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Review

Treatment of Restless Legs Syndrome: An Evidence-Based Review and Implications for Clinical Practice

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Abstract: Only in the last three decades, the restless legs syndrome (RLS) has been examined in randomized controlled trials. The *Movement* Disorder Society (MDS) commissioned a task force to perform an evidence-based review of the medical literature on treatment modalities used to manage patients with RLS. The task force performed a search of the published literature using electronic databases. The therapeutic efficacy of each drug was classified as being either efficacious, likely efficacious, investigational, nonefficacious, or lacking sufficient evidence to classify. Implications for clinical practice were generated based on the levels of evidence and particular features of each modality, such as adverse

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Additional Supporting Information may be found in the online version of this article.

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events. All studies were classed according to three levels of evidence. All Level-I trials were included in the efficacy tables; if no Level-I trials were available then Level-II trials were included or, in the absence of Level-II trials, Level-III studies or case series were included. Only studies published in print or online before December 31, 2006 were included. All studies published after 1996, which attempted to assess RLS augmentation, were reviewed in a separate section. The following drugs are considered efficacious for the treatment of RLS: levodopa, ropinirole, pramipexole, cabergoline, pergolide, and gabapentin. Drugs considered likely efficacious are rotigotine, bromocriptine, oxycodone, carbamazepine, valproic acid, and clonidine. Drugs that are considered investigational are dihydroergocriptine, lisuride, methadone, tramadol, clonazepam, zolpidem, amantadine, and topiramate. Magnesium, folic acid, and exercise are also considered to be investigational. Sumanirole is nonefficacious. Intravenous iron dextran is likely efficacious for the treatment of RLS secondary to end-stage renal disease and investigational in RLS subjects with normal renal function. The efficacy of oral iron is considered investigational; however, its efficacy appears to depend on the iron status of subjects. Cabergoline and pergolide (and possibly lisuride) require special monitoring due to fibrotic complications including cardiac valvulopathy. Special monitoring is required for several other medications based on clinical concerns: opioids (including, but not limited to, oxycodone, methadone and tramadol), due to possible addiction and respiratory depression, and some anticonvulsants (particularly, carbamazepine and valproic acid), due to systemic toxicities.

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

EXTENDED SUMMARY

BACKGROUND

It is only in the last 3 decades that restless legs syndrome (RLS) has been examined in randomized controlled trials. The *Movement* Disorder Society (MDS) commissioned a task force to perform an evidence-based review of current treatment strategies commonly used to manage patients with RLS. In this review, the task force evaluates the therapeutic efficacy of each drug and reports on implications for clinical practice and research according to standardized methods of evidenced-based medicine. The task force has also chosen to include a section on augmentation, which is considered an important therapy-related side effect specific to RLS. The task force's recommendations for practical use are given in the *implications for clinical practice* section after the review of each drug or class of drugs. Because of varied country-specific regulations, the task force can only provide general recommendations for clinical practice. The different levels of efficacy used in this review can be seen in Table S1; definitions for specific recommendations are given in Table S2; Table S3 contains the data of all trials included in this review (Tables S1–S3 can be consulted online).

METHODS

The task force performed a search of the published (print or online before December 31, 2006) literature using electronic databases (Medline [Pubmed; 1966-2/2007, Embase (1980-3/2007], the Cochrane Central Register of Controlled Trials [CENTRAL; issue 1, 2007], and systematic checking of reference lists published in review articles and other clinical reports. The reported therapeutic efficacy of each drug was then evaluated, and implications for clinical practice were reported. All studies with ≥5 subjects and a minimum treatment and follow-up duration of 1 week were classified according to three levels of evidence. All Level-I trials were included in the efficacy tables (Table S3); if no Level-I trials were available then Level-II trials were included, if neither Level-I nor -II were available then Level-III studies were included. The qualitative approach taken by the task force seeks to highlight the available evidence and the areas that require further research. For the separate section on augmentation, all trials (irrespective of level of evidence) published after 1996 that mentioned or described augmentation within the trial were included.

RESULTS

Dopaminergic Agents

Levodopa/benserazide or levodopa/carbidopa, at dosages of 100/25 to 200/50 mg is considered efficacious for the treatment of RLS, however, the number of patients (n = 462) involved in Level-I studies is not large when compared with other dopaminergic drugs, and the duration of double-blind studies only exceeded 4 weeks in one study.[1–9] The 4-week side-effect profile of levodopa is favorable; however, problems with augmentation develop with higher dosages and longer treatment duration. Long-term prospective studies are needed in order to better assess and quantify the risk of side effects.

Nonergot-Derived Dopamine Agonists

General considerations: The nonergot derived dopamine agonists ropinirole and pramipexole are currently the only agents licensed for the treatment of RLS in the USA, European Union, Australia, Brazil, Mexico,

Korea, and Canada. Special monitoring for valvular fibrosis is not necessary.

Ropinirole (0.25–4 mg, mean: 2 mg) is efficacious for treating RLS in patients with moderate to severe clinical symptomatology.[10–16] Sleep and general RLS severity improved in all trials. From the available published clinical trials, the incidence of adverse reactions is similar to that of other available dopamine agonists. There are no specific concerns about hypersomnolence in RLS patients. There was no specific monitoring for augmentation or dopamine dysregulation syndrome within the trial program.

Pramipexole [0.54 mg of base (0.75 mg of salt)] is efficacious for treating RLS symptoms in patients with moderate to severe clinical symptomatology.[17–21] Sleep, general RLS severity (measured with the IRLS), and daytime symptoms improved in all trials. From the available published clinical trials, the incidence of adverse reactions is similar to that of other available dopamine agonists. There are no specific concerns about hypersomnolence in RLS patients. In some countries patients are advised not to drive due to a risk of somnolence.

Rotigotine patch is likely efficacious without special monitoring.[22] The current results from clinical studies in RLS are limited but promising. Local site reactions to the patch have been observed.

General Implications for Clinical Research

Long-term comparative trials need to be undertaken comparing the different dopamine agonists with each other and to assess for augmentation. The potential side effects of dopamine agonists need to be studied further. Comparative studies are not available and are needed for tailoring of individual treatment.

Ergot-Derived Dopamine Agonists

General consideration: All ergot-dopamine agonists require special monitoring due to increased incidence of cardiac valvular fibrosis and other fibrotic side effects.[23] Because of their negative side-effect profile, especially the potential to induce fibrosis, ergot-derived dopamine agonists are not recommended for the treatment of RLS as first choice therapy. If used, cardiopulmonary monitoring for fibrosis is necessary.

Bromocriptine (7.5 mg)[24] is considered likely efficacious for the treatment of RLS, as one small study has shown that it has a significant effect on subjective RLS symptoms and PLMS, but it is currently rarely used for RLS treatment.

Pergolide (0.25–0.75 mg)[4,25–27] has been shown to be efficacious in RLS for a therapeutic period up to 1 year proven by subjective sleep evaluation, the IRLS, and poysomnographic data.[27]

Cabergoline (0.5–3 mg, mean: 2 mg):[9,28,29] has proven to be efficacious for the treatment of RLS. At the time of writing, cabergoline is the only dopamine agonist that has been studied against levodopa in a controlled large-scale trial and has been shown to be significantly superior with an increased efficacy and a lower rate of augmentation assessed by clinical interviews.

Dihydroergocriptine (DHEC) (flexible dose, maximum dosage 60 mg/day)[30] is considered investigational for the treatment of RLS.

Transdermal lisuride (3–6 mg) is investigational for the treatment of mild RLS as shown in 1 week proof-of-principle study that used subjective criteria.[31] Because of a unique spectrum of 5HT receptor binding, it remains unsure whether special monitoring for fibrosis is required.

Opioids

Oxycodone (mean dose 15.9 mg) is likely efficacious for the treatment of RLS in patients with significant daily symptoms. Only one small, 4 week trial is available with improvement of subjective and polysomnographic data.[32]

Methadone (15.5 $\pm$ 7.7 mg/day) is investigational for the treatment of refractory RLS.[33] It should be used cautiously due to its potency and its respiratory depressant effect, especially in those with preexisting respiratory compromise.

Tramadol (50–150 mg/day) is considered investigational for the treatment of RLS. One open trial is available.[34] It may share some of the limitations of the dopaminergics in regard to long-term complications such as augmentation.

General Conclusion

Opioids taken at sufficient analgesic dose do cause a series of minor and major adverse effects: dizziness, nausea, vomiting, urinary retention, and constipation. Respiratory depression is a major concern. The addiction potential of opioids should be kept in mind when considering treatment in potentially predisposed patients. Furthermore, controlled large-scale trials with long-term follow-up are urgently needed, as those agents are used with increasing frequency in RLS therapy.

Sedative Hypnotics

Benzodiazepines

Clonazepam (dosage: 0.5–1 mg) is considered investigational.[35,36] It has a very long half life and may

cause daytime somnolence, it may cause unwanted blunting of consciousness, especially in the elderly, and can also decrease balance. Patients should be monitored for development of excessive sedation or pathologic dependence.

Benzodiazepine-Receptor Agonists

Zolpidem (fixed dosage: 10 mg) is considered investigational for RLS.[37] The role of the sedative-hypnotics, perhaps as adjuvant medications to benefit sleep in RLS, remains to be defined in well controlled trials that also need to examine safety issues, including daytime sedation and sleep disruptive parasomnias.

Anticonvulsants

Gabapentin (dosage: 200 mg up to 2,000 mg, mean: 800–1,855 mg) is efficacious for the treatment of RLS.[8,10,38,39] It has been studied in comparison with other agents.[8,10] There are no major safety concerns. Less serious adverse effects include dizziness, somnolence, and peripheral edema. Side effects may be dose dependent. Unlike dopaminergic agents, gabapentin has been used in divided doses in trials.

Carbamazepine is likely efficacious.[40,41] Typical anticonvulsant side effects have been noted, close monitoring is necessary because of the rare occurrence of well-known toxic side effects.

Valproic acid is likely efficacious for the treatment of RLS, with special monitoring.[7] Side effects include the normal anticonvulsant adverse effects and tremor. There have been rare reports of hepatotoxicity, thrombocytopenia, and prolonged coagulation times, so regular blood monitoring is recommended.

Topiramate is considered to be investigational.[42] Side effects include the normal anticonvulsant adverse effects. However, there is concern about topiramate's carbonic anhydrase inhibition, which has been reported to cause a significant acidosis, requiring some prophylactic monitoring.

General Implications for Clinical Research

This particular set of specific antidepressant medications provide a possible therapeutic alternative to dopaminergics; however, these particular anticonvulsants can all reduce pain and improve sleep. Further studies are needed to investigate whether this set of anticonvulsants are globally effective for treatment of RLS symptoms, rather than restricted to merely improving sleep and ameliorating painful RLS.

N-Methyl-D-aspartic acid (NMDA) Antagonists

Amantadine is investigational for the treatment of RLS.[43] Up to one-third of patients may have central nervous system adverse effects. It should be used with caution in the elderly due to its extended duration of action in these subjects and the dose reduced in those with renal insufficiency. Its safety in the elderly needs to be established by well-designed controlled trials; the possible dopaminergic effects of amantadine also need further examination.

Clonidine

Clonidine is likely efficacious in RLS for those patients who are primarily bothered by symptoms at bedtime.[44] Its major side effects are xerostomia and sedation with some patients having mental changes and headache.

Minerals and Vitamins

Oral iron is not an efficacious treatment for RLS in iron-sufficient individuals.[45] It is investigational for the treatment of RLS in iron-deficient RLS patients and should be used with appropriate evaluations to ensure the patients do not develop an iron overload indicating possible hemochromatosis.[46]

Intravenous Iron dextran is likely efficacious for the treatment of RLS secondary to end-stage renal disease.[47] Intravenous iron remains investigational for RLS patients with normal renal function with special monitoring.[48,49] There is concern about toxic iron load and with higher molecular weight dextran formulations, there is also risk of an anaphylactoid reaction. This likely does not apply to low molecular weight formulations.

Folic acid is considered investigational in RLS, it can be administered without special monitoring.[50]

Magnesium is considered investigational in RLS.[51] Caution has to be exercised in patients with renal failure, as magnesium can accumulate and lead to neuromuscular blockade.

For all minerals and vitamins well-designed randomized controlled trials are necessary to establish their efficacy as a treatment for RLS.

Other

Exercise is investigational in reducing RLS symptoms.[52] It may be difficult for those in a deconditioned state to embark upon an exercise program.

External counterpulsation is nonefficacious in RLS.[53]

Augmentation

Most of the data on augmentation comes from retrospective analysis. Augmentation with levodopa

treatment has been shown to be clinically significant.[9] Although clinically significant cases have been reported after treatment with ropinirole and pramipexole, currently available studies have included too few patients and have had too short a duration of follow-up to provide an adequate evaluation of augmentation. Cabergoline has been shown to have a low rate of augmentation rate in a 1 year open follow-up study[28] and in one 30-week study.[9] Even in large, long-duration trials, such as those with pramipexole, the evaluation of augmentation has not been clearly defined. However, diagnostic criteria have recently been updated based on clinical data,[54] and these criteria will now facilitate the comparison of augmentation across trials.

INTRODUCTION

Although restless legs syndrome (RLS) was first studied clinically in the 1940s by Ekbom,[55] it is only in the last 20 years that the condition and its treatment have been examined in controlled trials. The pathophysiology of the disease continues to be poorly understood, and therefore, only symptomatic treatment strategies are available, no causal regimens are known.

In recent years, dopaminergic drugs have been licensed for the treatment of RLS but are not necessarily available for widespread use worldwide. The strategy used in the latest RLS trials consists mostly of a single bedtime dose; divided doses have not yet been studied in large controlled trials, and therefore, the dopaminergic therapeutic strategy for treating RLS is different from that used in Parkinson's disease (PD). This different treatment regimen may be one reason why the doses required in RLS are much smaller than those used in PD. In addition, specific adverse events like augmentation and rebound (see Part II) that are not seen in the dopaminergic therapy of PD patients have been observed in patients with RLS.

Research programs on specific therapeutic interventions are frequently established by the pharmaceutical industry as part of the drug development process. Such programs in RLS obviously fill gaps in the available clinical evidence. For nondopaminergic drugs, however, there is an absence of industry-supported research programs, and it is therefore likely that they have been insufficiently investigated relative to their therapeutic potentials.

To assess the current state of treatment for RLS, its implications for clinical practice and to ascertain which gaps in the knowledge need to be filled, it is necessary to perform an evidence-based review of the literature. In this article, the original definition of evidence-based medicine (EBM) proposed by Sackett et al. is accepted[56]:

To contribute to EBM, the Movement Disorder Society (MDS) commissioned a task force to perform an evidence-based review of current treatment strategies commonly used to manage patients with RLS, similar to the review performed for PD.[57] Although there is a substantial amount of research about PD and its treatment, this is not the case in RLS where there are a limited number of controlled trials and other therapeutic interventions with a sufficient number of patients to show effect sizes or risk-benefit relationships. The members of this MDS-appointed task force are movement disorder specialists with extensive experience in treating RLS, from Europe and North America, and are the authors of this article.

STRATEGIC OPTIONS

In this review, the task force evaluates the therapeutic efficacy of each drug and reports on implications for clinical practice and research. The task force has also chosen to include a section on augmentation, a side effect primarily induced by dopaminergic medications that is specific to RLS.

Single treatments are reviewed independently rather than as part of a management strategy. Currently, only single treatments are available in clinical trials; combination therapies have not yet been investigated in Level-I and -II RLS trials and therefore could not be analyzed. However, some of the Level-III trials that were included for review include patients receiving other therapy simultaneous with experimental medication. The task force's recommendations for practical use are given in the implications for clinical practice sections after the review of each drug or class of drugs. These recommendations cannot take into account country-specific regulations, and therefore, the task force is only able to make general recommendations for clinical practice.

The different levels of evidence used in this review can be seen in Table S1. These were agreed upon by the members of the task force. Definitions for specific recommendations are given in Table S2. In the efficacy tables (Table S3), all Level-I trials are included when available, and drug trials of other levels are excluded for these drugs. Level-II studies are included when Level-I trials are not available, and when neither Level-I nor -II studies are available then Level-III studies are included.

Augmentation was first defined in 1996,[58] and therefore, the task force has included all studies (all levels and case series) published after this time when the term "augmentation" was mentioned within the publi-

TABLE 1. *Summary of recommendations*

Efficacious treatment in RLS			
Dopaminergic agents (mostly for moderate to severe RLS)			
Non-ergot-derived dopamine agonists	Ropinirole (no restriction)	Pramipexole (no restriction)	
Ergot-derived dopamine agonists	Pergolide (restricted use because of side effects)	Cabergoline (restricted use because of side effects)	
Levodopa/DDCI	Levodopa/benserazide (no large-scale trials, the dopamine agonist cabergoline is superior to levodopa/benserazide)		
Anticonvulsants	Gabapentin (no large scale trials)		
Likely efficacious treatments in RLS			
Non-ergot-derived dopamine agonists	Rotigotine (large-scale trials in abstracts)		
Ergot-derived dopamine agonists	Bromocriptine		
Opioids	Oxycodone		
Anticonvulsants	Carbamazepine (restricted use due to side effects)	Valproic acid	
Alpha-adrenergic agonists	Clonidine (restricted use due to side effects)		
Minerals and vitamins	Intravenous (IV) iron dextran is likely efficacious for the treatment of RLS secondary to end-stage renal disease		
Investigational treatments in RLS			
Ergot-derived dopamine agonists	Dihydroergocriptine	Lisuride patch (large-scale trials in abstracts)	
Opioids	Tramadol	Methadone in severe RLS (special monitoring because of side effects)	
Sedative hypnotics	Clonazepam	Zolpidem	
Anticonvulsants	Topiramate		
NMDA antagonists	Amantadine		
Minerals and vitamins	IV iron is investigational in subjects with normal renal function	Magnesium	Folic acid
Non-pharmacological methods	Exercise		
Non-efficacious treatments in RLS			
Non-ergot-derived dopamine agonists	Sumanirole		
Non-pharmacological methods	External counterpulsation		
Minerals and vitamins	Oral iron is non-efficacious in iron sufficient subjects (its benefit for patients with low peripheral iron status has not been adequately evaluated)		

cation, and when augmentation was measured and described in a clinically relevant way (Table S4). Although the original description of augmentation was based on its primary clinical characteristics, more formal defining criteria were not established until 2003[59]; these have recently been slightly modified based on data from an augmentation study.[54] These differing criteria complicate comparisons between the studies.

This evidence-based review does not include quantitative summaries (no metaanalyses 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 two sections within each paragraph entitled: (1) implications for clinical practice and (2) implications for clinical research.

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 publication and language bias may inflate positive results,[60–62] although it is not likely that major trials have been overlooked because of the selection of languages.

Another methodological limitation is caused by the fact that the primary sources of evidence were electronic databases, which provide incomplete lists of papers.[63] For Level-II and-III studies (defined below), the risk of missing relevant papers is greater than with Level-I studies because there is a small possibility that studies of a more descriptive, nonrandomized, or uncontrolled design are not published in mainstream, peer-reviewed journals.

AIMS AND GOALS

The aims of this evidence-based review are to evaluate the evidence on therapeutic interventions for RLS published to date (print and online publication until end-December 2006) and to assess the clinical efficacy, safety, and RLS-specific safety problems of these interventions. In addition, the implications of this evidence for clinical practice will be considered.

The specific goals are to:

1. Review the literature and identify the clinical evidence that supports specific 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.
3. Identify where specific evidence is lacking, so future research efforts may be directed toward addressing these specific areas of need
4. Identify the RLS-specific side effect, which is augmentation.

Treatments identified for inclusion in this review are pharmacological and nonpharmacological interventions. Only a few articles are available on nonpharmacological interventions such as exercise. This selection of studies was based on consensus among the task force members.

METHODS

Identification of Published Material

A search of the published literature was performed using electronic databases including Medline (Pubmed; 1966-2/2007), Embase (1980-3/2007), the Cochrane Central Register of Controlled Trials (CENTRAL; issue 1, 2007), and systematic checking of reference lists published in review articles and other clinical reports. A highly sensitive search strategy was used to identify randomized controlled trials,[63] and all terms were searched as free text and standardized subject terms.

Each member of the task force was allocated to review studies of specific classes of drugs, and each reference was discussed with all members and a consensus on inclusion was reached. Full text copies of potentially relevant studies were obtained, and the reviewers assessed them for inclusion in the review according to the following inclusion/exclusion criteria with special exceptions noted in each of the respective chapters below.

Inclusion Criteria

1. Randomized controlled trials (Level I), if no Level-I trials were available then Level-II trials were included, if neither Level-I nor Level-II trials were available then Level-III trials were considered.
2. Patients with an established diagnosis of RLS (idiopathic and secondary RLS) made using predefined criteria.
3. Predefined instruments for measuring change in target symptoms or objective findings.
4. Minimum of ≥5 subjects with a minimum treatment and follow-up duration of 1 week.
5. Study report published in English or other major European languages (see earlier).
6. Full paper citation published (print or electronic publication) before December 31, 2006 (abstracts were excluded).
7. For augmentation, all trials (irrespective of level of evidence) published after 1996 that mentioned or

described augmentation within the trial were included.

Exclusion Criteria

1. Duplicated publications.
2. Use of unconventional outcome measures: i.e., no description of methods was given or outcome measures were insufficiently defined.
3. Incomplete follow-up: i.e., less than 1-week follow-up after intervention.

Classification of Evidence

Once the studies were identified for inclusion, details from each published report were extracted and summarized into evidence tables. This review is based on a hierarchical organization of evidence.[64] Randomized controlled trials, if methodologically sound, are considered less biased and consequently the most valid studies providing clinical evidence. The next level of evidence is supported by nonrandomized, controlled clinical trials, followed by observational controlled studies (cohort and case-control studies). The lowest level of evidence considered was noncontrolled case series. Clinical evidence was classified into three levels (Table S1). If randomized controlled trials were available (Level-I studies), other levels of evidence were considered unnecessary. Thus, Level-II and -III studies are considered secondary sources of evidence.

For this analysis of RLS trials, a rating of the study quality scores was not undertaken. All Level-I studies were accepted for the tables of efficacy, whereas Level-II and Level-III trials were only included if higher grade trials were not available. The content of the efficacy tables have been agreed on by a consensus among the members of the task force.

Safety Evaluation[65]

As previously mentioned, the efficacy and safety profiles have been analyzed separately. RLS-specific treatment side effects have been analyzed separately in the section on augmentation, which contains not only Level-I and -II trials but also smaller trials and cohort studies as well as retrospective case series. The task force has chosen not to include a separate section on the known side effects of the different drugs, concentrating instead on the RLS-specific side effect of augmentation. However, along with efficacy findings, the safety results from the trials are summarized in each section.

Evidence-Based Conclusions

Following a review of the literature, the EBM task force members reached a consensus on the efficacy and safety of each therapeutic intervention as well as implications for clinical practice and research. For those therapeutic agents, where there was a lack of data, the task force was unable to make a relevant recommendation pertaining to efficacy. Where no evidence was available, this was clearly stated. Further, methodological descriptions can be identified from online material (Table S2).

PART 1: EFFICACY

Dopaminergic Agents

Levodopa

Basic pharmacology. Levodopa (L-dopa, L-3,4,-dihydro-oxy-phenyl-alanine) is naturally synthesized in dopaminergic cells and within these cells it is metabolized to either dopamine (DA) or 3-*ortho*-methyldopa (3-OMD). Oral doses of L-dopa are usually rapidly absorbed at the level of the small intestine through an active transport system for aromatic amino acids. Absorption can be significantly influenced by amino acids taken with meals, gastric emptying, and the pH of gastric acid. Therefore, the plasma levels of L-dopa can fluctuate and are significantly related to nutrition. L-Dopa reaches peak plasma levels between 0.5 and 2 hours after oral administration with a short half-life of 1 to 3 hours. In PD and other neurological diseases the active transporter system that enables L-dopa to pass the blood–brain barrier is important. After passing the blood–brain barrier, L-dopa is taken up by amino acid transport into dopaminergic cells where it is metabolized. It may also be metabolized outside of the DA cells by catechol-*O*-methyltransferase (COMT).[66]

Review of clinical studies. Nine randomized controlled trials[1–9] (Level I) were qualified for inclusion in this review.

Level I: Brodeur et al.[1]: This was a small (n = 6; 3 women; mean age, 51.3 years), 2-week randomized, double-blind, placebo-controlled crossover study in patients with idiopathic RLS (defined as paresthesia leading to an urge to move at bedtime, and prolonged sleep latency). Efficacy was assessed using polysomnography (PSG), the suggested immobilization test (SIT), and the multiple sleep latency test (MSLT) as well as through daily evening questionnaires on sleep and daytime alertness. In comparison with placebo, L-dopa/benserazide (100/25 mg) significantly reduced

periodic limb movements of sleep (PLMS) ($P = 0.0001$), PLMS with arousals (PLMSA) ($P = 0.0078$) and reduced sleep latency as measured by PSG ($P = 0.04$). There was no significant difference between L-dopa and placebo as measured by the MSLT, the questionnaires or the SIT scores.

Trenkwalder et al.[2]: This was a 4-week randomized, double-blind, crossover study of L-dopa vs. placebo in 17 patients (5 women; mean age, 53 years) with idiopathic RLS (diagnosed with study-specific criteria similar to the IRLSSG criteria) and 11 patients (5 women; mean age, 49 years) with uremic RLS. The three primary end points were the periodic limb movement index (PLMI), sleep time, and subjective quality of sleep. Secondary measures were PSG recordings, actigraphy, and subjective patient and physician reports. L-Dopa/benserazide (mean L-dopa 146 mg) was shown to be more effective than placebo in reducing PLMI ($P = 0.005$) and improving sleep (longer sleep time $P = 0.045$; improved subjective sleep quality by 36%; $P = 0.002$) in patients with idiopathic RLS. In patients with uremic RLS, L-dopa reduced PLMI by a mean of 29% compared with placebo ($P = 0.005$) and also improved sleep (longer sleep time; improved subjective sleep quality by 42%, $P = 0.002$). The effect of L-dopa on PLMI was only significant in the first 4 hours of bedtime after administration. For both idiopathic and uremic RLS patients' subjective evaluation confirmed improvement of quality of life [QoL; as measured on a visual analogue scale (VAS)], better life satisfaction ($P = 0.01$), and less negative feelings and complaints ($P = 0.024$). The physicians' evaluation noted improved severity ($P = 0.045$) and global assessment of change ($P = 0.025$) in both idiopathic and uremic RLS patients. One severe adverse event occurred with L-dopa.

Walker et al.[3]: This was a small, 1-week randomized, double-blind, placebo-controlled, crossover study in 5 patients (4 women; mean age, 66 years) with uremic RLS (ICSD-1 criteria). After a 1-week preentry washout period, patients received a single bedtime dose of controlled-release (CR) L-dopa/carbidopa (100/25 mg) for 1 week. The primary outcome measures were the PLMI and improved sleep; PSG measures were also recorded. L-Dopa reduced PLMI by 40% ($P = 0.006$), PLMA by 61% ($P = 0.05$). No improvement was seen in subjective measures of RLS symptoms or sleep, and PSG did not show any improvement in sleep latency. Slow wave sleep (SWS) was increased ($P = 0.01$).

Staedt et al.[4]: This was a small (n = 11; 5 women; 50–60 years), double-blind, randomized, crossover study of 0.125 mg pergolide (titrated up to 0.50 mg) vs. 250 mg L-dopa/carbidopa (titrated up to 500 mg) in patients with idiopathic RLS (RLS diagnosis criteria not specified). Clinical efficacy was determined through PSG and clinical interviews. The study duration was 18 days for each active drug. Only 1 in 11 patients experienced complete relief of motor restlessness with L-dopa/carbidopa (mean dose, 363 mg), whereas with pergolide (mean dose, 0.159 mg) 9 of 11 patients experienced complete relief, and 2 of 11 had partial relief of motor restlessness. L-Dopa reduced "nocturnal myoclonus time" (NMT) by 45% ($P < 0.025$), and pergolide reduced NMT by 79% ($P < 0.001$). Furthermore, pergolide significantly increased time in bed and sleep time compared with L-dopa ($P < 0.05$).

Collado-Seidel et al.[5]: This 4-week randomized, double-blind, crossover study compared a combination of regular-release (RR) and CR L-dopa/benserazide with monotherapy of RR L-dopa/benserazide in treating patients with idiopathic and secondary RLS. Thirty patients (19 women; mean age, 58 years) with RLS (according to IRLSSG criteria), a PLMSI > 5, sleep latency > 25 min, and sleep efficiency $\leq 85\%$, underwent a 2-week preentry washout period and then received RR L-dopa for 2 weeks, followed by additional CR L-dopa/benserazide or placebo. Primary end points were improvement in PLMI, percentage of time in bed (%TIB) without leg movements measured by actigraphy; the subjective quality of sleep during the past week was also documented. RR-L-dopa/benserazide (100/25 mg) was shown to markedly improve RLS during the first-half of the night in 77% of subjects. The combination of RR-L-dopa and CR-L-dopa was shown to have a greater efficacy than RR-L-dopa alone (PLMSI, $P < 0.0001$; %TIB without leg movements, $P < 0.0001$; subjective quality of sleep during last week, $P < 0.001$). QoL did not improve.

Benes et al.[6]: This was a 4-week randomized, double-blind, placebo-controlled, crossover, multicenter study that sought to investigate the efficacy and safety of L-dopa/benserazide in the treatment of uremic and idiopathic RLS. RLS was defined according to IRLSSG criteria, patients also had to have a PLMSA index (PLMSA-I) > 5, and sleep latency $>$ 30 m and/or sleep efficiency $\leq 85\%$ and had to undergo a 2-week preentry washout period. Parameters used to assess efficacy were the PLMSI, %TIB without leg movements, measured by actigraphy and PSG as well as the subjective quality of sleep. Thirty-two patients (19 women; mean age, 56 years) completed the study. L-Dopa/benserazide (100/25 mg, 1 hour before bedtime) was superior to placebo in

reducing PLMSI ($P < 0.0001$) by actigraphy, in increasing %TIB without leg movements ($P < 0.0001$), and in improving quality of sleep ($P = 0.0004$) but only during the first half of the night. Subjective sleep quality also significantly improved, as sleep latency was shorter ($P < 0.0001$), sleep duration longer ($P = 0.0002$), and the patients got up less during the night ($P = 0.0261$). RLS severity was also reduced, at sleep onset ($P = 0.0061$) and during the night ($P = 0.0011$), RLS symptoms reappeared as soon as treatment was discontinued.

Eisensehr et al.[7]: This was a randomized, double-blind, placebo-controlled crossover study that sought to compare the efficacy of valproic acid with L-dopa in 20 patients (12 women; mean age, 58.9 years) with idiopathic RLS (IRLSSG criteria) who had a PLMI > 10 and daily symptoms for 6 months. Clinical efficacy was assessed using an hourly diary that recorded minutes of symptoms, a VAS of overall severity and PSG. Although valproic acid (600 mg CR) was shown to significantly decrease symptoms (according to the diary and overall subjective intensity score) L-dopa/benserazide (200 mg CR/50 mg) did not. However, L-dopa significantly decreased PLMI ($P \leq 0.005$) but significantly increased arousals not associated with PLMS ($P = 0.002$).

Micozkadioglu et al.[8]: This 4-week randomized, controlled, open-label study compared the efficacy of gabapentin (100–200 mg) with L-dopa/carbidopa (100/25 mg/day) in patients with secondary RLS (defined according to IRLSSG criteria) undergoing hemodialysis (n = 15; 5 women; mean age, 45.8 years). Primary end points were improvements in IRLS score (abbreviated form), SF-36, and Pittsburgh Sleep Quality Index (PSQI) scores. Gabapentin (200 mg fixed dose after each dialysis session and before bedtime) was shown to significantly improve the abbreviated IRLS score, SF-36 domains of general health, body pain, and social functions compared with L-dopa ($P < 0.001$). The final dosages of L-dopa, however, were not defined. Gabapentin was superior to baseline and L-dopa in improving sleep parameters on PSQI sleep quality subjective sleep latency ($P < 0.001$) and sleep disturbance.

Trenkwalder et al.[9] (see Cabergoline section below).

Conclusions. L-Dopa in RLS has been examined in four randomized, double-blind, placebo-controlled trials[1–3,6] and is considered efficacious. Moreover, other Level-I trials have comparatively explored the efficacy of different formulations of L-dopa (RR vs. CR,[5] and the efficacy of L-dopa compared with pergolide,[4] CR valproic acid,[7] gabapentin,[8] and cabergoline).[9] In summary, L-dopa/benserazide or L-dopa/carbidopa, at dosages of 100/25 to 200/50 mg (mean L-dopa dosage 146 mg in Trenkwalder et al.[2]) given 1 hour before bedtime (or with a second dose 3 hours after bedtime) was efficacious in controlling the motor and sensory disturbances of RLS (RLS severity reduced at both sleep onset and during the night,[6] even though no subjective improvement in RLS symptoms or sleep was reported in one of four studies by Walker et al.[3] in uremic RLS). Patients reported better life satisfaction and less negative feelings, and physicians noted an improvement of the severity of RLS.[2] PLMSI and PLMS-AI were significantly decreased. Quality of sleep, sleep latency, and sleep time were also improved.[1,2,6] A superior efficacy of the combination therapy RR-L-dopa and CR-L-dopa compared with RR-L-dopa alone was shown in a comparative trial.[5] In another comparative trial of L-dopa/carbidopa vs. pergolide, pergolide at a mean dose of 0.159 mg at bedtime gave complete relief of RLS symptoms in 9 of 11 patients, compared with only 1 of 11 patients on L-dopa at the mean dose of 363 mg.[4] In another comparative trial of CR valproate 600 mg vs. CR-L-dopa/benserazide 200/50 mg, valproate significantly decreased the intensity of RLS and duration during the 24-hour period, whereas L-dopa decreased intensity of RLS only between the first 4 hours of sleep but not over the 24 hours.[7] In a comparative study of L-dopa vs. gabapentin, gabapentin was shown to be superior to L-dopa in improving sleep parameters.[8] In a large comparative study of cabergoline vs. L-Dopa, cabergoline proved better at reducing the IRLS score and produced less augmentation than L-dopa.[9] However, there were 38 dropouts because of adverse events in the cabergoline group compared with 26 in the L-dopa group.[9] It must be noted that the duration of most of the trials with L-dopa never exceed 4 weeks, and in 1 case was as short as 1 week.[3] This short duration and the low doses employed in the trials likely contribute to the reported generally good safety profile of L-dopa. Adverse events were minor and within the pharmacological profile of the dopaminergic drugs (nausea, gastrointestinal symptoms, dry mouth, dizziness); only one[2] or two[9] severe adverse events were reported for L-dopa. L-Dopa can thus be assessed as posing acceptable risks without the need for specialized monitoring in the treatment of RLS. L-Dopa/benserazide was licensed for RLS therapy first in Germany and Switzerland in 2001, and in other countries between 2004 and 2007 (Austria, Croatia, Poland, Brazil).

Implications for clinical practice. The limitation of L-dopa consists mainly of augmentation. Although the side effect profile of L-dopa is favorable, problems with augmentation develop with higher dosages (see

Part II below). The study by Trenkwalder et al.[9] showed cabergoline to be superior in efficacy to L-dopa in the treatment of RLS and produced less augmentation. Dropouts were, however, more numerous with cabergoline due to side effects. Based on these data, the task force believes that cabergoline may be used in preference to L-dopa but special monitoring is necessary (see below).

Implications for clinical research. Although L-dopa has proved efficacious for the symptomatic treatment of RLS, the number of patients involved in these studies is not large when compared to other dopaminergic drugs, and this probably reflects the early date at which most of these trials were performed. The total number of patients involved in the trials for L-dopa alone was only 100, and in some trials a clear distinction between idiopathic and uremic RLS was not made. It is also important to note the short duration of the trials that in most cases never exceeded 4 weeks. In view of the need for long-term treatment in patients with severe/chronic RLS, and the possibility that long-term use of L-dopa may be cumulatively associated with side effects that can require the drug to be stopped [e.g. augmentation of RLS symptoms, dopamine dysregulation syndrome (DDS)]. Long-term, prospective studies are needed in order to better assess and quantify the risk. Prospective studies examining the rates of augmentation in relation to dosage and special populations should employ specifically designed diagnostic criteria and rating scales.

Ergot-Derived Dopamine Agonists: Bromocriptine

Basic pharmacology. Bromocriptine is a tetracyclic ergoline compound derived from plant alkaloids. It is the first DA agonist marketed for the treatment of PD. Bromocriptine is a D2-like receptor agonist and a partial D1-like receptor agonist (which means that it has some weak D1 antagonistic effects on normosensitive receptors). Bromocriptine is a partial 5-HT_{2B} receptor agonist and has mild adrenergic effects. Bromocriptine lowers prolactin plasma levels, induces nausea, and lowers blood pressure.

After oral administration, bromocriptine is not completely absorbed (in humans), and maximal plasma levels are reached after 70 to 100 min with high variations among individuals. The absolute oral bioavailability is <10% because 90% of it undergoes first-pass hepatic metabolism. Bromocriptine plasma elimination half-life is about 6 to 8 hours. Ninety percent is bound to plasma proteins. Only a small amount is excreted unchanged in the urine (5%). The high level of metabolism that occurs increases the risk of drug interaction. Macrolides, acting as enzyme inhibitors and displacing bromocriptine from the binding protein, may lead to increased plasma bromocriptine concentrations and toxicity.

Review of clinical studies. *Level I*: Only one Level-I study met the review inclusion criteria.[24]

Walters et al.[24]: In this small (n = 6; 4 women), randomized, double-blind, prospective, placebo-controlled, crossover trial, patients with idiopathic RLS (defined as a history of restlessness and paresthesias that were worse at night) received 7.5 mg bromocriptine for 30 days. Primary and secondary end points are not specified separately. Five patients subjectively responded to treatment and showed a significant decrease of PLMSI ($P < 0.025$) compared with placebo.

Conclusions. This small study has shown a significant effect of bromocriptine on subjective RLS symptoms and PLMS. However, the task force is unable to consider this Level-I study as being of reasonable quality due to the fact that the end points were not clearly defined. Therefore, bromocriptine is considered likely efficacious for the treatment of RLS, as one small study has shown a significant effect of bromocriptine on subjective RLS symptoms and PLMS. There was no specific monitoring for augmentation or DDS.

Implications for clinical practice. Because of its side effect profile and limited data, the ergot-DA agonist bromocriptine is not currently used for RLS treatment. Special concerns about "sleep attacks" have not been raised.

Implications for clinical research. There are no further implications for clinical research.

Ergot-Derived Dopamine Agonists: Pergolide

Basic pharmacology. Pergolide is a synthetic ergoline DA agonist that acts at both D1-like and D2-like receptors. Although pergolide has mixed D1/D2 receptor activity, it has high intrinsic activity at D2-like receptors, where its effects predominate. Unlike other ergoline DA agonists (e.g., bromocriptine, which has partial D1 effects and thus, partially antagonizes D1 receptors and thereby, reduces cAMP production), pergolide stimulates adenylate cyclase activity (although only at high concentrations). Pergolide, like most ergot derivatives, also acts on non-DA receptors. It is a full agonist at 5-HT_{2B} receptor which has been proposed to be responsible, as one possible mechanism,

for fibrotic side effects. In vivo, pergolide reduces prolactin plasma levels and reduces blood pressure. Pergolide pharmacokinetic properties are poorly understood. Pergolide is rapidly absorbed from the gastrointestinal tract, reaching peak-plasma concentrations within 1 to 2 hours. Complete elimination of a single radio-labeled dose from the body is achieved within 4 to 5 days, with a mean elimination half-life of about 24 hours. Many metabolites have been detected, which do not appear to be produced by glucuronidation or sulfate conjugation.

Review of clinical studies. Four randomized controlled trials[4,25–27] (Level I) were qualified for inclusion in this review.

Level I: Staedt et al.,[4] see Levodopa section earlier.

Earley et al.[25]: This was a small (n = 16; 8 women; mean age, 59.5 years), 18-day, randomized, double-blind, prospective, parallel treatment, placebo-controlled, multicenter trial that sought to assess the efficacy of pergolide in RLS (IRLSSG criteria, PLMS >15/hour). Patients underwent a 4-day preentry washout period before being randomized to receive either placebo or pergolide (flexible titration, twice a day, at dinner and 2 hours before bedtime), 0.1 to 0.65 mg (median 0.35 mg). Primary end points were PLMSI, sleep efficiency, hours per day with RLS, global improvement score (in %). Pergolide significantly improved all outcome measures compared with baseline or placebo. PLMSI improved from 48.9 to 14.5 ($P < 0.05$); sleep efficiency improved from 61 to 79% ($P < 0.05$); hours with RLS decreased from 7.0 to 1.8 hours/day; and global improvement was 61% with pergolide, compared with 19% with placebo.

Wetter et al.[26]: This was a 4-week multicenter, randomized, double-blind, prospective, crossover, placebo-controlled study in 28 patients with idiopathic RLS (IRLSSG criteria). Inclusion criteria were a PLMI > 5, sleep latency > 25 min, and sleep efficiency < 75%. Psychoactive medications were stopped at least 2 weeks before baseline, and there was a 1-week washout in-between. Primary outcome measures were PLMI, total sleep time and subjective sleep quality as measured using a VAS. Pergolide (mean dose 0.51 mg/day 2 hours before bedtime) was more effective than placebo in reducing PLMI (6 vs. 55; $P > 0.001$), and PLMSA-I (2 vs. 32), and improving sleep efficacy (78% vs. 55%), total sleep time (min) (373.6 vs. 261.9; $P = 0.0001$), subjective sleep quality (3 vs. 2.2; $P = 0.0001$).

Trenkwalder et al.[27]: In this randomized, double-blind, prospective multicenter study, 100 patients with idiopathic RLS (IRLSSG criteria), who had sleep disturbances for 3 months and a PLMSA-I > 5, were randomly assigned to pergolide (0.25–0.75 mg, in the evening) or placebo, for 6 weeks during the first phase of the study. In the second phase of the study, responders continued to be treated double-blinded for 12 months, whereas nonresponders were switched to pergolide and continued treatment in an open phase for the same period. There was a preentry washout period of 10 days. Primary outcome measures were PLMSA-I and sleep efficiency, whereas secondary outcome measures were TST, PLMI, IRLS, CGI, and patient global impression of improvement (PGI-I) scale scores, as well as sleep diary recordings. All measures were performed at 6 weeks, 6 months, and 12 months. At Week 6, pergolide was more effective than placebo in reducing PLMI (−12 vs. −2) and PLMSA-I (−13 vs. −4; $P = 0.004$), as well as improving IRLS score ($P < 0.001$). No significant improvements were seen in sleep efficiency (11.3% vs. 6.1%; $P = 0.196$) or TST ($P = 0.145$). After 12 months, the blinded group on pergolide continued to show improvements in PLMSA-I and PLMI. Six patients remained on placebo for 1 year with a subjective benefit, but no objective improvement was noted in PSG parameters compared with baseline.

Conclusions. Pergolide has been shown to be efficacious in RLS but requires special monitoring due to increased incidence of valvular fibrosis and other fibrotic side effects.[23] The American Food and Drug Agency (FDA) has withdrawn pergolide from the market following recent safety information published in the *New England Journal of Medicine* (January 2007) confirming the association of valvular heart disease in PD patients exposed to pergolide.[23] In those countries in which pergolide is still licensed for the indication PD (e.g. Germany and other European countries) a boxed warning was added to product labeling regarding the increased risk of developing cardiac valvular disease. Accordingly, pergolide is considered second-line therapy in PD patients who do not respond to, nor tolerate nonergoline DA agonists. If therapy is initiated, an echocardiographic examination has to be performed before, after 3 to 6 months, and at regular intervals of 6 to 12 months. Pergolide is contraindicated in patients with a history of cardiac, pulmonary or retroperitoneal fibrosis, or signs of cardiac valve abnormalities. This side effect was not reported in controlled RLS trials, but cardiologic investigations have not been performed regularly in RLS studies. RLS pleuropulmonary disease due to pergolide treatment has been reported in a case series.[67] Common side effects in RLS are nausea (up to 59%), headache (up to 32%), asthenia (18%), rhinitis (up to 21%), vomiting

(up to 18%), and dizziness (up to 22%). In contrast to cabergoline, which has the advantage of a long half-life compared with orally available nonergot DA agonists, pergolide is generally no longer used in RLS patients due to its potential side effects. It is not known if fibrosis is dose dependent in pergolide. Special concerns about "sleep attacks" are based on one case report. There was no specific monitoring for augmentation or DDS.

Implications for clinical practice. There is sufficient evidence to conclude that pergolide is effective in the management of RLS. Sleep and RLS severity considerably improved. Because of its negative side-effect profile and in particular the potential to induce fibrosis, pergolide is not recommended for the treatment of RLS. If used, cardiopulmonary monitoring for fibrosis is necessary.

Implications for clinical research. Because of the side effect profile, there are no implications for further research in RLS therapy.

Ergot-Derived Dopamine Agonists: Cabergoline

Basic pharmacology. Cabergoline is an orally administered synthetic tetracyclic ergoline derivative that acts in vitro and in vivo as a selective D2 receptor agonist, with no substantial affinity for D1 receptors. As with other ergotamine derivatives, it has also some affinity for nondopamine receptors (noradrenergic and serotonergic). It is a full agonist at 5-HT_{2B} receptors that has been proposed to be responsible for fibrotic side effects. Cabergoline lowers prolactin secretion, and like all effective D2-agonists, induces nausea, vomiting, and orthostatic hypotension in healthy volunteers. One major characteristic of cabergoline is its long duration of effect with oral administration, probably because its elimination half-life is ~65 hours. Cabergoline suppresses prolactin levels with duration of action up to 21 days after a single 1 mg oral dose. Such a pharmacokinetic profile allows a once-daily dosing treatment regimen. The cabergoline TMax is observed at 2.5 hours, and it is metabolized into several metabolites predominantly by the liver, and excreted mainly by the fecal route.

Review of clinical studies. Three randomized controlled trials (Level I) were qualified for this review.[9,28,29]

Level I: Stiasny-Kolster et al.[28]: This was a 5-week randomized, double-blind, prospective, parallel, placebo-controlled, multicenter trial that assessed the efficacy and safety of cabergoline in 85 patients (60 women; mean age, 56 ± 10 years,) with idiopathic RLS (IRLSSG criteria, IRLS ≥4 at night). After a 1-week preentry washout (2 weeks for those on L-dopa), patients were randomly assigned to receive placebo or cabergoline 0.5 mg, 1 mg, or 2 mg once daily. The primary end point was RLS-6 severity scores during the night. Secondary end points were RLS-6, IRLS scores, and the rate of remission (i.e. 0 points in RLS-6 severity scales or IRLS). All doses of cabergoline improved the severity of RLS-6 scale scores during the night in comparison with placebo ($P < 0.0001$). IRLS scores also improved significantly (−13.1 for 0.5 mg dose, $P < 0.01$; −13.5 for 1 mg dose, $P < 0.01$; and −15.7 for 2 mg dose, $P < 0.001$). The most significant improvement in RLS-6 severity scores at bedtime, during the day, and RLS-6 sleep satisfaction were seen in the cabergoline 1 mg group ($P < 0.05$). Eleven patients dropped out of the study due to adverse events.

Oertel et al.[29] performed a 5-week randomized, double-blind, prospective, parallel, placebo-controlled multicenter trial (also known as the CATOR study) that sought to assess the efficacy and safety of cabergoline in 40 patients (mean age, 56 ± 10 years, 30 women), with idiopathic RLS (IRLSSG criteria). The inclusion criteria were IRLS > 10, RLS-6 at night > 4, and a PLMSA-I > 5. Patients underwent a washout period of 5 half-lives before the start of the trial. Primary outcome measures were PLMSA-I and sleep efficiency; RLS severity was assessed using IRLS and RLS-6 scales, CGI, SF-A, and the QoL-RLS. At a fixed dose of 2 mg/day, cabergoline was superior to placebo as measured by PLMS-AI scores (−18 vs. −5; $P = 0.0014$), significantly improved sleep efficiency (+6.2% vs. +3.3%; $P = 0.0443$), and IRLS total score (−23.7 ± 11.2 vs −7.9 ± 11.0 placebo; $P = 0.0002$), subjective measurements also improved. Three patients dropped out of the study due to adverse events.

Trenkwalder et al.[9]: In this large (n = 361; 256 women; mean age, 58 ± 12 years), 30-week randomized, double-blind, prospective study, 2 to 3 mg cabergoline (n = 178) and 200/50 to 300/75 L-dopa/benserazide (n = 183) were compared for treatment of idiopathic RLS that was diagnosed according to IRLSSG criteria (CALDIR study). Inclusion criteria were an IRLS > 10, and RLS-6 at night ≥4. Patients underwent a 1-week preentry washout period. The primary outcome measure was change in IRLS score; secondary efficacy measures were the SF-A, RLS-QoL, ASRS (4-item version), CGI, and the RLS-6. Mean change from baseline to Week 6 in IRLS sum score was d = −16.1 in the cabergoline group and d = −9.5 in the L-dopa group (d = −6.6, $P < 0.0001$).

Concerning doses administered, 83.1% had 2 mg cabergoline, and 55.7% had 200 mg L-dopa/50 mg benserazide. Eighteen patients in the L-dopa group discontinued due to augmentation, compared with 7 patients in the cabergoline group. A total of 38 patients dropped out of the cabergoline group and 26 dropped out of the L-dopa group due to adverse events. Two serious adverse events were recorded in each group. The most frequent adverse events were gastrointestinal symptoms.

Conclusions. Cabergoline has proven to be efficacious for the treatment of RLS, but special monitoring is necessary. One of the controlled trials used the RLS-6 scales and found a dose-dependent reduction of RLS symptoms, including during the daytime, paralleling its long half-life.[28] To date, cabergoline is the only DA agonist that has been studied against L-dopa in a controlled large-scale trial and has been shown to be significantly superior. The most common side effects in double-blind studies were nausea (up to 35%), constipation (up to 20%), and headache (up to 20%). Fibrosis was not observed within the controlled clinical trials (maximum of 12 weeks) but was not specifically assessed. Other side effects seen with DA agonists such as DDS[68] were not specifically assessed.

In those countries in which cabergoline is licensed for the indication of PD, a boxed warning was added to product labeling regarding the increased risk of developing cardiac valvular disease with dosages higher than 3 mg. Accordingly, in PD, cabergoline is considered as second-line therapy for patients who do not respond to, nor tolerate nonergoline DA agonists. It is contraindicated in patients with a history of cardiac, pulmonary or retroperitoneal fibrosis, or signs of cardiac valve abnormalities.

Implications for clinical practice. 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 DA agonist to be compared with L-dopa in a large-scale controlled trial and has been shown to be superior to the latter. The mean effective daily dose of cabergoline is about 2 mg (range 0.50–3 mg) given 2 to 3 hours prior to bedtime. Augmentation has reliably been assessed by clinical interviews in several trials revealing a lower incidence compared with L-dopa. Concerns about fibrosis have not been addressed in RLS studies. Cardiopulmonary monitoring for fibrosis is necessary. Special concerns about "sleep attacks" have not been raised.

It is important to note that in the US, where the FDA has withdrawn the ergot-DA agonist pergolide from the market, cabergoline was not licensed for PD.

Implications for clinical research. Long-term trials with cabergoline need to be undertaken with better monitoring of the potential side effects such as fibrosis (especially heart valve fibrosis), its possible dose dependency and compulsive behavior. These have not been investigated in previous RLS trials. Comparison trials indicating the most appropriate drug for the treatment of RLS should include cabergoline as available data on this drug show a good efficacy and tolerability profile in RLS.

Ergot-Derived Dopamine Agonists: Dihydroergocriptine (DHEC)

Basic pharmacology. Dihydroergocryptine (DHEC) is a dihydro-derivative of ergocryptine acting as a D2 agonist and a partial D1 agonist. Therefore, DHEC has a pharmacodynamic profile quite comparable with that of bromocriptine. Like all ergotamine derivatives, DHEC has effects on serotonergic and adrenergic receptors. In healthy volunteers, its effects on D2 receptors reduce prolactin plasma levels and induce nausea and hypotension. DHEC, like other ergot derivatives, has linear kinetics. Its oral bioavailability after first pass effect is low (below 5%). It has linear metabolism with generation of active metabolites, and it is eliminated through feces and has no interference with L-dopa kinetics.

Review of clinical studies. *Level III*: One open-label trial (Level III) has investigated DHEC in RLS patients.[30]

Tergau et al.[30]: This was a 4-week open, multicenter study examining the efficacy of DHEC in treating patients (n = 16; 10 women) with RLS (IRLSSG criteria). Patients underwent 1-week preentry washout period before being treated with DHEC (flexible dose, maximum dosage 60 mg/day). The primary end point was an improvement in RLS during the night as measured on a VAS. RLS symptoms during the night improved significantly, from 55.7 ± 27.3 to 20.1 ± 17.5 ($P < 0.003$), that is, overall complaints decreased by 63.9 ± 38.1% as measured on the VAS. One patient dropped out of the study due to nausea.

Conclusions. DHEC is considered investigational for the treatment of RLS. There was no specific monitoring for augmentation or DDS.

Implications for clinical practice and clinical research. Because of the limitations of DHEC due to its possible side effects, there are no further implications for clinical practice and research.

Ergot-Derived Dopamine Agonists: Lisuride

Basic pharmacology. Lisuride is an alpha-aminoergoline with D2, D3, and D4 receptor agonist properties and partial agonism at D1 receptors. In contrast to other ergot derivatives, lisuride behaves as a 5-HT_{2B} receptor antagonist and is also a strong 5-HT_{1A} agonist. In its oral form lisuride has been used for many years as an anti-Parkinson and prolactin-lowering drug. It is currently being developed as a matrix-type transdermal patch to be applied every second day to achieve continuous dopaminergic stimulation. Patches with a surface of 10 cm^2 have a nominal release rate of 0.1 mg/24 hours. Greater patch surfaces result in proportionally higher release rates, and there are no significant differences according to application site, gender, or age. Lisuride is rapidly oxidized in the liver (after oral application involving CYP 2D6 and 3A4), with no known active metabolites. After patch removal, lisuride plasma levels fall with a t/2 of 5 to 8 hours. In contrast to the tablet form, there is very little variability in plasma levels with the lisuride patch and little or no uptitration is needed. Lower doses are to be used in patients with moderate hepatic or renal impairment.

Review of clinical studies. Only one randomized controlled trial[31] (Level I) was qualified for inclusion in this review.

Level I: Benes[31]: This small, 1-week randomized, double-blind, parallel treatment, prospective, placebo-controlled trial was preceded by a 2-week open-label pretreatment phase. Nine patients (3 women; mean age, 58 years) with RLS (IRLSSG criteria, IRLS $\geq$ 10; RLS-6 severity of RLS during the day $\geq$ 3) who had responded previously to L-dopa and had responded to lisuride in the open-label phase were randomly assigned to receive lisuride transdermal patch (fixed dose 3 or 6 mg) or placebo. Clinical efficacy was assessed through IRLS and RLS-6 scores, and the incidence of PLM as measured through actigraphy. In the open-label phase, IRLS scores improved compared with baseline (1 patch, 3 mg: IRLS, 23.3 $\pm$ 11.6; 2 patches, 6 mg: IRLS, 22.0 $\pm$ 12.5; all together IRLS, 22.1 $\pm$ 11.6). In the double-blind phase, the IRLS score of patients who remained on lisuride continued to improve [final IRLS score (mean $\pm$ SD): 6.8 $\pm$ 12.0], whereas the IRLS score of the placebo group worsened (final IRLS score: 18.5 $\pm$ 7.5).

Conclusions. Transdermal lisuride showed promising results in mild RLS patients in one small proof-of-principle study. However, due to methodological limitations, the task force does not consider this study to be of reasonable quality, and therefore, transdermal lisuride can only be considered investigational, and it is unsure whether special monitoring for fibrosis is required. There was no specific monitoring for augmentation or DDS.

Implications for clinical practice. One Level-I placebo-controlled trial with 9 RLS patients, which used subjective criteria for measuring improvements in RLS, was evaluated and was in favor of lisuride. Adverse events included local site reactions of the patch and nausea.

Implications for clinical research. The data available are promising, but long-term data and safety monitoring for side effects are necessary. Augmentation has not been reported and not monitored in the current trial. An interesting aspect is the antagonistic properties on 5-HT_{2B} receptors.

Nonergot-Derived Dopamine Agonists: Ropinirole

Basic pharmacology. Ropinirole is a selective DA agonist with nonergoline structure. In vitro and in vivo studies have shown that it is a full agonist for the D2 receptor subfamily and also has a high affinity for the D3 receptor subtype. Like other D2 agonists, ropinirole decreases prolactin secretion and induces nausea and hypotension in healthy volunteers.

After oral administration, ropinirole is rapidly absorbed and has a median TMax of about 1.5 hours after dosing. It has a bioavailability of 50% and a mean elimination half-life of about 6 hours. Ropinirole for RLS is recommended as a once-only dosage 2 hours before bedtime.

Plasma protein binding is low and concentration independent. Ropinirole is metabolized predominantly by the liver. The drug is oxidized, mainly through the cytochrome P450 1A2 pathway. Drug interactions (macrolides) and altered pharmacokinetics in patients with hepatic insufficiency are, therefore, theoretically possible, although no such events have been reported in the clinical literature. Theophylline has been shown not to interact with ropinirole, whereas hormone replacement therapy (estradiol) enhances ropinirole plasma levels.

Review of clinical studies. *Level I*: Seven randomized, placebo-controlled trials[10–16] (Level I) have been qualified for this review.

Happe et al.[10]: This 4-week randomized, open, head-to-head clinical trial examined the efficacy of gabapentin (mean dosage 800 ± 397 mg) and ropinirole (mean dosage 0.78 ± 0.47 mg) in 16 patients (5 women; mean age, 56 years) with idiopathic RLS (IRLSSG criteria). Efficacy end points were measured using the IRLS, PSG, and the Epworth sleepiness scale (ESS). In comparison with baseline, a significant improvement was seen in IRLS scores ($P \leq 0.018$), reduction of PLMS ($P < 0.03$), and PLMSI ($P < 0.02$) in both groups. The ESS remained unchanged. Sleep efficiency was superior in the gabapentin group.

Adler et al.[11]: This double-blind, placebo-controlled, crossover 4-week study was completed by 18 patients (16 women; mean age, 60 years) with primary RLS (IRLSSG criteria, IRLS ≥ 10). Patients had not received RLS medication for 2 weeks prior to the baseline visit. The mean dose of ropinirole was 4.6 mg/day (range 1–6 mg); 14 patients received 6 mg/day. Efficacy was assessed using IRLS and ESS scales as well as an RLS diary that was completed twice a week. The IRLS score improved ($P < 0.001$) from a mean (SD) of 25 (7) during placebo treatment to 13 (12) during ropinirole treatment. The ESS score did not change. The diary (filled-in by 19 patients) recorded the mean rate of RLS to be 23% during placebo treatment and fell from 50% to 12% following treatment with ropinirole. Two patients dropped out of the study due to adverse events under ropinirole, and 1 patient due to adverse events under placebo. Adverse events included nausea and dizziness.

Allen et al.[12]: This was a double-blind, parallel-group, placebo-controlled, 12-week study completed by 59 patients (age 18–79 years) with RLS and PLMS. Inclusion criteria were primary RLS (IRLSSG criteria), PLMSI >5/hour, an IRLS score ≥ 15, and a minimum of 15 nights of RLS symptoms in the month prior to study entry. Patients receiving medications that affected RLS or sleep underwent a preentry washout phase of a minimum of 7 days or 5 half-lives. Efficacy of ropinirole (0.25–4 mg/day) was determined by PLMS and IRLS; the MOS scale was used as a secondary outcome measure. At Week 12 LOCF (last observation carried forward) there was a significant decrease in PLMS/hour under ropinirole (48.5–11.8), compared with placebo (35.7–34.2; adjusted treatment difference: −27.2; 95% CI: −39.1, −15.4; $P < 0.0001$). PLMA/hour decreased from 7.0 to 2.5 with ropinirole but increased from 4.2 to 6.0 with placebo (adjusted treatment difference: −4.3, 95% CI: −7.6, −1.1; $P = 0.01$). Ropinirole improved sleep efficiency ($P = 0.011$), but the increased sleep time was not different to placebo ($P = 0.11$). The subjective MOS scale showed improvements that were significant only for sleep adequacy ($P = 0.0316$). No significant improvement was seen in IRLS scores. No serious adverse events occurred in either group.

Trenkwalder et al.[13]: In this 12-week prospective, double-blind, placebo-controlled trial, 284 patients (age 18–79 years) with RLS (IRLSSG criteria) from 10 European countries were randomly assigned (1:1) to receive either ropinirole (n = 146) or placebo (n = 138). All patients had an IRLS score of ≥15, and had either experienced at least 15 nights with RLS symptoms in the previous month, or reported that they had such a frequency of symptoms prior to treatment. Patients taking medications that affected RLS or sleep, or caused drowsiness, underwent a preentry washout period of 7 consecutive nights or 5 half-lives. The primary efficacy end point was mean change from baseline to Week 12 in total IRLS score. Secondary end points were improvements as measured on the CGI scale, the MOS sleep scale, the RLS-QoL scale, and the work productivity and activity impairment (WPAI) questionnaire. Improvement in IRLS scores at Week 12 was greater in the ropinirole group [mean (SD) dose, 1.90 (1.13) mg/day] compared with placebo [mean (SE): −11.04 (0.719) vs. −8.03 (0.738) points; adjusted difference = −3.01 (95% CI, −5.03 to −0.99); $P = 0.0036$]. More patients in the ropinirole group showed improvement on the clinical global impressions–improvement (CGI-I) scale at Week 12 than in the placebo group [53.4% vs. 40.9%; adjusted odds ratio = 1.7 (1.02–2.69); $P = 0.0416$]. Ropinirole was also shown to improve sleep adequacy ($P = 0.0015$), sleep quantity ($P = 0.0331$), daytime somnolence ($P = 0.0064$), and QoL as measured on the RLS-QoL scale ($P = 0.0314$). No significant improvement was seen in WPAI and SF-36 total scores. Sixteen patients in the ropinirole group and 6 patients in the placebo group dropped out of the study due to adverse events. The most common adverse events were nausea and headache.

Walters et al.[14]: This was a 12-week, multinational (Australian, Europe, N. America), double-blind, randomized, parallel-group, placebo-controlled study completed by 266 patients (age 18–79 years) with idiopathic RLS (IRLSSG criteria), who had an IRLS score ≥15 and had experienced 15 nights of RLS symptoms in the previous month. Patients requiring daytime treatment of RLS symptoms were excluded from the study. As in the previous study, patients taking medications that affected RLS or sleep underwent a preentry washout period of seven consecutive nights or five half-lives. Efficacy end points were the same as previously

described.[13] Patients were randomly assigned (1:1) to receive 0.25 to 4.0 mg/day of ropinirole administered 1 to 3 hours before bedtime (n = 131) or placebo (n = 136). Improvements in IRLS scores were significantly greater at Week 12 for ropinirole compared with placebo (−11.2 [SE 0.76] vs. −8.7 [0.75]; adjusted treatment difference −2.5 [95% CI, −4.6, −0.4], P = 0.0197). All secondary end points also improved: CGI-I, 59.5% vs. 39.6% ($P < 0.001$); sleep disturbance, sleep adequacy, sleep quantity ($P = 0.0001$), and sleep somnolence ($P = 0.0043$). Nine patients in the ropinirole group and 11 patients in the placebo group dropped out of the study due to adverse events.

Bliwise et al.[15]: This 6-week study consisted of a 4-week open-label phase and a 2-week double-blinded, randomized, placebo-controlled efficacy phase. Twenty-two patients (13 women; mean age, 50.8 years; mean duration of symptoms, 26.1 years) with primary RLS (IRLSSG criteria), and who were drug-free the evening before baseline, first entered an open-label dose-titration period of 2 weeks. This first period was then followed by another 2-week sustained open-label efficacy period. Patients were then randomly assigned to receive either ropinirole (n = 9; 0.25–1.5 mg at bedtime, maximum daily dosage, 6 mg) or placebo (n = 13) for a further 2 weeks. Primary outcome measures were assessment of PLMS recorded with nocturnal PSG, and RLS symptoms as assessed with the IRLS. A secondary outcome measure was sleep macroarchitecture (TST, sleep efficiency). Ropinirole, at a mean dose of 1.4 mg significantly decreased PLMS and RLS symptoms as measured by the IRLS. Sleep macroarchitecture did not change. The NREM/PLMS index (events/hour) in the placebo group was 19.2 (4.6–33.9) at baseline and 76.4 (37.3–115.5) at Week 6; compared with 19.7 (0–45.6) in the ropinirole group at baseline, and 19.8 (0–44.4) at Week 6. No patients dropped out of the study due to adverse events. Side effects included nausea, headache, and daytime somnolence.

Bogan et al.[16]: In this 12-week multicenter, double-blind, placebo-controlled, flexible-dose study, 331 patients with primary RLS (IRLSSG criteria) and no augmentation were randomly assigned to receive ropinirole (n = 164; 0.25–4.0 mg/day) or placebo (n = 167). The primary outcome measure was change in IRLS total score, whereas secondary outcome measures were CGI and MOS scores. Ropinirole significantly improved IRLS scores compared with placebo (adjusted mean treatment difference, −3.7; 95% CI, −5.4 to −2.0; $P < 0.001$). At Week 12 LOCF, the mean improvement of IRLS scores were significantly improved for ropinirole compared with placebo [−13.5 (1.2) vs. −9.8 (1.2)]. Ropinirole was associated with significantly greater improvements in subjective measures of sleep disturbance, problems, and adequacy ($P < 0.001$) as well as with sleep quantity ($P = 0.005$). Daytime somnolence did not change ($P = 0.10$). Seven patients in the ropinirole group and 9 patients in the placebo group dropped out of the study due to adverse events.

Montplaisir et al.[69]: This was a randomized, placebo-controlled, multicenter trial that sought to investigate the long-term efficacy of ropinirole in treating idiopathic RLS (IRLSSG criteria) patients who had experienced symptoms on 15 nights during the previous month and had an IRLS > 15. Patients underwent a preentry washout period of five half-lives or seven nights. In the first part of the study, which was single-blinded, patients (n = 202; 51 women, age 18–79 years) received ropinirole for 24 weeks. In the second part of the study, patients (n = 92 of the 202 initial population) were randomly assigned to double-blind treatment with either ropinirole or placebo for a further 12 weeks. The mean and median dose at Week 20, after which no more changes in dose were allowed, was 2.05 and 2.00 mg/day, respectively. At Week 24, 15.8% of patients were receiving the maximum dose of 4.0 mg/day. The primary end point was the proportion of patients relapsing during double-blind treatment. Secondary end points were the time to relapse, withdrawals due to lack of efficacy, improvement in CGI-I and IRLS scores during double-blind treatment, and changes in MOS and QoL parameters. At Week 36 LOCF, significantly fewer patients relapsed on ropinirole than on placebo (32.6% vs. 57.8%; $P = 0.0156$). CGI-I assessments of "much/very much improved" were greater in the ropinirole group compared with the placebo group (68.9% vs. 46.7%, $P = 0.0298$). Ropinirole improved IRLS scores compared with placebo (+4.1 vs. 8.2; $P = 0.0246$). Sleep parameters (MOS sleep disturbance, $P = 0.0003$; somnolence, $P = 0.0136$) and QoL measures also improved with ropinirole compared with placebo (17 vs. 5.2, $P = 0.004$). Thirty-seven patients in the single phase and 1 patient in the double-blind phase dropped out of the study due to adverse events.

Conclusions. Over 1,000 patients with idiopathic RLS have been included in controlled trials with ropinirole. Of the seven studies described earlier, six were placebo-controlled trials,[11–16] and one was a gabapentin-controlled study.[10] Primary end points were the IRLS and sleep laboratory measurements such as PLMS and sleep efficiency. All placebo-controlled tri-

als were in favor of ropinirole, adverse reactions were similar to those reported for ropinirole in PD studies and included nausea, somnolence, and dizziness. No cases of dyskinesia or sleep attacks were observed. Patients were usually followed for 12 weeks, in sleep laboratory studies some only for 4 weeks.

Ropinirole was efficacious for treating RLS symptoms without special monitoring. 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 agonist, there are no specific concerns about hypersomnolence in RLS patients. There was no specific monitoring for augmentation or DDS.

Implications for clinical practice. There is sufficient evidence to conclude that ropinirole is clinically useful for the management of RLS in patients with moderate to severe clinical symptomatology. Sleep and general RLS severity improved in all studies. One trial comparing ropinirole with gabapentin found that both were equally efficient in treating RLS, but only 9 patients were treated for 4 weeks.

The mean effective daily dose of ropinirole reported in clinical trials was about 2 mg as a single dose at night; the maximum licensed dosage is 4 mg, although in the early studies[11,15] 6 mg was used.

It is important to note that there are different regulations/recommendations worldwide: these include formal licensing of ropinirole for the treatment of RLS in Europe, USA, and Australia, with each country carrying individual warnings for treatment. There are differences in the policies for driving in different countries: in some countries patients must simply be informed of the risk of somnolence, whereas in others patients taking ropinirole are advised not to drive.

Implications for clinical research. Apart from the general implications for the clinical research of DA agonists (see later), there are specific implications for ropinirole: it is necessary to perform a trial with a patient population that can be treated in the afternoon with a divided dosage. This regimen is commonly used in clinical practice. Although appropriate trials may have been performed or completed, no publication meeting the task force's inclusion criteria was available at the time of this review. Furthermore, a detailed analysis of treatment response compared with placebo response may help to better understand and identify subpopulations that will benefit the most from ropinirole treatment. The very consistent dosage of $\sim$2 mg that is derived from several independent ropinirole studies may be used as a basis for future trials with sustained release formulations.

Nonergot-Derived Dopamine Agonists: Pramipexole

Basic pharmacology. Pramipexole is an orally active, nonergoline, DA agonist. In vitro and in vivo studies have shown that it is a full agonist for the D2 receptor subfamily, with preferential affinity for the D3 receptor subtype. Like other D2 agonists, pramipexole decreases prolactin secretion and induces nausea and hypotension in healthy volunteers. Putative antidepressant properties also have been considered for pramipexole.

Pramipexole is rapidly and completely absorbed after oral administration. Its bioavailability is greater than 90%. Maximal plasma concentration (TMax) is reached within 1 to 3 hours. Pramipexole does not bind significantly to plasma protein. The plasma elimination half-life of pramipexole (T1/2) is about 10 hours. The drug is metabolized, only to a minor degree, and urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Nonrenal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. This mode of elimination may account for some pharmacokinetic differences related to age, gender, and potential interaction with drugs like cimetidine.

Review of clinical studies. Five randomized, placebo-controlled trials (Level I)[17–21] have been qualified for this review.

Montplaisir et al.[17]: This 10-week, double-blind, placebo-controlled, crossover, randomized trial was completed by 10 patients (5 women; mean age, 49.3 $\pm$ 11.5 years) with primary RLS (IRLSSG criteria), who had a PLMI $>$ 10 and RLS symptoms that interfered with sleep onset or with sleep continuity on more than three nights a week for at least 1 year. Medications that affect sleep architecture or motor manifestations were stopped 2 weeks before baseline, and there was a 2-week washout period between treatments. Primary outcome variables were PLMSI, PLMI during wakefulness (PLMWI); home questionnaires about leg restlessness during the day and night were also used. Pramipexole (0.75–1.5 mg/day) was shown to reduce the PLMSI to normal values (Wilcoxon, $P = 0.005$). The PLMWI was also significantly reduced (Wilcoxon, $P = 0.007$).

Partinen et al.[18]: This was a 3-week, double-blind, placebo-controlled, parallel-group, dose-finding study in 109 patients (79 women; age 27–76 years) with primary RLS (IRLSSG criteria) who had an IRLS score $\geq$15, and PLMS $\geq$5/hour, as well as weekly RLS symptoms that had disrupted sleep within the previous 3 months. Patients were randomly assigned to prami-

pexole (fixed doses, 0.125, 0.25, 0.50, 0.75 mg/day) or placebo. The primary efficacy end point was PLMI; secondary efficacy end points were additional PSG measures and IRLS, CGI, PGI, and QoL scores. Pramipexole, at all doses, was shown to improve PLMI ($P < 0.0001$), IRLS scores ($P = 0.0274$, 0.125 mg; $P < 0.0001$, all other doses), CGI ratings ("much improved" or "very much improved" in 61.9–86.4% of patients in the pramipexole groups, compared with 42.9% in the placebo group; $P < 0.05$ in the 0.25, 0.50, and 0.75 mg groups). One patient dropped out of the study due to adverse events.

Winkelman et al.[19]: This 12-week randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of pramipexole in patients (n = 344; 62.2% women; mean age, 51.4 years) with moderate to severe idiopathic RLS (IRLSSG criteria) with an IRLS >15 and symptoms on at least 2 to 3 days per week during the 3 months previous to study initiation. Patients were randomly assigned to pramipexole (fixed doses, 0.25, 0.50, 0.75 mg/day) or placebo. The primary efficacy end points were IRLS and CGI-I scores. Secondary efficacy end points were RLS QoL, PGI, VAS, and ESS scores. IRLS and CGI-I scores showed pramipexole to be superior to placebo: IRLS adjusted mean change from baseline to Week 12 was −9.3 (1.0) for placebo, and −12.8 (1.0) for 0.25 mg/day, −13.8 (1.0) for 0.50 mg/day, and −14.0 (1.0) for 0.75 mg/day (all $P < 0.01$); the increase in the CGI-I rating of "much" or "very much improved" was 51.2% for placebo and 74.7%, 67.9%, and 72.9% for pramipexole; all $P < 0.05$). In comparison with placebo, pramipexole was also shown to significantly improve QoL (RLS QoL: $P = 0.0041$ for 0.25 mg/day; $P = 0.0002$ for 0.50 mg/day; $P = 0.0029$ for 0.75 mg/d). Eleven percent of patients dropped out of the study due to adverse events. The most common adverse events were nausea and somnolence.

Trenkwalder et al.[20]: This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter withdrawal study in 150 patients (109 women; mean age, 59.6 years) with idiopathic RLS (IRLSSG criteria), an IRLS > 15 and who had responded to pramipexole (mean dose, 0.50 mg) during a 6-month run-in period. After this first phase, patients were randomly assigned to receive either placebo or to continue with pramipexole (0.125–0175 mg/day) for 3 months. The primary end points were a predefined worsening of CGI-I and IRLS scores. More patients in the placebo group experienced a worsening in their symptoms compared with patients receiving pramipexole (85.5% vs. 20.5%; $P < 0.0001$). Patients on placebo also reached the primary end points quicker than those receiving pramipexole (5 vs. 42 days).

Oertel et al.[21]: This was a 6-week randomized, double-blind, placebo-controlled multicenter study in 345 (ITT 338) patients (222 women; 18–80 years) with idiopathic RLS (IRLSSG criteria) with an IRLS >15 and symptoms at least 2 to 3 days/week in the 3 months prior to study entry. All pharmacological treatment for RLS was discontinued 14 days before study start. Patients were randomly assigned to receive either placebo (n = 115) or pramipexole (n = 230). Pramipexole was administered at a starting dose 0.125 mg/day and was individually optimized according to PGI assessment up to a maximum dose of 0.75 mg/day. Primary end points were changes in IRLS score compared with baseline, and CGI-I assessments of "much/very much improved" at Week 6. Secondary endpoints were PGI and IRLS responder rates, IRLS scores improved by 5.7 (±0.9) from 24.9 to 19.2 for placebo and by 12.3 (±0.6) from 24.7 to 12.4 for pramipexole (difference endpoint to baseline of pramipexole vs. placebo: > 6; $P < 0.0001$). In the pramipexole group 62.9% of patients had a CGI-I assessment of "much/very much improved" at Week 6 compared with 32.5% of patients in the placebo group ($P < 0.0001$). PGI responder rates were improved in 61.6% of the pramipexole group compared with 31.6% in the placebo group ($P < 0.0001$). Eleven patients (5 placebo, 6 pramipexole) dropped out of the study due to adverse events.

Conclusions. Over 1,000 patients with idiopathic RLS have been included in controlled trials with pramipexole. All four of the randomized trials mentioned earlier were placebo-controlled. Trials used the IRLS, and sleep laboratory trials used the PLMS and the PLMI as main outcome criteria. All placebo-controlled trials were in favor of pramipexole, adverse reactions were similar to those reported for pramipexole in PD studies and included nausea, somnolence, and dizziness. Sleep attacks were not observed within the clinical trials, which is different from trials in PD patients. Patients were followed for 4 to 12 weeks, in sleep laboratory studies some only for 2 weeks. Pramipexole was efficacious for treating RLS symptoms without special monitoring. 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 agonist, there are no specific concerns about hypersomnolence in RLS patients. There was no specific monitoring for augmentation or DDS.

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. Sleep and general RLS severity improved. There are no comparative trials other than to placebo. The mean effective daily dose of pramipexole reported in clinical trials was between 0.25 and 1 mg (=0.18 and 0.70 mg) as a single dose at night. The maximum approved dose is 0.50 mg/day in the USA and 0.75 mg/day in Europe.

There are different regulations/recommendations worldwide: these include the formal license for RLS in Europe and the USA with each country carrying individual warnings for treatment. There are differences in the policies for driving in different countries; in some countries patients must simply be informed of the risk of somnolence, whereas in other countries, patients on pramipexole are advised not to drive.

Implications for clinical research. Apart from the general implications for the clinical research of DA agonists (see later) it may be worth conducting studies that investigate pramipexole as a drug for immediate or intermittent use in RLS therapy, as some studies that do not meet the inclusion criteria of this report have shown promising results (see paragraph on further perspectives later). The rapid onset of efficacy may allow other—or no—titration schemes in addition to those currently licensed. Different titration regimens should be prospectively evaluated in further trials. A more detailed prospective analysis of side effects such as DDS, sleepiness, or sudden sleep onset would be required in long-term studies, although one retrospective study did not show an increased risk of sleepiness with pramipexole therapy.[70]

Nonergot-Derived Dopamine Agonists: Rotigotine

Basic pharmacology. Rotigotine is a D3/D2/D1 DA agonist developed as a matrix-type transdermal patch for once-daily dosing. The active compound is continuously delivered to the skin (average nominal dose: 0.2 mg/cm^2/24 hours). Rotigotine is extensively metabolized by enzymes catalyzing conjugation and several multiple cytochrome P450 (CYP) isoenzymes. After removal of the patch, plasma levels decrease with a half-life of 5 to 7 hours. Rotigotine and its metabolites are primarily excreted in urine and to a smaller amount in feces. Rotigotine displays dose-proportional pharmacokinetics over a range of 1 mg/24 hours to 16 mg/24 hours. Rotigotine has a low drug–drug interaction potential. No dose adjustment is recommended based on age or in subjects with moderate impairment of hepatic function and in subjects with different stages of renal impairment. Like other D2 agonists, rotigotine decreases prolactin secretion and induces nausea and hypotension in healthy volunteers.

Review of clinical studies. One randomized controlled trial (Level I) was qualified for inclusion in this review.[22]

Level I: Stiasny-Kolster et al.[22]: This is a 1-week multicenter, double-blind, randomized, parallel-group, placebo-controlled, proof-of-principle trial, 63 (ITT) patients (64% women; mean age, 58 $\pm$ 9 years) with idiopathic RLS (IRLSSG criteria) and an RLS-6 score $\geq$3. There was a preentry washout of at least 3 days or of five half-lives depending on which was longer if the patient was taking the following medications: neuroleptics, hypnotics, antidepressants, anxiolytic drugs, anticonvulsive therapy, psychostimulatory drugs, L-dopa, or opiods. There was also a run-in period of 7 + 3 days without patch application. The primary efficacy measure was the total IRLS score. The RLS-6 scale, the CGI, and a sleep diary were also used. RLS severity improved related to dose by 10.5 (1.125 mg/day, $P = 0.41$), 12.3 (2.25 mg/day, $P = 0.18$), and 15.7 points (4.5 mg/day, $P < 0.01$) on the IRLS compared with placebo (8 points). The CGI supported the favorable efficacy of the 4.5 mg dose. One patient in the placebo group dropped out of the study due to adverse events.

Conclusions. Rotigotine patch is likely efficacious without special monitoring. According to the task force's inclusion criteria only one Level-I trial with 63 RLS patients compared with placebo could be evaluated. This study, using subjective criteria for measuring improvements in RLS, was in favor of rotigotine. Adverse events were similar to those reported for rotigotine in PD studies and included local site reactions of the patch and nausea. Sleep attacks were not observed in the clinical trial. From the available published trial there is no evidence that the incidence of adverse reactions, except site reactions of the patch, is lower or higher than with any other available DA agonist, there are no specific concerns about hypersomnolence in RLS patients. In the long-term more patch reactions would be expected. There was no specific monitoring for augmentation or DDS.

Implications for clinical practice. Rotigotine patch is currently used for the treatment of PD with an indication for PD monotherapy and combined therapy with L-dopa in PD in various countries worldwide. The current results from clinical studies in RLS are limited but promising. Several large trials have been conducted and are available in abstract form, but additional full papers did not meet the inclusion cut-off date of this EBM report.

Implications for clinical research. Apart from the general implications for the clinical research of DA ago-

nists (see later), it may be of particular interest, if the continuous plasma level provided by the patch application may result in lower rates of augmentation than with a pulsatile application of a DA agonist. Comparative trials would further enhance the knowledge of the mode of action in dopaminergic RLS therapy.

Nonergot-Derived Dopamine Agonists: Sumanirole

Basic pharmacology. Sumanirole is a nonergot D2 DA agonist. Clinical pharmacology studies have shown sumanirole with the profile of a DA agonist with reducing serum prolactin levels, and to induce symptomatic postural hypotension, nausea, and vomiting. The sumanirole dose range studied for RLS was 0.5 to 4 mg of sumanirole in a bilayer dual-release tablet. A delayed release formulation was developed specifically to fit a target pharmacokinetic profile. The 50:50 immediate release/extended release combination formulation is expected to achieve both targets. Sumanirole has been developed for use in PD and RLS.

Review of clinical studies. One randomized controlled trial (Level I) was qualified for inclusion in this review.[71]

Level I: Garcia-Borreguero[71]: This was a 9-week randomized, double-blind, placebo-controlled, parallel-group, dose-response study, completed by 270 patients (162 women; age 18–75 years) with idiopathic RLS (IRLSSG criteria) who had a PLMSI ≥11, an IRLS-10 score ≥20, and a history or presence of RLS symptoms that interfered with sleep onset or maintenance on ≥4 nights per week for ≤12 weeks. Patients were randomly assigned to receive sumanirole 0.50, 1.0, 2.0, or 4.0 mg, or placebo. Medications that were likely to affect sleep or motor manifestation during sleep were discontinued prior to baseline. The primary outcome measure was IRLS-10 score, secondary outcome measures were PLMSI and CGI scores. No statistically significant change in mean IRLS or in CGI scores was seen between the groups, although the mean IRLS change with the 4 mg dose was numerically greater than the other doses and placebo. There was a significant dose-related improvement in PLMS (2.0 and 4.0 mg, $P < 0.0001$; 1 mg, $P = 0.0631$; 0.50 mg, $P = 0.1748$). The authors state that the dose range of sumanirole in this study may have been too low. Five patients dropped out of the study due to adverse events.

Conclusions. According to the task force's criteria, sumanirole at the doses used is considered noneffacious for treating RLS. No special monitoring is necessary. The drug is not available on any market, nor it is approved for RLS, therefore, no further implications for clinical use or research are given. There was no specific monitoring for augmentation or DDS.

Nonergot-Derived Dopamine Agonists: General Implications for Clinical Research

Long-term comparative trials need to be undertaken comparing the DA agonists among themselves and with L-dopa to decide on factors for optimized application in RLS. Strategy trials would indicate the most effective drug for the treatment of RLS, and provide data on when patients should switch therapies. In the available trials only single evening doses have been investigated, and patients who needed medication earlier than at bedtime have been excluded from trials. Different medication regimens are therefore needed. Long-term comparative trials will also enable the assessment of augmentation, as well as providing data on whether patients' sleep problems, daytime symptoms, and QoL are improved by this class of drugs. The potential side effects of DA agonists need to be studied further. For example, fibrosis and compulsive behavior as seen in PD, as well as DDS have not been investigated in previous RLS trials. In addition, future trials should consider the treatment of RLS with different release formulations; these are currently being investigated in PD and may be available on the market in the near future.

Opioids

Basic pharmacology. The opioid drugs are all considered to work primarily through the endogenous opiate receptors, which are found throughout the central nervous system. There are three major receptor classes (mu, kappa, delta), which have overlapping, but distinctive distributions. Opioid analgesia is considered to work primarily through the mu receptor, with some contribution from the kappa receptor. All the receptors are G-protein coupled receptors that decrease cyclic-AMP formation and lead to reduced calcium currents that foster synaptic release and increased potassium conductances that hyperpolarize cells. It is suspected that opioid analgesia is largely subcortical but at locations spanning from the spinal cord dorsal root ganglia up to the thalamus. A major adverse effect of opioids, constipation, is due to mu receptors in the alimentary tract. Another effect of opioids is respiratory depression, mediated primarily through a direct action on the respiratory centers of the lower brainstem.[66]

Oxycodone

Basic pharmacology. Oxycodone is chemically related to morphine but closer to codeine. It is also a hydroxylated analogue of hydrocodone. Like other related compounds, its action is primarily through the mu opioid receptor.[66]

Review of clinical studies. One Level-I study[32] was qualified for inclusion in this review.

Level I: Walters et al.[32]: This was a randomized, double-blind, placebo-controlled crossover study in 11 patients (5 women; age 36–74 years) with idiopathic RLS (IRLSSG criteria) and PLM >5/hour. The duration of the study was 4 weeks (2 weeks per phase). Clinical efficacy was measured using a nonvalidated subjective scale for RLS features; PSG measures of sleep and PLM. Oxycodone (titrated from 2.5 mg to a maximum of 25 mg, mean dose 15.9 mg) was superior to placebo in improving sensory discomfort, subjective motor restlessness, and daytime alertness; PSG showed decreased arousals and improved sleep efficiency; oxycodone also reduced PLM by 65%. Sleep apnea was noted in four subjects and did not worsen during the duration of the study.

Conclusions. Based on one well-controlled study,[32] oxycodone is likely efficacious for the relief of the symptoms of RLS in those with significant daily symptoms and 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.

Implications for clinical practice. See general implications for clinical practice later.

Implications for clinical research. See general implications for clinical research later.

Methadone

Basic pharmacology. Methadone is a synthetic opioid with distinct structure but has similar pharmacological properties to morphine. Its action is primarily through the mu receptor. It is a very potent opioid, and its use is allowed only for substitution therapy in addiction in several European countries.[66]

Review of clinical studies. One Level-III study has been included for review.[33]

Level III: Ondo et al.[33]: This was a case series in patients with severe idiopathic or secondary RLS (IRLSSG criteria) who were not responsive to at least two dopaminergic agonists. Clinical efficacy was assessed using the CGI. Seventeen of the initial 27 patients (14 women; mean age, 58.4 years) remained on methadone (15.5 ± 7.7 mg/day) for 23 ± 12 months. All scored ≥3 on the CGI (3: 75% to 99% improved; 4: only residual sleep problems; 5: no symptoms or sleep problems). Five patients dropped out of the study due to adverse events.

Conclusions. Based on one Level-III study,[33] methadone is investigational for the treatment of refractory RLS. This therapy has only been studied in those with refractory RLS who have failed multiple previous therapeutic regimes and should be restricted to such patients. Because of its potency and its respiratory depressant effect, it should be used cautiously, especially in those with preexisting respiratory compromise.

Implications for clinical practice. See general implications for clinical practice later.

Implications for clinical research. See general implications for clinical research later.

Tramadol

Basic pharmacology. Tramadol is a synthetic derivative of codeine. It is not only a weak mu agonist but also has the effect of inhibiting uptake of norepinephrine and serotonin. It is thus unclear whether its actions in RLS are based on the weak opioid action or the uptake inhibition. However, its uptake inhibitory actions may be linked to the reports that tramadol can induce augmentation, an adverse effect otherwise unknown with nondopaminergic medications.

Review of clinical studies. Only one open study (Level III)[34] investigates the efficacy of tramadol for the treatment of RLS.

Level III: Lauerma et al.[34]: This is an open trial in 12 patients (6 women; mean age, 57 years) with RLS (IRLSSG criteria) who received tramadol 50 to 150 mg/day, with only 1 patient receiving >100 mg for a mean duration of 22.8 months (5–26 months). Clinical efficacy was assessed by patients' general satisfaction as well as a nonvalidated symptom severity scale that ranged from 1 to 100. Ten patients reported that tramadol was more effective than other drugs, whereas 1 patient experienced modest improvement, and another patient reported no improvement. Symptom severity, as measured on the symptom severity scale, improved from a median of 90 to a median of 5 ($P = 0.0039$, Mann-Whitney). No patients dropped out of the study due to side effects.

Conclusions. Based on this single study,[34] the efficacy of tramadol for the treatment of RLS is considered investigational. The reports of augmentation (see Part II) with this medication suggest that it may share

some of the limitations of the dopaminergics in regard to long-term complications.

Implications for clinical practice. See general implications for clinical practice later.

Implications for clinical research. See general implications for clinical research later.

Opioids: General Conclusions

With regard to safety, the opioids taken at sufficient analgesic dose do 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 one 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.[72] This is a 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.

Opioids: General Implications for Clinical Practice

Opioids do not have an indication for RLS in any country, although they are used off-label in the USA and Europe. Many patients are treated with opioids either as monotherapy or in combination with dopaminergic drugs, although trials are not available of combination therapy. Little is known about the long-term efficacy in RLS. Only oxycodone is likely efficacious as concluded from the single controlled study available, whereas methadone and tramadol are considered investigational. It is noted, however, that opioids are often used to treat 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 lack of controlled studies. The single controlled study of oxycodone[32] covers only one of the drugs which is commonly used 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 the opioids. Additional controlled and comparative studies would be very beneficial.

Sedative Hypnotics: Benzodiazepines

Basic pharmacology. The sedative hypnotics generally act through binding to the alpha subunit of the $GABA_A$ receptor. The bound ligand-receptor complex then potentiates the effects of GABA binding to the receptor. The GABA receptor is very widely, almost universally distributed within the nervous system and comes in a very large variety of different subtypes, dependent on the particular selection of the four subunits (drawn from seven main types and numerous subtypes). The particular flavor of the receptor influences the degree of benzodiazepine binding and subsequent GABA potentiation. The general effect of the GABA receptor with bound GABA is to open a chloride channel that has a hyperpolarizing and inhibitory effect. The general result of benzodiazepine action is to reduce alertness and induce sedation and to blunt the effects of noxious or disturbing stimuli. Although there are many marketed benzodiazepines, the only one studied in trials that met our inclusion criteria was clonazepam.[66]

Clonazepam

Two Level-I studies[35,36] were qualified for inclusion in this review.

Level I: Boghen et al.[35]: This was a small (n = 6; 3 women; age 31–61 years) randomized, double-blind, placebo-controlled, crossover, prospective study in patients with RLS (clinically diagnosed but whether idiopathic or secondary is not mentioned). Study duration was 8 weeks (4 weeks per phase). The PGI and CGI were used to assess clinical efficacy. Clonazepam (0.50 mg 1/2 hour before bedtime) showed no benefit on either the PGI or the CGI, compared with placebo. Subjects reported sleepiness with clonazepam. No benefit compared with placebo was observed on either CGI or PGI.

Montagna et al.[36]: This 3-week randomized, double-blind, crossover, placebo-controlled trial examined the efficacy of clonazepam and vibration in improving RLS symptoms in 6 patients (3 women; mean age, 54.3 years). Clinical efficacy was measured through the subjective assessment of sleep, sensory discomfort, and nocturnal leg jerking. Clonazepam (1 mg 1/2 hour before bedtime) improved subjective reports of sensory discomfort and sleep compared with vibration (15 min with mechanical vibrator at 120 Hz). Leg jerking did not improve. Vibration was not shown to have a significant impact on outcome measures.

Conclusions. The two reviewed studies do not provide consistent evidence of clinical benefit, and therefore, the efficacy of clonazepam can only been considered investigational. The study by Boghen et al.[35]

could not show any benefit of clonazepam for treating RLS, therefore, there is no clear evidence that either subjective or objective (PLM) measures of therapeutic benefit have been achieved. One of the earliest drugs studied, it has not been the subject of research interest in the past two decades, although it has been a fairly common drug given to RLS patients over this period.

Implications for clinical practice. Clonazepam has a very long half-life and, therefore, may cause daytime somnolence, although this has neither been mentioned in the two studies earlier, nor has it been monitored. It may cause unwanted blunting of consciousness, especially in the elderly, and can also decrease balance. Benzodiazepines also create dependence with possible difficulties during medication withdrawal. Although clinical experience suggests that many patients can be safely managed with clonazepam, patients should be monitored for development of excessive sedation or pathologic dependence.

Implications for clinical research. Given the paucity of recent studies using validated instruments and improved diagnostic standards, it would be helpful to have new studies that examine the possibility and nature of any benefit of these medications in RLS, either as monotherapy or especially as combination therapy with other drugs used to treat RLS.

Sedative Hypnotics: Benzodiazepine-Receptor Agonists

Basic pharmacology. These drugs in general have actions similar to those of the benzodiazepines, acting upon the alpha subunit of the $GABA_A$ receptor. The distinction is that they have a different chemical structure than the class-wide benzodiazepine core. There are, however, numerous specific subtypes of the alpha subunit and different drugs may have a different specificity for the different subtypes. These drugs have been studied more recently in longer trials. Like benzodiazepines, these drugs may theoretically benefit RLS by reducing insomnia, promoting early entrance into sleep, and reducing the sleep-disruptive impact of PLMS. The single agent studied in RLS, zolpidem, is in an IR formulation.[66]

Zolpidem

Basic pharmacology. This drug is an imidazopyridine. The IR formulation has a half-life of about 2 hours. In contrast to benzodiazepines, it has little effect on sleep architecture and does not produce as great a rebound when withdrawn, although long-term studies are still lacking. The short half-life of zolpidem, enables it to be used especially for problems with falling asleep or insomnia that are sometimes induced by DA agonists.[66]

Review of clinical studies. One open-label case series (Level III) has been included for review.[37]

Level III: Bezerra et al.[37]: This was an open-label case series examining the efficacy of a fixed dose of zolpidem (10 mg) in patients (n = 8; 5 women; mean age 50.9 years) with idiopathic RLS (IRLSSG criteria). The duration of the study and follow-up ranged from 12 to 30 months, and efficacy was measured using a patient symptom report. All patients had a total remission of RLS symptoms within 5 days (mean 4 days).

Conclusions. This single Level-III study,[37] although supporting the benefit of zolpidem, is not controlled and has various design deficiencies and is therefore considered investigational for RLS. More extensive studies on sleep benefit have been conducted recently with an ER formulation, but there are no published studies of this formulation in RLS.

Implications for clinical practice. Zolpidem was well tolerated in this Level-III study and no adverse events were reported. However, there have been recent reports of parasomnias, including nocturnal eating syndrome and complex somnambulism which raise concerns about the introduction of abnormal sleep states in patients.[73,74]

Implications for clinical research. The role of the sedative-hypnotics, perhaps as adjuvant medications to benefit sleep in RLS, remains to be defined in well-controlled carefully managed trials. At the current time, the evidence for benefit of these medications in RLS is quite sparse. Such studies also need to examine safety issues, including daytime sedation and sleep disruptive parasomnias.

Anticonvulsants

Gabapentin

Basic pharmacology. Gabapentin is an analogue of the amino acid, GABA, but its actions do not appear to either mimic or enhance gaba-ergic activity. Its mode of action, in general, is not well described. It has been found to be clinically useful not only in seizures but also in pain syndromes. How it benefits RLS is not clear, but there may be a combination of its sedative and sensory modulating actions. Gabapentin has a half-life of 5 to 7 hours and is secreted unchanged by the kidney.[66]

Review of clinical studies. Two randomized double-blind controlled studies[38,39] and two randomized

controlled studies[8,10] (Level I) were included for review.

Level I: Thorp et al.[38]: This was a randomized, double-blind, placebo-controlled, crossover study in 16 patients (1 woman; mean age, 64 years) with secondary RLS (IRLSSG criteria) and on dialysis. Each phase of the study lasted for 6 weeks; for the gabapentin phase, patients received gabapentin 300 mg, three times a week after their dialysis session. Clinical efficacy was measured using a nonvalidated 0 to 2 subjective scale for 4 RLS features. Gabapentin was significantly superior to placebo [lower summed score (0–8)] and 11 of 13 completers rated gabapentin as the only effective agent.

Garcia-Borreguero et al.[39]: This was a randomized, double-blind study that sought to investigate the efficacy of gabapentin in improving sensory and motor symptoms in 22 patients with idiopathic RLS (IRLSSG criteria) and 2 patients with RLS secondary to iron deficiency. After a 2-week preentry washout period, patients were randomly assigned to receive gabapentin or placebo (6 weeks for each phase with a 1-week washout period in-between). Clinical efficacy was assessed using the IRLS rating scale, CGI, PGI, PSQI, and PSG measures. Gabapentin (mean dose, 1 855 mg) was superior to placebo on all measures and was shown to be statistically significantly superior as measured on the IRLS (8.3 pts), CGI-C, PGI-C (VAS), PSQI, and PLMI. In addition, gabapentin decreased Stage-I sleep and increased SWS. Patients with painful symptoms benefited the most from gabapentin. A low level of adverse events was recorded and no serious adverse events occurred.

Happe et al.,[10] see ropinirole section earlier.

Micozkadioglu et al.,[8] see Levodopa section earlier.

Conclusions. These controlled[38,39] and comparative Level-I studies[8,10] indicate that gabapentin is efficacious for the treatment of RLS. Gabapentin is relatively unique in that it has been studied in comparison with other agents—both a DA agonist in the treatment of idiopathic RLS and a L-dopa preparation in treatment of patients with RLS and renal failure on dialysis.

In patients with normal kidney function, effective doses were within the range typically used for seizure or pain control.[39] However, much lower doses were used in the dialysis samples, because gabapentin is eliminated only through the kidney.

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. Less serious adverse 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 which 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 further explored. 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, as with some other anticonvulsants is whether the sedative aspect of the drug might be especially helpful in those with RLS emergent primarily immediately before or during sleep.

Carbamazepine

Basic pharmacology. Carbamazepine is chemically related to the tricyclic antidepressants. Its primary mode of action is to reduce repetitive neural discharge through inhibition of sodium current. This drug has a complex pharmacology; it has a long half-life that is reduced with repeated doses. It is also metabolized by the hepatic C450 system, and, therefore interacts with many other medications.[66]

Review of clinical studies. Two randomized, controlled studies (Level I) examining the efficacy of carbamazepine were qualified for inclusion in this review.[40,41]

Level I: Lundvall et al.[40]: In this randomized, double-blind, placebo-controlled, crossover study in 6 patients (2 women; mean age, 53 years) with RLS (no indication as to whether idiopathic or secondary), the authors investigated the efficacy of carbamazepine (200 mg bid or tid). Clinical efficacy was measured using an ad hoc subjective scale in a diary format. No statistics are given, but the authors note nevertheless that carbamazepine was superior to placebo.

Telstad et al.[41]: This was a 5-week randomized, double-blind, parallel study completed by 174 patients (122 women, age 17–86 years) with clinically diagnosed RLS (unpleasant leg sensations at rest, worst at night). Outcome measures were VAS scores and the number of attacks per week. Compared with placebo,

carbamazepine (average dose 239 mg) significantly decreased the number of attacks.

Conclusions. Although there are two Level-I studies, one[40] is inconclusive due to a lack of statistics, and therefore, the task force concludes that carbamazepine is only likely efficacious. These studies were performed many years ago at a time when no validated measurements were available and when the diagnosis of RLS was not fully formulated. The placebo effect first noted in the Telstad study, however, has been a relatively constant feature of more recent large-scale trials.

Implications for clinical practice. With regard to the safety of carbamazepine, typical anticonvulsant side effects have been noted, but carbamazepine therapy needs to be fairly closely monitored because of the rare occurrence of toxic epidermal necrolysis, Stevens-Johnson syndrome, pancytopenia, or hepatic failure. There is a very extensive clinical experience with carbamazepine, which may have facilitated detection of these more rare serious adverse events.

Implications for clinical research. Carbamazepine has not been used regularly for the treatment of RLS. Given its adverse outcome profile, it is not considered useful to study carbamazepine as measures validated in RLS therapy (i.e. the IRLS or PSG parameters) would be necessary to establish its clear efficacy in RLS.

Valproic Acid

Basic pharmacology. Valproic acid is a simple branch-chained carboxylic acid. It is readily absorbed, has a half-life of about 9 to 16 hours, and is metabolized by the liver. It acts to reduce repetitive neural firing and reduces discharge propagation in various model systems.

Review of clinical studies. One randomized controlled study examines the efficacy of valproic acid in RLS.[7]

Level I: Eisensehr et al.,[7] see Levodopa section earlier.

Conclusions. Based on the one Level-I comparative trial,[7] we conclude that valproic acid is likely efficacious for the treatment of RLS, with special monitoring. It should be noted that this study used a sustained-release formulation of valproate that has an extended half-life and might have covered both nighttime and daytime symptoms.

Implications for clinical practice. Concerning safety, the normal anticonvulsant adverse effects, as well as tremor are seen with valproic acid. There have been rare reports of hepatotoxicity, thrombocytopenia, and prolonged coagulation times, so regular blood monitoring is recommended.

Implications for clinical research. Further studies are required to establish the efficacy of valproic acid. The impact on sleep and PLM needs particular investigation. It has to be considered, however, that given its adverse outcome profile, similar to carbamazepine, it may not be useful to study valproic acid further for RLS therapy.

Topiramate

Basic pharmacology. Topiramate is a sulfamate-substituted monosaccharide. It acts to reduce voltage-gated sodium channels and also enhances postsynaptic GABA-receptor currents and limits activation of the AMPA-kainate types of glutamate receptors. It is also a carbonic anhydrase inhibitor. It is well absorbed, excreted largely unchanged in the urine, and has a half-life of about 24 hours.

Review of clinical studies. One prospective study[42] (Level III) has been included for review.

Level III: Perez Bravo[42]: In this 90-day prospective case series, a total of 19 patients [4 women; mean age, 62 years; 12 idiopathic RLS (ICSD criteria), seven unspecified secondary RLS] underwent a 1-week preentry washout period before receiving topiramate (42.1 mg/day $\pm$18.7 mg, flexible dose). Clinical efficacy was assessed through CGI and PGI values, as well as through reporting of symptoms and sleep hours. Symptom severity, as measured on the CGI scale decreased from 79% to 37%. PGI values also decreased from 73% to 37%. Eleven of 17 patients had an improvement in sensory symptoms, and motor symptoms resolved for 11/17 patients. Sleep improved, but this was not shown to be statistically significant. Two patients dropped out of the study due to sleepiness, whereas the third patient dropped out of the study because of paresthesia.

Conclusions. The efficacy of topiramate is considered to be investigational. The number of atypical clinical features in the patient sample needs confirmation, as the majority of patients were men, and the symptoms were largely confined to the feet.

Implications for clinical practice. Topiramate has typical anticonvulsant side effects. One unique concern depends on its carbonic anhydrase inhibition, which has been reported to cause a significant acidosis, requiring some prophylactic monitoring.

Implications for clinical research. There need to be larger, multicenter controlled trials to confirm efficacy of topiramate.

Anticonvulsants: General Implications for Clinical Research

This group of medications is a therapeutic alternative to dopaminergics. However, before this alternative can be clearly established, a number of additional studies are required. There is a remaining issue that anticonvulsants are generally effective only for patients with pain, perhaps due to comorbid peripheral neuropathies, or are not generally as effective as the better dopaminergics. This needs to be resolved by head-to-head trials with a suitable dopaminergic and recruiting a suitable range of patients. Another issue is the relation of anticonvulsants to sedation. On the one hand, this may be a benefit of these agents, providing an improvement in sleep that may not be seen with dopaminergics. On the other hand, daytime sedation may be more of an issue with these agents, some of which have quite extended half-lives. There is probably greater likelihood that these issues may be explored with newer agents or novel formulations.

N-Methyl-D-Aspartic Acid (NMDA) Antagonists

Amantadine

Basic pharmacology. Amantadine was first noted for its antiviral properties as an inhibitor of influenza-A replication, but it also has central nervous system activity as an enhancer of DA release and a reuptake blocker and also as a competitive blocker of NMDA receptor. Amantadine is well absorbed after oral administration, has a half-life of 12 to 18 hours, and is excreted unchanged in the urine. Because of this route of absorption, it has a notably increased persistence in those with renal impairment.

Review of clinical studies. One prospective study[43] (Level III) has been included for review.

Level III: Evidente et al.[43]: This prospective open-label case series examined the efficacy of oral amantadine, administered as a flexible dose between 100 and 300 mg/day according to symptoms, in 21 patients (18 women; mean age, 70 years with idiopathic and secondary RLS (criteria for diagnosing RLS were not specified). There was no preentry washout, and patients were able to stay on other medications (L-dopa 10, pergolide 1, benzodiazepine 4, opioid 2, gabapentin 1, nonopioid analgesics 1, multiple drug types 4). Clinical efficacy was assessed through a positive response (>25%) to medication; as well as using a 10-point response to medication (≥25% improvement); 10-point RLS rating scale.[46] Eleven of 21 (52%) patients had subjective benefit from amantadine, with a mean degree of response of 69% among responders. The overall RLS score dropped from a mean of 9.8 to 6.6 ($P = 0.001$ Wilcoxon signed-rank test). The duration of response was 0 to 13 months (mean, 3.6 ± 4.5). Two patients dropped out of the study due to adverse events that included leg edema, fatigue, drowsiness, and weight loss.

Conclusions. Based on the single Level III study, there is insufficient evidence to support the use of amantadine in RLS. It needs to be considered, based on the published evidence, a drug that remains investigational in nature.

Implications for clinical practice. Up to one-third of those receiving amantadine may have central nervous system adverse effects. Its use in the elderly must be made with caution due to its extended duration of action in these subjects and restrictions in renal insufficiency.

Implications for clinical research. The efficacy of amantadine and its safety in the elderly must be established by well-designed controlled trials. In addition, future trials should examine the possibility that amantadine has dopaminergic effects.

Clonidine

Basic pharmacology. Clonidine stimulates alpha-adrenergic receptors. Its action on α-2 receptors in the brainstem is thought to be responsible for its action in reducing blood pressure. It is well-absorbed orally and half eliminated through the kidney; it has an elimination half-life of ~12 hours, but this is quite variable. How it might benefit RLS is unknown.

Review of clinical studies. *Level I*: Wagner et al.[44]: This 4-week randomized, double-blind crossover trial in 10 patients with clinically diagnosed idiopathic RLS (3 women; mean age, 44.5 years). The primary end points were subjective scales (0–4) for sensory and motor symptoms; PSG measures of sleep latency, sleep efficiency, and PLMS. Clonidine (mean = 0.05 mg/day) was reported to improve leg sensations ($P = 0.02$) and motor restlessness ($P = 0.001$). Clonidine was also shown to improve sleep onset compared with placebo [12 vs. 30 min; baseline 47 min ($P = 0.006$)]. The benefit of clonidine was restricted to the waking period and sleep onset; many minor side effects were reported in the clonidine group including: dry mouth (n = 8), lightheadedness (n = 6), decreased thinking (n = 6), somnolence (n = 5), constipation (n = 4) but no dropouts due to adverse events were reported.

Conclusions. Based on a single, small Level-I trial that demonstrated selective benefit of RLS symptoms at bedtime, clonidine is likely efficacious in RLS for those patients who are primarily bothered by symptoms at bedtime.

Implications for clinical practice. The major side effects of clonidine are xerostomia and sedation with some patients having mental changes and headache.

Implications for clinical research. The ability of clonidine to benefit RLS 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 in respect to its side effect profile.

Minerals and Vitamins

Iron Preparations: Oral Iron Preparations

Basic pharmacology. Iron is an essential element which is needed for the normal function of a number of proteins and enzymes, such as hemoglobin and tyrosine hydroxylase. Through a likely combination of still unknown sites, iron is indispensable for normal development and neural function. Iron for medical use is formulated as a salt of elemental iron. All the studies have used iron sulfate, although iron is prepared in several different formulations. Iron absorption through the gut is minimal (<2% absorbed) except in cases of iron deficiency. A significant series of research studies have supported the concept that central iron deficiency is a risk factor for RLS, but as of yet the exact mechanism through which this risk factor works has not been elucidated, although iron seems to be needed for the correct level of function in the DA system.

Review of clinical studies. One randomized controlled study[45] (Level I) in patients with idiopathic and secondary RLS were qualified for inclusion in this review. Iron deficiency is a major cause of secondary RLS, although iron may also be involved in the pathophysiology of idiopathic RLS, and it is for this reason that the task force has included a case series[46] (Level III), examining the efficacy of oral iron in idiopathic RLS and not RLS secondary to iron deficiency.

Level I: Davis et al.[45]: This randomized, double-blind, placebo-controlled trial examined the efficacy of oral ferrous sulfate in RLS. Twenty-eight patients (19 women; mean age, 59.2 years) with idiopathic and secondary RLS (all but 4 met IRLSSG criteria) were randomly assigned to receive either ferrous sulfate 325 mg b.i.d. or placebo for 12 weeks. Patients continued taking prior medications. Clinical efficacy was assessed during 2 weeks through daily measures of sleep, percent of days with RLS symptoms, and VAS summary on effect of RLS. No significant difference in any measures was seen between iron and placebo groups. The impact of RLS was reduced ($P = 0.11$) in 8 patients who completed 14 weeks on iron. Three patients in the iron group dropped out of the study due to adverse events.

Level III: O'Keeffe et al.[46]: In this controlled case series, 18 patients (13 women, age 70–87 years) with clinically diagnosed RLS, and who were matched to 18 control subjects, received a fixed dose (200 mg t.i.d.) of oral ferrous sulfate for 8 to 20 weeks. Clinical efficacy was assessed using the PGI scale (maximum score 10). At baseline, the serum ferritin levels of RLS patients were reduced compared with controls (median 33 μg/L vs. 59 μg/L, $P < 0.01$). RLS symptoms improved in patients with a serum ferritin < 45 μg/L.

Conclusions. These two studies of oral ferrous sulfate have somewhat different conclusions. The Davis et al. study[45] is a well-controlled study that reveals that oral iron treatment of individuals with adequate body stores is unlikely to have a therapeutic benefit. We can conclude that oral iron is not an efficacious treatment for RLS in iron-sufficient individuals. In contrast, the O'Keeffe et al. study[46] included a substantial segment of patients who were iron deficient. This study raises the possibility that oral iron may be an effective treatment for RLS patients with some degree of iron deficiency. As the study is a Level-III study, however, we can conclude that the current evidence of oral iron therapy in iron-deficient RLS patients is investigational.

Implications for clinical practice. There is a possibility of iron overload in those with tendencies to 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 include nausea, reflux, abdominal pain, and diarrhea.

Implications for clinical research. The efficacy and safety of oral iron treatment, especially in those with low iron indices, needs 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.

Iron Preparations: Intravenous Iron Dextran

Basic pharmacology. Iron can be prepared either as an intravenous solution or an intramuscular depot. Iron dextran is a colloidal solution of ferric oxyhydrox-

ide complexed with polymerized dextran. After injection, this colloidal solution is taken up by the reticuloendothelial system from which it is released after dissociation from dextran. It is then transported by transferrin to sites of utilization.

Review of clinical studies. One randomized controlled study[47] and two Level-III studies were qualified for inclusion in this review. As the Level-I study concerns only secondary RLS, therefore, the two Level-III studies that examine the efficacy of intravenous iron in idiopathic RLS have also been included.[48,49]

Level I: Sloand et al.[47]: This was a 4-week double-blind, placebo-controlled trial investigating the effects of intravenous iron dextran on RLS symptoms. Twenty-five patients with RLS (IRLSSG criteria) secondary to end-stage renal disease were randomly assigned to receive either iron dextran (n = 11; 5 women; mean age, 58 years; 55% white); 1,000 mg (30 mg test, then after 1 hour, the rest infused over 3 hours) or placebo (n = 14; 4 women; mean age, 53 years; 78% white). Clinical efficacy was assessed on a 10-point scale (0–4 for frequency of symptoms; 0–3 for distress; 0–3 for duration). A significant improvement in RLS symptom scores compared with baseline was seen after infusion at Weeks 1 ($P = 0.03$) and 2 ($P = 0.01$) for the iron dextran group but not in the placebo group. At Week 4, RLS symptom scores were still improved in the treatment group but were increasing toward baseline scores. One patient dropped out of the trial due to adverse events.

Level III: Nordlander[48]: In this open-label case series 21 patients (12 women; age 19–75 years) with clinically diagnosed idiopathic and secondary RLS received intravenous colloidal iron administered in one to several doses (100–200 mg of elemental iron given every 1–4 days). The primary outcome measure was RLS symptom relief. The maximum study duration was 12 months. Twenty patients achieved a complete sustained relief after variable dosing (17 required 1–3 injections, three required more injections). Some of the responders had normal iron status.

Earley et al.[49]: This was an open-label case series that sought to examine the safety and efficacy of intravenous iron dextran in treating idiopathic RLS (IRLSSG criteria). Ten patients (4 women; age 51–74 years) who had >20 PLM/hour as measured with actigraphy received a single 1,000 mg infusion of intravenous iron dextran. Primary efficacy end points were PLM/hour as measured by actigraphy, and the PGI of severity (PGI-S) scale (0–6). Secondary outcome measures were TST as measured using a 5-day paper sleep diary for hours of symptoms and hours of sleep and changes in magnetic resonance imaging (MRI)-determined iron concentrations in the substantia nigra. Six of the 10 patients reported as responding to treatment and required no other therapy at 2 weeks postinfusion. Overall at 2 weeks, there was a 54 (±41)% decrease in PGI-S; 28 (±32)% decrease PLM/hour; 57 (±37)% decrease in diary hours with symptoms; 18 (±25)% increase TST as measured from the diary. Brain iron concentrations at 2 weeks postinfusion as determined by MRI were increased in the substantia nigra and prefrontal cortex. One patient had a possible allergic reaction (shortness of breath) seen after 30 mg of iron had been infused and was excluded from the study.

Conclusions. One Level-I study has shown intravenous iron dextran to be likely 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 iron in RLS without renal failure were positive, but because of the lack of controlled trials, intravenous iron must remain investigational for those RLS patients with normal renal function with special monitoring.

Implications for clinical practice. 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 toxic iron load. In addition, with the dextran formulation there is the risk of an anaphylactoid reaction can occur with as many as 3% of those given this formulation. The risk is higher in those with preexisting autoimmune or rheumatoid disorders. As with oral iron, therapy must include long-term monitoring for development of iron overload and/or toxicity, with careful attention to the possibility that patients may have a tendency to hemochromatosis.

Implications for clinical research. The efficacy and safety of intravenous iron needs to be established with well-designed controlled trials. A particular issue is, how long the effects last and whether repeated doses will lead to adverse effects of iron accumulation. Other formulations for intravenous injection—sodium ferric gluconate and iron sucrose—do not contain polymerized dextran and have not, to date, been associated with anaphylaxis. It will be important to investigate these formulations as well, as the risks may be reduced. In general, we need to know more about how iron is handled in RLS, which may be a primary ab-

normality in many patients, and how a deficiency of brain iron may play a role in the development of symptoms.

Folic Acid

Basic pharmacology. Folic acid is an essential nutrient which is metabolized to form essential intermediate compounds needed for multiple synthetic processes, including the synthesis of DNA. How folic acid might alleviate the symptoms of RLS is unknown.

Review of clinical studies. One case series (Level III) was included for review.[50]

Level III: Botez et al.[50]: This was a case series in 16 folate-deficient patients (12 women; age 26–76 years), with RLS that was diagnosed using clinical criteria (bilateral leg discomfort at night with an urge to move legs, relieved by movement). Patients received either 3 mg folic acid IM/week or 30 mg po qd for 6 to 12 months. Clinical efficacy was examined through assessment of global symptoms. Fifteen of the 16 patients achieved remission with folate.

Conclusions. Based on the nonreplicated Level-III study, folic acid is considered investigational in RLS.

Implications for clinical practice. Folic acid taken orally is generally without any notable side effects in a normal therapeutic range. It can be administered without special monitoring.

Implications for clinical research. There is a need for well-designed randomized controlled trials to establish the efficacy of folic acid as a treatment for RLS.

Magnesium

Basic pharmacology. Magnesium is an essential mineral which acts as a cofactor in thousands of enzymatic reactions (such as the functioning of the Na/K ATPase enzyme system). Serum magnesium levels are maintained by the kidney and the gastrointestinal tract. A magnesium deficiency (in body stores as well as serum levels) can lead to mental changes and neural hyperexcitability. Magnesium is used to stabilize membranes, generally in the face of magnesium deficiency such as in eclampsia. Its mode of action in RLS is unknown; whereas early studies suggested a magnesium deficiency, this was not true of the patients studied in Hornyak et al.[51]

Review of clinical studies. One case series[51] (Level III) was qualified for inclusion in this review.

Level III: Hornyak et al.[51]: In this open case series, 10 patients (4 women; mean age, 57 years) with insomnia related to PLMS (n = 4) or mild-to-moderate RLS (n = 6; IRLSSG criteria and a PLMA-I <30) received oral magnesium oxide (12.4 mmol/evening) for 4 to 6 weeks (mean 5.1 weeks). Clinical outcome was measured using PLMI, PLMAI, PSQI, a morning sleep questionnaire, and PGI-change for response. PLMAI reduced by >50% in 4/6 RLS patients, and 5/6 RLS patients reported improvement on PGI-change; in all 10 subjects, PLMI, PLMAI decreased, SE increased significantly; no significant changes were seen in PSQI, or on the morning sleep questionnaire.

Conclusions. Based on the nonreplicated Level-III study, magnesium is considered investigational in RLS.

Implications for clinical research. Oral magnesium is generally nontoxic when taken in therapeutic doses. In those with renal failure, magnesium can accumulate and lead to neuromuscular blockade. In individuals with normal function, this treatment can be undertaken without special monitoring.

Implications for clinical practice. There is a need for well-designed randomized controlled trials to establish the efficacy of magnesium as a treatment for RLS. One appropriate trial with magnesium has recently been performed, but results have not been published in peer-reviewed literature, and therefore, cannot be included in this report.

Other

Exercise: Basic Mechanism

Exercise is considered to generally support metabolism and improve muscular and cardiopulmonary function as well as assist with weight control. Although some studies have suggested that lack of exercise is associated with RLS, the mechanism by which an exercise regime would reduce RLS is unknown. Acute, excessive exercise is known anecdotally as a precipitant of RLS symptoms in predisposed individuals.

Review of clinical studies. One randomized controlled trial[52] was qualified for inclusion in this review.

Level I: Aukermann et al.[52]: This was a randomized, controlled trial that sought to examine the effectiveness of an exercise program on idiopathic RLS (IRLSSG criteria) patients whose severity was milder than in most studies with medications. Subjects were randomly assigned to exercise (n = 11; 4 women) or control groups (n = 17; 13 women). The exercise group underwent a program of aerobic and lower-body resistance training 3 days per week. Primary end points were the IRLS and PGI. At Week 12, a significant

improvement was seen in symptoms in the exercise group compared with controls ($P = 0.001$ for the IRLS and $P < 0.001$ for the ordinal scale); PGI decreased from 1.7 (6 weeks) to 2.0 (12 weeks) compared with no decrease in the control group. Two of the controls were on pramipexole, whereas two exercise subjects were on gabapentin, and the control group did not receive placebo.

Conclusions. Based on a single Level-I study, an exercise regime, as provided, is investigational in reducing RLS symptoms.

Implications for 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. Given the single promising study, it would be important to conduct additional confirmative trials of Level-I quality. As 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.

External Counterpulsation

Basic mechanism. External counterpulsation is applied to enhance venous return during diastole to increase cardiac filling and assist with cardiac function. It is not known by what mechanism this modality would improve RLS.

Review of clinical studies. *Level I*: Rajaram et al.[53]: This randomized, parallel double-blind placebo-controlled study examined the efficacy of enhanced external counter pulsation (EECP) in treating 6 patients (all women; mean age, 58.7 years) with RLS (IRLSSG criteria). Patients were randomly assigned to receive either EECP (cuffs inflated to maximum pressure) or EECP-placebo for 1 hour a day, 5 days a week for 7 weeks, with a follow-up at 6 months. Clinical efficacy was assessed through IRLS scores, PSG as well as through clinical follow-up and a reduction in medications. There was no significant difference in decreased IRLS total score (-10 in active; -9 in placebo) between groups. There was no change from baseline in the treatment group in amounts of REM and SWS or SE. PLMI was decreased in the treatment group compared with placebo, but the PLMS-AI increased with treatment. Clinical follow-up at 6 months showed no improvement in symptoms, and there was no reduction in medications.

Conclusions. Based on one Level-I study, external counterpulsation is nonefficacious in RLS.

Implications for clinical practice. There are no major safety issues with external counterpulsation.

Implications for clinical research. Although there is a need for well-designed randomized controlled trials to establish the efficacy of external counterpulsation as a treatment for RLS, the initial negative results are not encouraging. However, this was a very small study and not adequately powered to rule out a benefit.

PART II: AUGMENTATION

This section is based upon a nonsystematic search of the literature to include all levels of clinical data (Levels I–III) published since the first description of RLS augmentation in 1996.[58] This section included all the reports found that give a definition and measurement of augmentation within the publication and provide clinically relevant information on augmentation rate within those trials. All cases are listed, independent of likelihood of a causal relationship. The level of evidence is low and will therefore not be rated.

Although RLS augmentation has been recognized since 1996,[58] as one of the potentially serious adverse effects of dopaminergic treatment of RLS, it has unfortunately only rarely been systematically evaluated. Augmentation is defined according to the original 1996 publication,[58] although new criteria have recently been published which are more precise in defining augmentation.[54] The major characteristics of augmentation include a paradoxical response to treatment in which symptoms increase with higher doses. Typically, there is an earlier onset of symptoms that may be seen together with an increase in the severity of symptoms, a spread of symptoms to other body parts, or other measures of deterioration compared with the clinical state before initiation of therapy. Presently, a clinical interview is the gold standard for diagnosing augmentation. A standardized interview is currently being validated.

Augmentation with L-dopa treatment was initially reported to be common (73% affected) and severe (50% required medication change),[58] but its occurrence and severity for the DA agonist pramipexole appears to be less.[75,76] Unfortunately, augmentation has been rarely evaluated during adequately controlled treatment trials. This in part stems from the apparent tendency of this condition to emerge with longer-term treatments, so that a trial duration of less than 1 year essentially fails to provide an adequate time for expression of augmentation. The recent developments of an augmenta-

tion severity rating scale (ASRS)[77] and revised clinical criteria[54] for augmentation may benefit future studies, but these are too new to have been included in published trials. More significantly, studies remain hampered by lack of a validated tool that provides reliable identification of augmentation. Evaluating relative risks and severity of augmentation for a given medication really requires consistent validated methods and studies lasting at least 1 year but preferably 2 to 3 years. At this time we lack both of these and, therefore, can only make very limited assessments of the problem of iatrogenic augmentation of RLS. This seems particularly unfortunate as the occurrence of augmentation suggests an exacerbation of a pathology contributing to all of the primary symptoms of RLS. Such a change may have unexpected longer-term consequences and certainly poses the most significant limitation to dopaminergic treatment to date. It seems a bit unsettling to contemplate that we may be adding to the pathology of RLS even if we can mask this with higher doses of longer-acting dopaminergic medications.

The relevant literature summarized in Table S4 includes the initial report of augmentation based on a case series of variable treatment lengths (>4 weeks) followed by five small L-dopa trials[3–7] that were too short (3–4 weeks) to see the full range of augmentation development and none specifically looked for augmentation. Another study lasting 30 weeks with L-dopa treatment reported augmentation occurred for 14.2% and caused 9.8% of patients to drop out of the study.[9] Although this trial is not long enough to expose the full degree of augmentation, the dropout rate associated with L-dopa documents its clinical significance.

This same 30-week trial compared L-dopa with the long-acting DA agonist cabergoline. Augmentation occurrence for cabergoline was significantly less than for L-dopa (5.6% vs. 14.2%) but this remains a relatively significant rate of occurrence given the short duration of the treatment. Two other cabergoline trials[29,78] were both shorter (5 and 26 weeks) and lacked specific evaluation for augmentation. Both failed to notice any augmentation. One longer (47 weeks) open-label continuation trial found in a retrospective chart review that augmentation occurred for 3 to 9% of those treated with cabergoline.[28]

The three 12-week ropinirole trials[12,14,16] reported no augmentation, but these trials were neither long enough nor did they use any adequate method for assessing augmentation. One controlled withdrawal study reported 3 cases of augmentation in 202 patients treated with ropinirole over a maximum of 36 weeks.[69] Similarly the one trial on lisuride that reported no augmentation was far too short (1 week) to be considered valid.[31] A small trial of 13 patients treated with piribedil included only 3 patients with idiopathic RLS and reported no augmentation but clearly had too few patients to provide an adequate evaluation. The pramipexole studies, however, include five open-label trials that had adequate sample sizes, longer treatment durations (lasting 5–15 months, although most subjects were in the trials for less than 12 months) and also some evaluation of augmentation. The augmentation evaluations, however, were neither clearly defined nor apparently concurrent with the clinical trials. Three of these reported no augmentation,[20,79,80] whereas one[81] reported that 8.3% of patients developed augmentation. Two retrospective evaluations looking for augmentation in separate clinical series of patients treated with pramipexole for at least 4 months and as long as 46 months in some patients reported augmentation rates of 32 to 33%.[75,76] As these are retrospective case series with variable doses and therapy regimens, the results cannot be compared neither between different studies on the same DA agonist nor between studies on different DA agonists except to note that none of the augmentation rates on DA agonists approach the high rates reported for L-dopa. In one study,[75] the augmentation rate of pramipexole was 20% after 1 year but 30% after 2 years of treatment. This demonstrates that in order to evaluate the rate of augmentation long-term studies of between 2 and 3 years are needed.

There have been no reports of augmentation occurring with treatment of RLS using nondopaminergic medications except for one report of augmentation occurring with a small number of patients on tramadol.[82]

At this point, we can say very little about RLS augmentation with these medications. It appears to occur almost only for dopaminergic medications and maybe worse for L-dopa than DA agonists, it may be less for longer-acting medications and may occur more at higher doses. The general guidance to reduce the risk of augmentation is to severely limit the dosage of L-dopa as it carries a high risk of causing the problem and to use the DA agonists at the lowest effective dose not to exceed the approved regulatory limits.

FINAL COMMENT

The major goal of RLS treatment is to provide symptom relief. The pathophysiology of the disease is not yet known, and so, no strategy for disease modification has been sought. It is not known which specific sites are responsible for any clinical benefit in RLS. It is therefore necessary that physicians and researchers

understand the mechanisms of those treatments that are symptomatic and do not permit the specific identification of the mode of action in RLS patients. Although the clinical large-scale trials for treating RLS have been performed mainly in the last 10 years, a variety of smaller trials has been undertaken and provide a wide spectrum of options for RLS treatment. In addition to the evidence provided by these trials, it is necessary to take into account the many different decisions from health care providers, that is, the treatment of secondary conditions, specific side effects such as augmentation, and long-term QoL implications. It was therefore the goal of the task force to provide an understanding of those treatments that are: (1) investigational, i.e., not well studied in patients with RLS, (2) ineffective, or (3) in need of special monitoring.

The conclusions of this review, summarizing the clinical evidence for RLS treatment, are constrained by the following factors: (1) inclusion criteria to incorporate trials into the review process were chosen according to criteria given below and in the introduction; (2) publication practice bias mostly toward reports with efficacious treatment results; (3) the database analysis was restricted to either online or print publications published before the end-December 2006; consequently, the most recent interventions may not be included, although they may change treatment recommendations; (4) there may be some language bias, as only publications in English and major European languages (German, Italian, French, Portuguese, Spanish) were included; smaller trials published in other languages were excluded.

For the older medications such as carbamazepine, benzodiazepines, or opioids that were investigated during the early RLS therapeutic trials, the methods used and the number of patients included were not adequate for clinical evidence and far less convincing than the current large-scale trials. For some substances, such as the opioids that are widely used in pain therapy, there is currently no obvious financial interest in achieving a license for indication in RLS therapy. As a result, the task force's conclusions on efficacy are more favorable for recently marketed dopaminergic drugs than for opioids or other drugs; this reflects historical factors rather than true clinical differences. Other treatment alternatives consist of iron supplementation, this may be beneficial in a subgroup of RLS patients according to current publications, for the long-term, only case reports are available.[49] A summary of these findings is shown in Table 1 and reflects the different levels of evidence that result from our literature search of articles published before the end of 2006.

Years of experience with an older agent offer greater reliability regarding safety than the short follow-up of recent agents. Throughout this review, conclusions were more focused on proof of efficacy than safety, except for the specific safety problem of augmentation, which has been separately analyzed. The task force has chosen not to mention in detail the known side effects of certain drugs, such as those of the dopaminergic agents that have been used and examined in PD. In addition, analyzing randomized controlled trials is not the most adequate method of studying an intervention's adverse reactions, especially the less frequent ones. We have to clearly state that for efficacy the labeling of "investigational" or "insufficient evidence" only describes the lack of evidence, mostly lack of data from large-scale trials or randomized controlled trials. It does not mean, that the drug is literally "nonefficacious."

Although combination therapy is used in an increasing number of RLS patients in clinical practice, there are currently no data on such simultaneous combination treatment strategies as opposed to single interventions. This is also true for comparisons between single interventions. Therefore, no recommendations based on clinical evidence can be made among equivalent therapeutic options. These will mostly remain a matter of clinical expertise and individual preferences. Another important question concerns the intermittent treatment of RLS symptoms. Although RLS symptoms are known to vary widely in severity among patients, current treatment trials have only investigated daily treatment of RLS using single dosages at bedtime. All licensed drugs are currently approved for RLS therapy for administration in a single dose, no divided dosages of any drug are currently registered, although this regimen is widely used and some trials, that do not meet our inclusion criteria, have already been undertaken with such a regimen. In addition, it has to be mentioned that the DA agonists ropinirole and pramipexole are licensed only for treating moderate to severe RLS, and patients who needed treatment in the late afternoon or evening were excluded from the trial programs by definition.

For long-term application it is necessary to explore whether intermittent therapy given when needed is a tailored treatment that can reduce long-term complications. As RLS treatment trials have, for the most part, been undertaken in the previous decade, and large-scale studies only published in the last 3 years, the lack of data on long-term outcomes and side effects such as augmentation is a major drawback in the evidence of RLS therapy. Data on long-term QoL and

socioeconomic data are not available despite numerous epidemiological data on other sleep disorders such as insomnia or sleep apnea.

In the following paragraphs, the authors have selected important new trials or approaches for RLS treatment that did not meet the aforementioned previous study inclusion criteria as they were published after the December 31, 2006 deadline. No efficacy and safety evaluation is given according to evidence-based medicine criteria for these publications.

For the dopaminergic agents there have been four new trials published.[83–86] Polo et al.[83] in a randomized, double-blind, crossover, placebo-controlled study (n = 28) investigated whether a new L-dopa formulation containing L-dopa, carbidopa, and entacapone improves L-dopa action in RLS, however, this triple combination was not compared with slow release L-dopa/carbidopa. They found that this new formulation reduced PLMs in a dose-related way. Furthermore, a separate EBM review on the use of L-dopa in RLS was recently published and examined nine trials, concluding that the short-term L-dopa is effective and safe for the treatment of PLM, and that long-term trials are needed.[87]

With regard to ropinirole, Garcia-Borreguero et al.[84] in a 52-week, multicenter, open-label continuation study, found that ropinirole (mean 1.90 mg/day) improved measures of sleep and QoL and was well tolerated. For pramipexole, Manconi et al.[85] sought to evaluate the acute effects of a low-standard dose of pramipexole in RLS drug-naïve patients in a single-blind placebo-controlled study. Pramipexole (0.25 mg) was found to be effective for the treatment of RLS from the first night of administration. Oertel et al.,[86] in a 6-week placebo-controlled study (n = 341) reported that low dosages of rotigotine (0.5–2 mg/day) had a dose-dependent beneficial effect in RLS patients and identified the range for a maintenance dose of rotigotine to be from 1 mg/24 hours to 3 mg/day. Trenkwalder et al.,[88] in a 6-month randomized, double-blind, placebo-controlled trial found that 1 to 3 mg of rotigotine was effective in relieving the night-time and daytime symptoms of RLS. Concerning augmentation with dopaminergic therapy, Trenkwalder et al.[89] found that augmentation in RLS is associated with low-serum ferritin, and therefore, that this marker could become a biomarker for the development of augmentation under dopaminergic therapy.

As far as IV iron therapy is concerned, a randomized, double-blind, placebo-controlled trial conducted by Earley et al.[90] failed to demonstrate any clinically significant benefit of IV iron sucrose for the treatment of RLS when given in one1,000 mg dose.

New pharmacological pilot trials include an observation study by Sommer et al.[91] who examined the efficacy of pregabalin (mean 305 mg/day) for the treatment of RLS. According to patients' self-rating pregabalin was reported effective for alleviating RLS symptoms.

A proof-of-concept trial conducted by Hornyak et al.[92] reported that cognitive behavioral group therapy significantly improves RLS-related QoL and the mental health status of patients.

We hope that the ongoing research on the pathophysiological mechanisms of RLS, its genetic background and molecular mechanisms will enhance the options for treatment and encourage the scientific community, as well as the pharmaceutical industry, to conduct the appropriate trials in RLS. Two recently published genome-wide association studies that have identified common variants in three genomic regions in patients with RLS[93,94] and PLM[93,94] in RLS may add substantial input to tailor new drugs for better care of RLS patients.

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