Clinical Research. Further studies with larger samples are required to evaluate the long-term efficacy and possible mechanisms of action of vitamins C and E in the treatment of uremic RLS.

Other

Exercise
Review of Clinical Studies: 1 New Study[69]; New
Conclusion: Likely Efficacious for the Treatment
of RLS in Uremic Patients

One randomized, controlled trial[70] was included in the previous review, and 1 new randomized,

controlled trial assessing 3 weekly intradialytic cycling sessions has been published since then that meets inclusion criteria.[69]

Conclusions. An exercise regimen, as provided (see supplementary material), is considered likely efficacious in reducing RLS symptoms in uremic patients.

Implications for Clinical Practice (unchanged from previous review)[2]. An exercise regimen, as provided (see supplementary material), is possibly useful in clinical practice. Exercise can cause difficulty in those in a deconditioned state and may be the cause of various injuries. Therefore, all individuals entering an exercise program should be screened to be sure they were not at greater risk for injury or strain.

Implications for Clinical Research (unchanged from previous review)[2]. Because exercise has many components and can be done at various times of the day, it may be important to define just which aspects of exercise contribute to alleviating RLS and when is the optimal time of day to exercise.

Pneumatic Compression Devices
Review of Clinical Studies: 1 New Study; New
Conclusion: Likely Efficacious

The previous review included no studies on pneumatic compression devices (PCDs). Since then 1 randomized, sham-controlled trial has been published that meets the inclusion criteria of the present review (see supplementary material).[71]

Conclusions. PCDs are considered likely efficacious in RLS.

Safety. PCDs are considered to pose an acceptable risk without the need for special monitoring.

Implications for Clinical Practice. PCDs are considered possibly useful in clinical practice and may be an effective adjunctive therapy for RLS treatment.

Implications for Clinical Research. Additional sham-controlled studies should be performed to confirm the efficacy of this treatment for RLS and determine its mechanism of action so that other, more practical solutions addressing the same mechanism can be developed.

Excluded From the Current Review
Trials investigating the efficacy of carbamazepine, valproic acid, topiramate, methadone, tramadol, clonazepam, zolpidem, amantadine, folic acid, magnesium, and external counterpulsation were included in the previous review. None of these studies meet current inclusion criteria, and no further trials have been

published, and therefore, according to the current evaluation criteria, these drugs and interventions are all considered investigational for RLS treatment.

Augmentation

Augmentation, an iatrogenic worsening of RLS symptoms following treatment with dopaminergic agents, has been recognized as an important issue in the management of RLS. Consequently, in addition to evaluating the efficacy of drugs in treating RLS, the task force reviewed each study for data on augmentation. Despite the number of quality studies reviewed, only 6 studies[23,32,35,55,69,72] assessed augmentation prospectively (see supplementary material). Given the sparse data and the variable durations and methods for evaluating augmentation in the abovementioned studies, it is impossible to make any evidence-based recommendations on augmentation.

Discussion

Since the first evidence-based review, the RLS field has made important strides by developing new drugs. The new data accrued in the last 10 years in high-quality trials have enabled updated conclusions on treatment options already studied in the previous review, but more important are the inclusion of pregabalin, gabapentin enacarbil, and oxycodone/naloxone, which were not mentioned in the previous review, and their classification as efficacious for the treatment of RLS, expanding the range of treatment options for RLS. However, further studies are needed to evaluate their use over the long term and to compare them with dopamine agonists. Furthermore, no study has explored combined therapies or addressed if the order of substances given has any influence on the course of RLS. In addition, in most studies, the medication was administered in the evening, in contrast with clinical practice in which the dose is often divided and adjusted to the time of daily onset of symptoms. Future studies should address these issues. Overall, all the medications discussed here can be classified as symptomatic treatments, but their precise mode of action in RLS is not known.

The evaluation of augmentation is limited, as only a few studies have assessed augmentation, and the methods used were variable, which make comparisons difficult. A recent task force established by the International Restless Legs Syndrome Study Group in conjunction with the European Restless Legs Syndrome Group and the RLS Foundation developed consensus-based recommendations for the prevention and treatment of long-term pharmacologic treatment of dopaminergic-induced augmentation in RLS.[73] These joint guidelines are based on expert opinion rather than on an evidence-based literature review.

They highlight the difficulties encountered when diagnosing augmentation and at the same time the lack of existing data on the treatment of augmentation. Finally, the group was able to conclude that the likelihood of augmentation increases with duration of treatment with dopaminergic agents. Future research on the basic mechanisms of augmentation in RLS is urgently needed to understand this phenomenon. In the future, treatment recommendations should be revised to address the prevention as well as the management of augmentation.

The identification of genetic risk variants and the functional follow-up of these variants have enabled the establishment of new concepts for the pathophysiology of RLS. Future studies should take the genomic profile of patients into account to provide a more tailored therapy for specific subgroups of RLS. Finally, we want to emphasize that this article provides a comprehensive evidence-based review of existing treatment studies but *not* guidelines for treating RLS. However, this document can be used as a base to set up treatment guidelines, which can be adjusted for different countries by taking local regulations and the availability of medications into account. ∎

References

1. Management of Parkinson's disease: an evidence-based review. Mov Disord 2002;17(Suppl 4):S1-S166.

2. Trenkwalder C, Hening WA, Montagna P, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord 2008;23:2267-2302.

3. Cook DJ, Mulrow CD, Haynes B. Synthesis of best evidence for clinical decisions. In: Mulrow CD, Cook DJ, eds. Systematic Reviews, Synthesis of Best Evidence for Health Care Decisions. American College of Physicians; 1998.

4. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997;315:640-645.

5. Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? J Clin Epidemiol 1995;48:159-163.

6. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286-1291.

7. Brodeur C, Montplaisir J, Godbout R, Marinier R. Treatment of restless legs syndrome and periodic leg movements during sleep with L-dopa: a double-blind, controlled study. Neurology 1988:1845-1848.

8. Trenkwalder C, Stiasny K, Pollmacher T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. Sleep 1995;18:681-688.

9. Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. Sleep 1996;19:214-218.

10. Staedt J, Wassmuth F, Ziemann U, Hajak G, Ruther E, Stoppe G. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double -blind randomized crosover trial of pergolide versus L-Dopa. J Neural Transm 1997;104:461-468.

11. 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.

12. 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.

13. 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.

14. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of Restless Legs Syndrome in hemodialysis patients: an open-label study. Ren Fail 2004;26:393-397.

15. Trenkwalder C, Benes H, Grote L, et al. 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.

16. Inoue Y, Shimizu T, Hirata K, et al. 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.

17. Oertel WH, Benes H, Garcia-Borreguero D, et al. Efficacy of rotigotine transdermal system in severe restless legs syndrome: a randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. Sleep Med 2008;9:228-239.

18. Hening WA, Allen RP, Ondo WG, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010;25:1675-1683.

19. Trenkwalder C, Benes H, Poewe W, et al. 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.

20. Garcia-Borreguero D, Allen R, Hudson J, et al. Effects of rotigotine on daytime symptoms in patients with primary restless legs syndrome: a randomized, placebo-controlled study. Curr Med Res Opin 2016;32:77-85.

21. Stiasny-Kolster K, Kohnen R, Schollmayer E, Moller JC, Oertel WH. 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.

22. 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.

23. 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.

24. Happe S, Sauter C, Klosch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology 2003;48:82-86.

25. Adler CH, Hauser RA, Sethi K, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology 2004; 62:1405-1407.

26. 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.

27. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al. Ropinirole in the treatment of restless legs syndrome: results from a 12-week, randomised, placebo-controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004;75:92-97.

28. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K. 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.

29. Bliwise DL, Freeman A, Ingram CD, Rye DB, Chakravorty S, Watts RL. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. Sleep Med 2005; 6:141-147.

30. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY. 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.

31. 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.

32. Högl 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.

33. 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.

34. 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.

35. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med 2014;370:621-631.

36. 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.

37. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology 1999;52:938-943.

38. 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.

39. Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006;67: 1034-1039.

40. Trenkwalder C, Stiasny-Kolster K, Kupsch A, Oertel WH, Koester J, Reess J. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome. Mov Disord 2006;21:1404-1410.

41. Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord 2007; 22:213-219.

42. Stiasny-Kolster K, Benes H, Peglau I, et al. Effective cabergoline treatment in idiopathic restless legs syndrome. Neurology 2004;63: 2272-2279.

43. 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.

44. 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.

45. 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.

46. 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.

47. Bogan RK, Bornemann MA, Kushida CA, Tran PV, Barrett RW. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. Mayo Clin Proc 2010;85:512-521.

48. 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.

49. Lee DO, Ziman RB, Perkins AT, Poceta JS, Walters AS, Barrett RW. 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.

50. Walters AS, Ondo WG, Kushida CA, et al. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol 2009;32:311-320.

51. Kushida CA, Walters AS, Becker P, et al. 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.

52. Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, Barrett RW. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. Neurology 2009;72: 439-446.

53. 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.

54. 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.

55. Trenkwalder C, Benes H, Grote L, et al. 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.

56. 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.

57. Walters AS, Winkelmann J, Trenkwalder C, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord 2001;16:1105-1109.

58. 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.

59. 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.

60. 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.

61. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. Eur Neurol 2000;43:70-75.

62. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing 1994;23:200-203.

63. 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.

64. Cho YW, Allen RP, Earley CJ. Clinical efficacy of ferric carboxymaltose treatment in patients with restless legs syndrome. Sleep Med 2016;25:16-23.

65. Earley CJ, Horska 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.

66. 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.

67. 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.

68. 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.

69. 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.

70. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med 2006;19:487-493.

71. 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.

72. 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.

73. Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of RLS/WED, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-Foundation. Sleep Med 2016:1-11.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.