Special Section in Sleep Medicine

The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group

Diego Garcia-Borreguero [a,*], Ralf Kohnen [b,c], Michael H. Silber [d,e], John W. Winkelman [f,g], Christopher J. Earley [h,i], Birgit Högl [j], Mauro Manconi [k], Jacques Montplaisir [l], Yuichi Inoue [m,n], Richard P. Allen [h,i,1]

[a] Sleep Research Institute, Madrid, Spain
[b] Research Pharmaceutical Services Inc., Fort Washington, PA, United States
[c] Department of Psychology, University of Erlangen-Nuremberg, Nuremberg, Germany
[d] Mayo Clinic College of Medicine, Rochester, MN, United States
[e] Center for Sleep Medicine and Department of Neurology, Mayo Clinic, Rochester, MN, United States
[f] Harvard Medical School, Boston, MA, United States
[g] Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States
[h] Department of Neurology, Johns Hopkins University, Baltimore, MD, United States
[i] Sleep Disorders Center, Johns Hopkins Bayview Medical Center, Baltimore, MD, United States
[j] Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
[k] Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital, Lugano, Switzerland
[l] Departments of Psychiatry and Neuroscience, Université de Montréal, Montreal, Canada
[m] Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan
[n] Department of Somnology, Tokyo Medical University, Tokyo, Japan

ARTICLE INFO

ABSTRACT

A Task Force was established by the International Restless Legs Syndrome Study Group (IRLSSG) to develop evidence-based and consensus-based recommendations for the long-term pharmacologic treatment of restless legs syndrome/Willis–Ekbom disease (RLS/WED). The Task Force reviewed the results of all studies of RLS/WED treatments with durations of 6 months or longer presented at meetings over the past 2 years, posted on Web sites of pharmaceutical companies, or published in peer-reviewed journals, asking the questions, "What is the efficacy of this treatment in patients with RLS/WED?" and "What is the safety of this treatment in patients with RLS/WED?"

The Task Force developed guidelines based on their review of 61 papers meeting inclusion criteria, and using a modified evidence-grading scheme. Pregabalin has been established as effective for up to 1 year in treating RLS/WED (Level A evidence). Pramipexole, ropinirole, and rotigotine have been established as effective for up to 6 months in treating RLS/WED (Level A). The following drugs have been established as probably effective (Level B) in treating RLS/WED for durations ranging from 1 to 5 years: gabapentin enacarbil, pramipexole, and ropinirole (1 year); levodopa (2 years); and rotigotine (5 years). Because of associated safety concerns, pergolide and cabergoline should not be used in the treatment of RLS/WED unless the benefits clearly outweigh the risks. Other pharmacologic therapies have insufficient evidence to support their long-term use in treating RLS/WED.

The IRLSSG Task Force also developed consensus-based strategies for the prevention and treatment of complications (such as augmentation, loss of efficacy, excessive daytime sleepiness, and impulse control disorders) that may develop with the long-term pharmacologic treatment of RLS/WED. The use of either a dopamine-receptor agonist or $\alpha_{2\delta}$ calcium-channel ligand is recommended as the first-line treatment of RLS/WED for most patients, with the choice of agent dependent on the patient's severity of RLS/WED symptoms, cognitive status, history, and comorbid conditions.

* Corresponding author. Address: Sleep Research Institute, Alberto Alcocer 19, 28036 Madrid, Spain. Tel.: +34 913454129; fax: +34 913509095.
E-mail address: dgb@iis.es (D. Garcia-Borreguero).
[1] On behalf of the International Restless Legs Syndrome Study Group (www.irlssg.org).

1. Introduction

Restless legs syndrome (RLS), also known as Willis–Ekbom disease (WED), is a commonly occurring neurologic disorder characterized by an irresistible urge to move the legs, usually accompanied by dysesthesias that are relieved by movement, exacerbated by rest, and worse in the evening and night [1]. Sleep and quality of life can be severely affected [2–5].

RLS/WED was largely unrecognized until the 1990s when studies documenting its clinical relevance were conducted and significant epidemiologic studies revealed RLS/WED to be a notable public health concern [6]. To date, evidence-based treatment guidelines [7–13] have been primarily based on studies lasting no longer than 12 weeks, whereas RLS/WED quite often is a lifelong disease [14]. Long-term clinical experience with the treatment of patients with RLS/WED has revealed both the significance of problems that arise during the short term (e.g., weight gain, impulse control disorders [ICDs], mood disturbances) and the emergence of new problems during long-term treatment (e.g., augmentation, loss of efficacy). Thus the current evidenced-based guidelines do not suffice for providing clinical guidance for the long-term treatment of RLS/WED.

2. Process and objectives

2.1. Task Force

The Executive Committee of the International RLS Study Group (IRLSSG) established an international Task Force to develop recommendations for the long-term treatment of RLS/WED. The members of the Task Force completed the IRLSSG conflict of interest statement (Appendix–Conflict of interest disclosures). Financial support for this endeavor was requested from all pharmaceutical companies involved in the treatment of RLS/WED; funding was ultimately provided by unrestricted education grants from Xenoport and UCB Pharma. Funders did not participate in the development of these guidelines and recommendations, and they were not privy to this document before publication.

2.2. Objectives

The objectives of the Task Force were (1) to develop evidence-based guidelines for the efficacy and safety of pharmacologic agents for the long-term treatment of RLS/WED and (2) given the limitations of current data, to complement these with consensus-based recommendations of experts regarding the long-term treatment of RLS/WED and management of common complications that may arise.

3. Methods

3.1. Literature search and strategy

Databases that were searched included MedLINE, CINAHL, clinicaltrials.gov, abstracts from key 2010 and 2011 meetings, and drug company Web sites using the freeform search term of *restless legs syndrome* in combination with each of the following terms: *treatment, therapy,* and *drugs* and the MeSH term *restless legs syndrome, therapeutics*. Inclusion criteria were any pharmacologic treatment of adults with RLS/WED, with the results published in any language over any timeframe and with a study duration of a minimum of 6 months. A review of the literature search strategy is detailed in the Appendix (Detailed literature search and data extraction).

3.2. Outcome measures

An overview of the primary tools used in RLS/WED trials to measure the efficacy of long-term pharmacologic treatments is provided in Table 1.

3.3. Data extraction and evaluation of the evidence

Evidence was graded based on Agency for Healthcare Research and Quality [15] and European Federation of Neurological Societies [16] systems, which were then adapted to support the evaluation of long-term treatment studies. Developing long-term treatment guidelines is complicated both by the limited number of studies of sufficient duration (i.e., ⩾6 months) and also by the need to adjust evidence criteria, taking into account the types of studies appropriate to convincingly document evidence of long-term treatments. In particular, obtaining data on efficacy for treatments of 1–10 years or longer generally would require retrospective or planned prospective case series. When these studies were performed well and met the criteria for Class III evidence except that they were prospective open-label studies or case series and not controlled trials, it was felt that they provided useful information for making a recommendation. Therefore, two subcategories were added to Class III (Tables 2 and 3) for prospective open-label studies and for prospective and retrospective case series without control groups (henceforth, the original Class III is denoted as Class IIIa$_{IRLSSG}$; the prospective open-label studies as Class IIIb$_{IRLSSG}$; and the prospective and retrospective case series without control groups as Class IIIc$_{IRLSSG}$). We felt that this was in line with the intention of the original Class III when applied to long-term studies. Data extraction is described in the online Appendix (Detailed literature search and data extraction).

3.4. Consensus-based clinical recommendations

Consensus was defined by at least 80% of the members of the Task Force agreeing on a clinical recommendation.

3.5. Approval of treatment recommendations

Summaries of both the evidenced-based and the consensus-based treatment recommendations were prepared and presented at the annual meeting of the IRLSSG on June 9, 2012, in Boston, Massachusetts. In addition, an e-mail was sent to all IRLSSG members with a link to an online copy of the recommendations. Members were given an opportunity to comment on the recommendations from June 9 to June 24, 2012. The Executive Committee of the IRLSSG approved the final recommendations on July 17, 2012.

4. Evidence-based guidelines for the long-term pharmacologic treatment of RLS/WED

Sixteen pharmacologic agents have been studied for the treatment of RLS/WED for at least 6 months. The following sections review the evidence and provide evidenced-based recommendations for each drug. The evidence discussed below is presented by study in the online Appendix (Table A1); a summary of the final evidenced-based recommendations is provided in Table 4.

4.1. Dopaminergic agents

4.1.1. Non-ergot-derived dopamine-receptor agonists
4.1.1.1. *Pramipexole.* double-blind 26-week study [17] (Class I) randomly assigned 331 patients with idiopathic RLS/WED to

Table 1
Overview of tools frequently used for the investigation of RLS/WED in clinical trials.

Objective	Method	Description
Severity of RLS/WED	IRLSSG severity rating scale	P/I: 10 items covering the severity and frequency of RLS/WED symptoms, sleep disturbance, daytime tiredness, impact of symptoms on daily activities, and mood; total score (maximum 40) and two subscales: symptom severity and symptom impact
	RLS-6 scales	P: six global scales on the severity of RLS/WED symptoms at bedtime, during the night, during the day when at rest or when involved in activities, on satisfaction with sleep, and on tiredness or sleepiness during the day. No total score is calculated, but items are individually evaluated to profile changes in symptoms over time
	Clinical global impressions	I: four scales are used to capture global impressions of investigators on severity and changes during treatment: severity of disease, general change from baseline, therapeutic effect, and impact of side effects
Augmentation	Augmentation severity rating scale	P/I: three items are used to assess the severity of augmentation: earlier onset of symptoms, shorter latency to symptom occurrence at rest, and spreading to other body parts. Augmentation severity is represented in a total score

Abbreviations: RLS, restless legs syndrome; WED, Willis–Ekbom disease; IRLSSG, International Restless Legs Syndrome Study Group; P, assessed by the patient; I, assessed by the investigator; P/I, assessed by both patient and investigator.

Table 2
Evidence classification scheme developed by the International Restless Legs Syndrome Study Group for evaluating long-term studies of therapeutic interventions for restless legs syndrome/Willis–Ekbom disease.

Class	Description
I	An adequately powered prospective, randomized, controlled, clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations The following 5 criteria must be met: • Randomization is concealed • Primary outcomes are clearly defined • Exclusion and inclusion criteria are clearly defined • Dropouts and crossovers are adequately accounted for, with numbers sufficiently low to have minimal potential for bias • Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
II	Prospective, matched-group, cohort study in a representative population with masked outcome assessment that meets all of the requirements for a Class I study or a randomized controlled trial in a representative population except that it lacks one of the five criteria for a Class I study
III	Any of the following study designs qualify
	a_{IRLSSG}. A controlled trial that includes well-defined natural history control subjects or patients serving as their own controls in a representative population in which outcome assessment is independent of patient treatment
	b_{IRLSSG}. A large prospective case series or prospective open-label clinical trial in a representative population, in which outcome assessment is well-defined and is independent of patient treatment
	c_{IRLSSG}. A large retrospective case series or retrospective evaluation of data from a clinical trial in a representative population, in which outcome assessment is well-defined and is independent of patient treatment
IV	An uncontrolled study, case series, case reports, or expert opinion

Adapted from Agency for Healthcare Research and Quality [15] and European Federation of Neurological Societies [16].

Table 3
Rating of recommendations for therapeutic interventions.

Rating	Requires at least	Intervention is
A	One convincing Class I study or at least two consistent, convincing, Class II studies	Effective, ineffective, or harmful
B	One convincing Class II study or overwhelming[a] Class III$_{IRLSSG}$ evidence	Probably effective, probably ineffective, or probably harmful
C	Two convincing Class III$_{IRLSSG}$ studies.	Possibly effective, possibly ineffective, or possibly harmful
Good practice points	Consensus of expert opinion	

[a] Overwhelming was interpreted for long-term studies to mean either one large well-defined prospective study of a long duration (3 or more y) with clear outcome results or several class III studies with almost all having the same result.

pramipexole (flexible dose of 0.125–0.75-mg daily) or placebo and showed superiority of pramipexole. A double-blind, 52-week, fixed-dose study [18] (Class I) randomly assigned 719 patients to 1 of 2 pramipexole doses (0.25 or 0.5 mg daily) or pregabalin (300-mg daily). After 1 year, pregabalin showed superior efficacy to both the 0.25-mg and 0.5-mg doses of pramipexole. Patients improved markedly under pramipexole; however, the study did not include a placebo in the long-term treatment period, the study was considered to provide Class II evidence. One Class IIIa$_{IRLSSG}$ 9-month study of 150 patients who had responded to pramipexole during a 6-month run-in period showed improvement in symptoms, sleep, and quality of life and no decline in the benefit and tolerability of pramipexole [19].

The long-term efficacy of pramipexole in flexible doses between 0.125- and 0.75-mg daily for 6 months or up to 1 year also was supported by two Class IIIb$_{IRLSSG}$ studies [20,21]. In these studies, patients' symptoms improved to an average severity level of mild. Five retrospective, large-scale (50–195 patients) case series (Class IIIc$_{IRLSSG}$) have analyzed the course of pramipexole therapy in routine practice of single centers for treatment periods between 2 and 10 years [22–26]. The mean dose of pramipexole was 0.125–0.75-mg daily, but the dose was increased to 2.5-mg daily [23] or 3.75-mg daily in individual patients [22]. Dose increases occurred in all flexible-dose studies, as indicated by higher mean doses of pramipexole at the end of the observation period compared with the time when treatment started. In addition, the results of two small Class IV case series with a mean observation time of 7.8 [27] and 39.2 [28] months support the findings of the efficacy of pramipexole under the conditions of routine practice.

Table 4
Evidence from clinical trials has shown the following commonly used drugs to be effective or probably effective for at least these durations.

Drug	Effective	Probably effective
Pramipexole	6 mo	1 y
Ropinirole	6 mo	1 y
Rotigotine	6 mo	5 y
Levodopa	–[a]	2 y
Gabapentin enacarbil	–	1 y
Pregabalin	1 y	–
Gabapentin	–	–

Abbreviations: mo, months; y, years.
[a] Indicates insufficient evidence to make a recommendation.

One objective of some long-term studies of pramipexole was to document the retention rate under therapy, often evaluated with its reverse measure, the rate of dropouts. Whether due to augmentation, adverse events (AEs), loss of efficacy, or loss to follow-up, dropout rates varied between 10% [22] and 22% [23] for a treatment period of 2–3 years. Silver et al [25] reported discontinuation rates of 17% during the first year; from years 2 to 10, this rate was fairly constant at 9% per year.

The most frequent AEs associated with the use of pramipexole in all of these studies are those well-known to be associated with the use of dopamine-receptor agonists: sleepiness (5–56%), nausea (12–25%), and insomnia (7–16%). These AEs occurred more commonly in the first months after the initiation of treatment than during the long-term therapy.

Recommendation: Pramipexole is effective for the treatment of RLS/WED for up to 6 months (Level A) and probably effective for 1 year (Level B). Pramipexole is also possibly effective for up to 10 years in the 10–40% of patients who tolerate therapy and do not experience augmentation or loss of efficacy.

4.1.1.2. Ropinirole. One Class I study [29] investigated the efficacy of ropinirole for a period of 6 months. This randomized, double-blind, placebo-controlled study of 404 patients with severe idiopathic RLS/WED (IRLSSG Rating Scale [IRLS] baseline score: 27.6 units) showed a small (by 2.5 IRLS units) but statistically significant superiority of ropinirole (median dose: 1.8 mg/d, range: 0.4–3.6-mg, flexible-dose design) over placebo.

One Class IIIa$_{IRLSSG}$ study [30] used a randomized withdrawal design: 206 patients were treated for 24 weeks in an open-label portion of the study with a median dose of ropinirole of 2.0-mg daily (range, 0.25–4.0 mg); 47.5% of patients dropped out of the study, mainly due to AEs (18.3%). In a second (i.e., double-blind) part of the study, the 92 patients whose symptoms responded to treatment with ropinirole (45.5% of the original population) were randomly assigned to continue ropinirole treatment or switch to placebo for an additional 12 weeks. The relapse rate was lower in those patients who received ropinirole (32.6%), as compared with those who received placebo (57.8%).

Two Class IIIb$_{IRLSSG}$, open-label, prospective studies [31,32] with large sample sizes showed improvement of symptom severity to a mild level under median ropinirole doses of 1.6- or 2.0-mg daily (ranges, 0.25–4.0 mg) after 1 year. In addition, two Class IV retrospective [28] or mixed retrospective and prospective [33] case series were conducted in which small numbers of patients (n = 8–36) received ropinirole for a mean duration of between 10 and 39 months.

AEs in studies of ropinirole were those known to occur with the use of dopamine-receptor agonists: nausea (25–50%), headache (7–22%), fatigue (1–19%), dizziness (6–18%), and vomiting (5–11%). These AEs occurred more commonly in the first months after the initiation of treatment than during the long-term therapy.

Recommendation: Ropinirole is effective for the treatment of RLS/WED for 6 months (Level A) and is probably effective for 1 year (Level B). There is insufficient evidence documenting the effectiveness of ropinirole to make a recommendation beyond 1 year of treatment.

4.1.1.3. Rotigotine. Two double-blind, randomized, fixed-dose studies (Class I) evaluated the rotigotine transdermal delivery system (patch application once daily for 24 h) for patients with moderate to severe idiopathic RLS/WED for 6 months [34,35]. In addition, 2 prospective, open-label, 1-year, extension studies [36,37] of the 2 double-blind studies and a prospective, open-label, 5-year, long-term study [38] were conducted (Class IIIb$_{IRLSSG}$).

The first study was from a European sample of 458 patients with fixed rotigotine doses of 1, 2, or 3 mg per 24 hours [35]. Seventy percent of patients completed the study. All doses were significantly efficacious compared with placebo based on the primary end points of the IRLS and Clinical Global Impression Severity Scale.

The second randomized, double-blind, 6-month study included 505 patients in the United States who used fixed doses of 0.5, 1, 2, or 3 mg per 24 hours compared with placebo [34]. Sixty-three percent of patients completed the study. Only the 2- and 3-mg doses were superior to placebo, based on the coprimary end points of IRLS and Clinical Global Impression Severity Scale.

Two prospective, open-label, flexible-dose studies (Class IIIb$_{IRLSSG}$) evaluated rotigotine treatment for moderate to severe RLS for 1 year [36,37]. The mean rotigotine doses (flexible dosing) were 1.89 [36] and 2.08 [37] mg per 24 hours (range, 0.5–3 mg/24 h). Both studies showed symptom reduction to an average level of mild symptoms beginning within 1 week and continuing for 1 year for most patients.

Long-term maintenance of efficacy also was demonstrated in the longest prospective clinical trial in RLS research (Class IIIb$_{IRLSSG}$) [38]. The mean rotigotine dose after initial titration was 2.4 mg per 24 hours and increased, on average, to 3.1 mg per 24 hours at the end of the 5-year study. Of the 295 patients initially enrolled in the study, 126 (43%) completed 5 years of therapy, receiving flexible rotigotine doses between 0.5 and 4 mg per 24 hours. Thirty-nine percent of the patients who completed the study were considered to be free of all RLS symptoms, providing overwhelming evidence of the efficacy.

AEs were mostly application-site reactions to the patch (22–58%). Other systemic AEs, such as nausea (7–19%), headache (4.1–10.8%), and fatigue (0.5–11%), occurred more frequently in patients receiving higher rotigotine doses. AEs occurred with decreasing frequency over time, as in other studies with dopaminergic medications, with the highest incidence occurring in the first few months after start of therapy.

Recommendations: Rotigotine is effective in the treatment of RLS/WED for 6 months (Level A). Rotigotine also is probably effective for up to 5 years in the approximately 43% of patients who tolerate the therapy and who do not experience augmentation and loss of efficacy (Level B).

4.1.1.4. Piribedil. Eleven of 13 patients in a prospective case series (Class IV) [39] who received open-label piribedil at a median dose of 50-mg daily (range, 25–350 mg) for up to 15 months reported subjective benefits, and eight patients had an RLS score of 0 after treatment.

Recommendation: Evidence is insufficient to make a recommendation on the use of piribedil in the long-term treatment of RLS/WED.

4.1.2. Dopamine precursor

4.1.2.1. Levodopa–carbidopa or levodopa–benserazide. Six studies evaluated the safety and efficacy of levodopa–carbidopa or levodopa–benserazide. A randomized, double-blind, multicenter study conducted in Europe compared levodopa–benserazide and cabergoline in a 30-week evaluation (core study) [40] and a double-blind extension for up to 2 years [41]. Cabergoline (dose level, 2 or 3 mg/d) was superior to levodopa (dose level, 200 or 300 mg/d) in improving RLS/WED symptom severity on the IRLS in both the core and long-term study. Although the authors commented that levodopa provided significant symptom relief, these studies provided only Class II evidence for levodopa because they lacked a placebo arm.

Two prospective Class IIIb_{IRLSSG} studies [42,43], one Class IIIc_{IRLSSG} study [44], and a small case series (Class IV) [45] provided further evidence for the efficacy of levodopa preparations when used in doses between 200- and 700-mg daily for a duration of between 6 and 31 months.

Considering the concatenated core and extension study [40,41], 24% of patients dropped out during the first 30 weeks and an additional 15.6% dropped out in the next 74 weeks; the most common cause of patient dropout was augmentation. A similar 40% dropout rate was reported in the 6-month, open-label, Class IIIb_{IRLSSG} study [42], with 11.7% due to augmentation, 11.7% due to loss of efficacy, and 5.0% due to AEs. The most frequent reasons for premature discontinuation in all the prospective studies were loss of efficacy, AEs, and augmentation. Across all studies, the most frequent AE was nausea, which was more frequently observed in the first months after start of therapy than under long-term treatment (9.3% vs 1.3% in the core and extension comparative studies of levodopa vs cabergoline).

Recommendation: Levodopa is probably effective for up to 2 years for the treatment of RLS/WED in the 24–40% of patients who tolerate therapy and who do not develop augmentation or loss of efficacy (Level B).

4.1.3. Ergot-derived dopamine-receptor agonists

4.1.3.1. Pergolide and cabergoline. Effectiveness in the long-term treatment of RLS/WED has been documented for both pergolide and cabergoline (see Appendix: Evaluating the efficacy of ergot-derived dopamine-receptor agonists). Reports to the US Food and Drug Administration have shown an association between the use of these drugs and fibrosis and valvulopathy [46–49]. Pergolide was voluntarily withdrawn by the manufacturers from the market in the United States in 2007.

Recommendation: Pergolide and cabergoline should no longer be used in the treatment of RLS/WED, except for those patients whose symptoms are refractory to all other treatments and in whom the benefits outweigh the risks. Patients who receive pergolide or cabergoline should undergo annual cardiac ultrasound assessments.

4.2. $\alpha_2\delta$ Calcium-channel ligands

4.2.1. Gabapentin enacarbil

One study using a randomized withdrawal design for a period of 36 weeks [50] (Class IIIa_{IRLSSG}) and two open-label extensions of double-blind controlled trials providing active treatment for 1 year (Class IIIb_{IRLSSG}) [51,52] provide evidence for the efficacy of gabapentin enacarbil in the long-term treatment of RLS/WED. The dose range in these studies was between 600 and 1800 mg daily. All studies showed an average improvement of symptom severity to a mild level.

AEs primarily occurred in the first weeks after commencing the treatment with gabapentin enacarbil. The most common AEs were somnolence (19.7–41%), dizziness (11.5–46%), and headache (7.2–12.6%).

Recommendations: Gabapentin enacarbil is probably effective for the treatment of RLS/WED for 1 year (Level B). There is insufficient evidence documenting the effectiveness of gabapentin enacarbil to make a recommendation beyond 1 year of treatment.

4.2.2. Pregabalin

A 52-week, randomized, double-blind study [18] (Class I) compared pregabalin with pramipexole in 719 patients. Following a 4-arm initial placebo-controlled phase for 12 weeks, patients on placebo were randomly assigned to pregabalin (300 mg/d) or 1 of 2 pramipexole groups (0.25 or 0.5 mg/d). At the 52-week evaluation, the pregabalin group had a statistically significant larger mean decrease in IRLS score from baseline than pramipexole; the decrease was 3.8 points greater than the decrease in the IRLS score of the 0.25-mg pramipexole group and 3.1 points greater than that of the 0.5-mg pramipexole group. However, over 1 year of treatment, more patients taking pregabalin (27.5%) than taking pramipexole (0.25 mg, 18.5%; 0.5 mg, 23.9%) discontinued the study due to AEs. The most frequent AEs in subjects taking 300-mg daily of pregabalin were dizziness (21%), somnolence (18%), fatigue (11%), and nausea (10%).

The findings of one Class IV study [53] that investigated pregabalin in 19 patients with secondary RLS/WED due to neuropathy showed favorable efficacy of pregabalin over a mean of 31 (±17) weeks with a mean dose of 305 mg daily.

Recommendations: Pregabalin is effective for the treatment of RLS/WED for 1 year (Level A). There is insufficient evidence documenting the effectiveness of pregabalin to make a recommendation beyond 1 year of treatment.

4.2.3. Gabapentin

Two Class IV studies [54,55] evaluated flexible doses of gabapentin for the treatment of RLS/WED (300–2400 mg/d) in 16 patients for 6–18 months (median, 8 months) and 8 patients (four of whom maintained treatment for at least 6 months), respectively.

Recommendation: Evidence is insufficient to make a recommendation on the use of gabapentin in the long-term treatment of RLS/WED.

4.3. Opioids and opioid-receptor agonists

4.3.1. Tramadol

One Class IV study examined the effects of tramadol at a mean dose of 100 mg over a mean of 22.8 months in the treatment of primary RLS/WED [56]. Most patients reported subjective benefits.

Recommendation: Evidence is insufficient to make a recommendation on the use of tramadol in the long-term treatment of RLS/WED.

4.3.2. Methadone

One Class IIIc_{IRLSSG} study [25] and one Class IV [57] study evaluated the use of methadone in the treatment of idiopathic and secondary RLS/WED. Both studies showed sustained therapeutic benefit over 2–10 years in patients who had failed treatment with other agents, largely due to augmentation; methadone doses ranged from 5- to 40-mg daily. Approximately one third of the patients in these two studies were on concomitant therapy. Dropout rates ranged from 13% to 30% and were due to lack of efficacy and AEs (sedation, depression or anxiety, altered consciousness).

Recommendation: Evidence is insufficient to make a recommendation on the use of methadone in the long-term treatment of RLS/WED.

4.3.3. Intrathecal morphine

Three case series [58–60] (Class IV) reported on the successful use of morphine, administered intrathecally via implantable pump for the treatment of refractory RLS/WED in a total of 13 patients for a period between 7 months and 3.5 years.

Recommendation: Evidence is insufficient to make a recommendation on the use of intrathecal morphine in the long-term treatment of RLS/WED.

4.3.4. Multiple opioids

In a retrospective, multicenter, Class IV study conducted in the United States and Europe (3 sites) [61], 32% of 113 patients were treated with an opioid monotherapy and 68% received opioids in combination with other RLS/WED treatments. A broad range of opioids were administered, with tilidine (25 mg) being the most commonly prescribed drug in Europe and oxycodone (5 mg) in the United States. Treatment records covered up to 23 years, with an average of 3–5 years. Treatment was well-tolerated, but the authors recommended evaluating patients for sleep apnea.

Recommendation: Evidence is insufficient to make a recommendation on the use of any single opioid in the long-term treatment of RLS/WED.

4.4. Other drugs

4.4.1. Tetrabenazine

One Class IV study showed mild if any benefit in the use of tetrabenazine in the treatment of RLS/WED in patients with comorbid hyperkinetic movement disorders [62].

Recommendation: Evidence is insufficient to make a recommendation on the use of tetrabenazine in the long-term treatment of RLS/WED.

4.4.2. Iron

Intravenously administered iron sucrose was not found to be efficacious in two short-term trials [63,64]. One of these trials [64], which reported dropout rates at 1 year after treatment that were significantly less for iron than placebo, did not, however, meet its primary end point showing treatment benefit for iron.

One randomized double-blind study (Class I) with ferric carboxymaltose given in two 500-mg doses 5 days apart showed significant improvement compared with placebo at 4 weeks after treatment [65]. Patients responding to initial treatment were followed up with knowledge of their prior treatment for up to 24 weeks after initial treatment, and 25% of subjects were found to be free of any significant RLS/WED symptoms [65].

Recommendation: Evidence is insufficient to make a recommendation on the intravenous use of ferric carboxymaltose or iron sucrose in the long-term treatment of RLS/WED.

4.4.3. Sedative hypnotics
4.4.3.1. Clonazepam. One Class IV study included 34 patients with RLS/WED or periodic limb movement disorder treated with clonazepam for at least 6 months with a mean initial dose of 0.9 mg, which increased to 1.35 mg [66].

Recommendation: Evidence is insufficient to make a recommendation on the use of sedative hypnotics in the long-term treatment of RLS/WED.

4.4.4. Levetiracetam

One Class IV study included two patients with severe RLS/WED and periodic limb movements who had a positive response to 1000 mg of levetiracetam for 21 and 26 months [67].

Recommendation: Evidence is insufficient to make a recommendation on the use of levetiracetam in the long-term treatment of RLS/WED.

5. Consensus-based recommendations for the long-term treatment of RLS/WED

During a meeting on January 20 to January 22, 2012, in Madrid, Spain, the Task Force established by the IRLSSG discussed the management of the primary AEs and complications that arise during the long-term treatment of RLS/WED and, through consensus developed practical recommendations. Consensus was reached when more than 80% of the members of the Task Force agreed on a given measure.

5.1. Recommendation regarding loss of efficacy and augmentation

Loss of efficacy and augmentation are the main causes of treatment failure that emerge later in the course of treatment of RLS/WED. Supporting information on these recommendations and additional details on other AEs that arise in the long-term pharmacologic treatment of RLS/WED can be found in the online Appendix (Adverse events related to the long-term treatment of RLS/WED).

5.1.1. For augmentation and loss of efficacy

- The patient's serum ferritin level should be measured, and, if the concentration is lower than 75 µg/mL, supplementation with orally administered iron is recommended unless poorly tolerated or contraindicated [68,69].
- It is important to ask the patient about any lifestyle changes, compliance with the current therapy, changes in medical factors (use of dopamine-receptor antagonists or antidepressants), or other extrinsic factors (sleep deprivation, blood loss, alcohol use) that might have contributed to an earlier onset or an increase in the severity of symptoms. Any extrinsic factors exacerbating RLS expression should be adjusted as much as possible to reduce the need for medication changes [70].

5.1.2. For loss of efficacy

- Loss of efficacy [71] commonly occurs for all drugs in the long-term treatment of RLS/WED [26]. If loss of efficacy occurs, doses of the current agent should only be adjusted above the approved levels with caution and with monitoring for adverse effects, development of augmentation, or progressive loss of efficacy. Instead, consideration should be given to adding another medication or changing medications.
- For patients experiencing loss of efficacy under monotherapy, a drug of another class (either dopamine-receptor agonists or $\alpha_2\delta$ ligands) could either be added without increasing the dose of the current drug or, alternatively, substituted for the current drug.

5.1.3. For augmentation

- Augmentation is a major clinical problem that emerges with the long-term treatment of RLS/WED. It can produce a severe exacerbation of RLS/WED symptoms, and is thus something to be carefully assessed and managed.
- Some degree of augmentation has been reported with the use of all investigated dopaminergic drugs [25,32,38,40,42] and also for tramadol [72]. In the virtual absence of direct comparative studies, the incidence rate seems to be highest during treatment with levodopa and higher for shorter-acting (pramipexole, ropinirole) than longer-acting (rotigotine, cabergoline) dopamine-receptor agonists. However, it is unclear whether this finding is related to the masking of earlier symptom onset by the longer-acting dopaminergic agents or if it is truly an augmentation-sparing effect.

- The risk of augmentation increases with longer duration of treatment and possibly with higher doses. It is unclear whether the apparent relationship between dose and augmentation rate is, in fact, secondary to patient characteristics such as disease duration or severity. Nevertheless, it is recommended that dose increases be carefully considered, particularly if they exceed usually accepted or approved dose levels. They should be limited to breakthrough of clinically important symptoms that cannot be managed behaviorally and should be balanced against the option of adding an alternate type of medication.
- If bothersome earlier onset of symptoms occurs with augmentation when the patient is taking a short-acting dopaminergic medication, a dose of the current medication can be added earlier, with possible reduction of the later dose, or the medication can be changed to a single dose of a longer-acting dopaminergic or other medication. If the total dopaminergic dose is increased, careful monitoring for progressive augmentation is needed [18].
- For severe or progressive augmentation, the dopamine-receptor agonist should be discontinued and an $\alpha_2\delta$ ligand, an opioid, or possibly another (perhaps longer-acting) dopamine-receptor agonist substituted.

5.2. Recommendations for managing other treatment-related challenges emerging during long-term therapy

5.2.1. For ICDs

- ICDs develop in 6–17% of patients with RLS/WED who take dopamine-receptor agonists [73]. ICDs may occur more often with higher doses of drugs and may be more likely to occur in women.
- Patients should be questioned about ICDs at each visit. If a significant ICD is present, the drug should be discontinued or at least the dose decreased to a level at which the ICDs cease. Other nondopaminergic drugs should be substituted or added.

5.2.2. For comorbid insomnia.
- If problems of insomnia or inadequate sleep develop or persist on the current medication, then a short-acting GABA active hypnotic or an $\alpha_2\delta$ ligand, if not already used, can be added to or substituted for the current treatment.

5.3. Recommendations regarding choice of agents

5.3.1. Recommendations for the selection of an agent for initial treatment of RLS/WED
The IRLSSG Task Force recognizes that choice of agent for the initial treatment of RLS/WED often affects patients' ability to tolerate the therapy over the long term. Therefore, the Task Force developed the following recommendations:

- Either dopamine-receptor agonists or the $\alpha_2\delta$ ligands are the first-line treatment for patients with RLS/WED.
- The choice of the initial treatment should be based on the individual clinical features of RLS/WED in a given patient (Tables 5 and 6).
- Medication administration should be related to the timing of the onset of clinically significant symptoms that cannot be effectively managed behaviorally. There is variation in the onset time of individual medications which needs to be taken into account.
- Patients with clinically significant daytime symptoms should be treated with a long-acting agent. Multiple daily doses of a short-acting agent can also be tried. Considerable caution should be exercised with frequent monitoring for loss of efficacy or the development or progression of augmentation with all dopaminergic agents.
- The use of $\alpha_2\delta$ ligands should be considered for initial treatment of patients with severe sleep disturbance (disproportionate to other RLS/WED symptoms), comorbid insomnia or anxiety, RLS/WED-related or comorbid pain, or a history of an ICD or anxiety.
- Dopamine-receptor agonists should be considered for initial treatment of patients with very severe symptoms, excessive weight, comorbid depression, increased risk of falls, or cognitive impairment.
- The availability and cost of drugs may need to be considered in making the choice of the initial treatment.
- Combination treatments of a dopamine-receptor agonist and an $\alpha_2\delta$ ligand should be considered for patients with symptoms that cannot be controlled with a low-dose monotherapy of either treatment class. There is a need for more clinical studies of combination treatments.

Table 5
Clinical consensus of the benefits and risks for each pharmacologic treatment of RLS/WED.

| | Levodopa | Nonergot DA | | Ergot-based DA | $\alpha_2\delta$ Ligand | Opioid | Clonazepam |
		Short-acting	Long-acting				
The potential of the drug to cause the following adverse events							
Augmentation	+++	++	+	++	0	NK	0
LoE	+++	++	NK	++	+	+	NK
ICD	0	+	0/+	NK	0	0	0
EDS	NK	++	+	++	+++	+	++
Negative mood	0	0	0	0	+	+	++
Weight gain	0	0	0	0	++	0	0
General toxicity	+	+	++	+++	+	++	+
The potential of the drug to have positive effect on these parameters							
Subjective nighttime sleep	0	+	+	+	++	++	++
Classic nighttime RLS/WED symptoms	+	++	++	++	++	++	0
QoL	NK	++	++	++	++	NK	NK
Pain reduction	+	+	+	+	++	+++	0

Abbreviations: RLS/WED, restless legs syndrome/Willis–Ekbom disease; DA, dopamine-receptor agonist; LoE, loss of efficacy; ICD, impulse control disorders; EDS, excessive daytime sleepiness; QoL, quality of life; NK, not known.
+++, is very likely to affect this parameter; ++, is somewhat likely to affect this parameter; +, is slightly likely to affect this parameter; 0, has no effect on this parameter.

Table 6
Clinical recommendations regarding factors that affect the selection of an agent for initial treatment in patients with restless legs syndrome/Willis–Ekbom disease.

Factor that impacts the choice of agent	Treatment choice
Time of day (daytime disturbance)	• Preferably a long-acting agent • Twice a day dosing of a short-acting agent
Sleep disturbance disproportionate to other symptoms of RLS/WED	$\alpha_2\delta$ Ligand
Comorbid insomnia	$\alpha_2\delta$ Ligand
Pregnancy risk	• Avoid both dopaminergic agents and $\alpha_2\delta$ ligands • Consider the use of iron
Impaired renal function	• Select a drug that is not renally excreted
Increased risk for falls	Dopamine-receptor agonist
Painful restless legs	$\alpha_2\delta$ Ligand
Comorbid pain syndrome	$\alpha_2\delta$ Ligand
History of or current ICD	$\alpha_2\delta$ Ligand
History of or current alcohol or substance abuse	Dopamine-receptor agonist or $\alpha_2\delta$ ligand
Severe symptoms of RLS/WED	Dopamine-receptor agonist
Excess weight, metabolic syndrome, or obstructive sleep apnea	Dopamine-receptor agonist
Availability[a]	Dopamine agonist or $\alpha_2\delta$ ligand
Cost[b]	Dopamine agonist or $\alpha_2\delta$ ligand
Comorbid depression	Dopamine-receptor agonist
Comorbid generalized anxiety disorder	$\alpha_2\delta$ Ligand
Daytime sleepiness	• Investigate the cause
Higher potential for drug interactions	• Select drug that is not hepatically excreted

Abbreviations: RLS/WED, restless legs syndrome/Willis–Ekbom disease; ICD, impulse control disorder.

[a] Drugs approved by regulatory agencies as of December 2012 for the treatment of restless legs syndrome/Willis–Ekbom disease (RLS/WED) include gabapentin enacarbil (United States), levodopa/benserazide (Germany and Switzerland), pramipexole (United States and European Union), ropinirole (United States and European Union), and rotigotine (United States and European Union).

[b] Generic drugs typically are less expensive than brand-name drugs. As of December 2012, generic drugs that also have regulatory approval for the treatment of RLS/WED include levodopa benserazide, pramipexole, and ropinirole.

5.4. Recommendations for opioids for RLS/WED refractory to other treatments

• At the time of writing these recommendations, there was insufficient long-term evidence to make a recommendation for any one opioid. The high-potency opioids (e.g., methadone, oxycodone), as a class of medications, however, can be considered possibly effective (Level C) in the long-term treatment of RLS/WED refractory to other treatments. Caution should be taken to exclude sleep-related breathing disorders before treatment is initiated with opioids, particularly in older patients.

5.5. Recommendation regarding treatment during pregnancy

• In general, pharmacologic treatment should be avoided for RLS/WED symptoms occurring during pregnancy; both dopamine-receptor agonists and $\alpha_2\delta$ ligands should be avoided. Consideration should be given to fully replenishing iron stores prior to pregnancy and maximizing nonpharmacologic treatments. Published literature about the practical treatment of RLS during pregnancy is very limited.

6. Discussion

This thorough review of evidence combined with a clinical consensus process produced significant new insights into the state of RLS/WED treatment. Four are particularly important. First, long-term treatment considerations changed the recommendations for initial treatment. Short-term studies of up to 3 months document safety and efficacy of the current widely approved short-acting dopamine-receptor agonists, and these drugs are usually considered to be the first choice for the treatment of RLS/WED. However, the results of long-term studies indicate that the problems of augmentation are serious enough to justify reconsidering whether short-acting dopamine agonists should always be the initial treatment of choice. Alternative drugs for initial treatment with reduced risk for augmentation include the $\alpha_2\delta$ ligands or possibly the long-acting dopamine-receptor agonists. Thus, this Task Force recommends that the choice of initial treatment be tailored to the needs of the patient, largely based on relative significance of the effects and cost of a drug for a particular patient. This choice is a significant advancement and represents a change in the treatment of RLS/WED.

Second, the process of evaluating long-term RLS/WED treatment studies revealed the inadequacies of typically used evidence-based standards for assessing efficacy in studies of RLS/WED lasting 6 months or longer. Studies lasting a few months can and should be placebo controlled, but this is neither practical nor ethical for long-term studies. Therefore, active-comparator studies become more important, and the criteria for a positive outcome need to be adjusted. Ideally, these studies would have an initial placebo-controlled phase demonstrating short-term efficacy of the medications. The criterion for long-term efficacy then becomes maintaining treatment efficacy, as indicated by superiority over short-term placebo response, and also possibly showing long-term superiority of one of the active drugs being compared. Thus maintained efficacy, rather than superiority over continued long-term placebo treatment, becomes the critical criterion for evidence-based long-term treatment of RLS/WED and could be used to define such studies as Class I studies. We recommend consideration of this change for defining Class I studies in the future, but, because implementing this change in defining Class I would have applied to only one study in our review, we chose to be conservative and did not apply this change; however, we did adjust the evidence-based criteria to better handle the wealth of data in our review from carefully conducted retrospective studies that inform about long-term treatments of RLS/WED. The results of these studies need to be included in evidenced-based evaluations of long-term treatment as potentially more than Class IV. In particular, we added a IIIb$_{IRLSSG}$ category to the typically used Class III criteria for prospective and a IIIc$_{IRLSSG}$ category for retrospective studies. Tables 2 and 3 present the criteria we developed for evidence-based long-term treatment guidelines. We recommend these categories for consideration in other long-term treatment guideline reviews.

Third, the distressing lack of knowledge about long-term treatment options and outcomes requires attention to expanding the types of clinical trials being conducted and focusing attention on the problems associated with long-term treatment, including augmentation. The available studies tend to be relatively short, and in fact there is only one published prospective study lasting more than 1 year. More longer-term studies are needed, and a structure is needed to enable such studies. Other areas identified by the review process as needing further attention include drug-combination studies, evaluation of opioids and new treatments, and development of animal and biologic models of RLS/WED and augmentation.

Finally, these treatment guidelines were based on available data, and specific recommendations were made only when experts reached consensus. The result is a report that only begins the process for producing treatment guidelines for RLS/WED as a chronic condition. Much more study is needed to meet the long-term treatment needs of patients with RLS/WED.

Conflict of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.05.016.

References

[1] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101–19.

[2] Gerhard R, Bosse A, Uzun D, Orth M, Kotterba S. Quality of life in restless legs syndrome. Influence of daytime sleepiness and fatigue [in German]. Med Klin (Munich) 2005;100:704–9.

[3] Giannaki CD, Sakkas GK, Hadjigeorgiou GM, Liakopoulos V, Anifandis G, Karatzaferi C, et al. Quality of life score is primarily affected by the mental rather than the physical component in patients with restless legs syndrome. Mov Disord 2010;25:135–6. author reply 6–7.

[4] Happe S, Reese JP, Stiasny-Kolster K, Peglau I, Mayer G, Klotsche J, et al. Assessing health-related quality of life in patients with restless legs syndrome. Sleep Med 2009;10:295–305.

[5] McCrink L, Allen RP, Wolowacz S, Sherrill B, Connolly M, Kirsch J. Predictors of health-related quality of life in sufferers with restless legs syndrome: a multi-national study. Sleep Med 2007;8:73–83.

[6] Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med 2010;11:807–15.

[7] Chesson Jr AL, Wise M, Davila D, Johnson S, Littner M, Anderson WM, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 1999;22:961–8.

[8] Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. Sleep 1999;22:970–99.

[9] Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27:560–83.

[10] Littner MR, Kushida C, Anderson WM, Bailey D, Berry RB, Hirshkowitz M, et al. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27:557–9.

[11] Vignatelli L, Billiard M, Clarenbach P, Garcia-Borreguero D, Kaynak D, Liesiene V, et al. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. Eur J Neurol 2006;13:1049–65.

[12] Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord 2008;23:2267–302.

[13] Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, O'Keeffe S, Trenkwalder C, Högl B, et al. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. Eur J Neurol 2012;19:1385–96.

[14] Walters AS, Hickey K, Maltzman J, Verrico T, Joseph D, Hening W, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology 1996;46:92–5.

[15] West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, et al. Systems to rate the strength of scientific evidence. In: Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011). Rockville (MD): Agency for Healthcare Policy and Research; 2002.

[16] Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. Eur J Neurol 2004;11:577–81.

[17] Högl B, Garcia-Borreguero D, Trenkwalder C, Ferini-Strambi L, Hening W, Poewe W, et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. Sleep Med 2011;12:351–60.

[18] Allen RP, Chen C, Winkelman J, et al. Long-term efficacy and augmentation assessment of an α2δ ligand (pregabalin) compared with a dopamine agonist (pramipexole) in restless legs syndrome: results of a randomized, double-bline, placebo-controlled trial. Mov Disord 2012;27:S576 [abstract].

[19] Trenkwalder C, Stiasny-Kolster K, Kupsch A, Oertel WH, Koester J, Reess J. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome. Mov Disord 2006;21:1404–10.

[20] Inoue Y, Kuroda K, Hirata K, Uchimura N, Kagimura T, Shimizu T. Long-term open-label study of pramipexole in patients with primary restless legs syndrome. J Neurol Sci 2010;294:62–6.

[21] Partinen M, Hirvonen K, Jama L, Alakuijala A, Hublin C, Tamminen I, et al. Open-label study of the long-term efficacy and safety of pramipexole in patients with Restless Legs Syndrome (extension of the PRELUDE study). Sleep Med 2008;9:537–41.

[22] Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med 2012;13:1280–5.

[23] Montplaisir J, Fantini ML, Desautels A, Michaud M, Petit D, Filipini D. Long-term treatment with pramipexole in restless legs syndrome. Eur J Neurol 2006;13:1306–11.

[24] Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep 2003;26:819–21.

[25] Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011;12:440–4.

[26] Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med 2004;5:9–14.

[27] Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol 2000;7(Suppl. 1):27–31.

[28] Ondo W, Romanyshyn J, Vuong KD, Lai D. Long-term treatment of restless legs syndrome with dopamine agonists. Arch Neurol 2004;61:1393–7.

[29] Glaxo-SmithKline. A randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of ropinirole for 26 weeks and to further evaluate the incidence of augmentation and rebound for a further 40 weeks open-label extension treatment period in subjects suffering from moderate to severe restless legs syndrome. unpublished 2008; ROR104836.

[30] Montplaisir J, Karrasch J, Haan J, Volc D. Ropinirole is effective in the long-term management of restless legs syndrome: a randomized controlled trial. Mov Disord 2006;21:1627–35.

[31] Garcia-Borreguero D, Grunstein R, Sridhar G, Dreykluft T, Montagna P, Dom R, et al. A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome. Sleep Med 2007;8:742–52.

[32] Garcia-Borreguero D, Hogl B, Ferini-Strambi L, Winkelman J, Hill-Zabala C, Asgharian A, et al. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis–Ekbom disease): results from a prospective, multicenter study over 66 weeks. Mov Disord 2012;27:277–83.

[33] Galvez-Jimenez N, Khan T. Ropinirole and restless legs syndrome. Mov Disord 1999;14:890–2.

[34] Hening WA, Allen RP, Ondo WG, Walters AS, Winkelman JW, Becker P, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010;25:1675–83.

[35] Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2008;7:595–604.

[36] Allen RP, Winkelman J, Ondo W, Fichtner A, Schollmayer E. Long-term treatment with transdermal rotigotine in patients with idiopathic restless legs syndrome (RLS): results from a 12-month open-label extension trial. Sleep 2010;33:A251 [abstract].

[37] Ferini-Strambi L, Benes H, Garcia-Borreguero D, et al. Safety and efficacy of long-term treatment with transdermal rotigotine in patients with idiopathic restless legs syndrome: a 12-month open-label extension study. J Sleep Res 2010;19:250–1 [abstract].

[38] Oertel W, Trenkwalder C, Beneš H, Ferini-Strambi L, Högl B, Poewe W, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol 2011;10:710–20.

[39] Evidente VG. Piribedil for restless legs syndrome: a pilot study. Mov Disord 2001;16:579–81.

[40] Trenkwalder C, Benes H, Grote L, Happe S, Högl B, Mathis J, et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord 2007;22:696–703.

[41] Högl B, Benes H, Kohnen R, Trenkwalder C, Group CS. Double-blind, multi-centre, 2-year long-term study comparing treatment with cabergoline and levodopa in severe restless legs syndrome. Sleep Med 2007;8:S65–6.

[42] Högl B, Garcia-Borreguero D, Kohnen R, Ferini-Strambi L, Hadjigeorgiou G, Hornyak M, et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. J Neurol 2010;257:230–7.

[43] Trenkwalder C, Collado Seidel V, Kazenwadel J, Wetter TC, Oertel W, Selzer R, et al. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? Mov Disord 2003;18:1184–9.

[44] Earley CJ, Allen RP. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. Sleep 1996;19:801–10.

[45] Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. Arch Neurol 1982;39:739.

[46] Pritchett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. Mayo Clin Proc 2002;77:1280–6.

[47] Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med 2007;356:29–38.

[48] Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac valvulopathy in Parkinson disease: a case-control study. Neurology 2006;67:1225–9.

[49] Zadikoff C, Duong-Hua M, Sykora K, Marras C, Lang A, Rochon P. Pergolide associated cardiac valvulopathy based on Ontario administrative data. Can J Neurol Sci 2008;35:173–8.

[50] Bogan RK, Bornemann MA, Kushida CA, Tran PV, Barrett RW. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. Mayo Clin Proc 2010;85:512–21.

[51] Ellenbogen AL, Thein SG, Winslow DH, Becker PM, Tolson JM, Lassauzet ML, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. Clin Neuropharmacol 2011;34:8–16.

[52] Inoue Y, Uchimura N, Kuroda K, Hirata K, Hattori N. Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients. Prog Neuropsychopharmacol Biol Psychiatry 2012;36:251–7.

[53] Sommer M, Bachmann CG, Liebetanz KM, Schindehutte J, Tings T, Paulus W. Pregabalin in restless legs syndrome with and without neuropathic pain. Acta Neurol Scand 2007;115:347–50.

[54] Mellick GA, Mellick LB. Management of restless legs syndrome with gabapentin (Neurontin). Sleep 1996;19:224–6.

[55] Adler CH. Treatment of restless legs syndrome with gabapentin. Clin Neuropharmacol 1997;20:148–51.

[56] Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry 1999;60:241–4.

[57] Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord 2005;20:345–8.

[58] Ross DA, Narus MS, Nutt JG. Control of medically refractory restless legs syndrome with intrathecal morphine: case report. Neurosurgery 2008;62:E263. discussion E.

[59] Lindvall P, Ruuth K, Jakobsson B, Nilsson S. Intrathecal morphine as a treatment for refractory restless legs syndrome. Neurosurgery 2008;63:E1209. author reply E.

[60] Jakobsson B, Ruuth K. Successful treatment of restless legs syndrome with an implanted pump for intrathecal drug delivery. Acta Anaesthesiol Scand 2002;46:114–7.

[61] Walters AS, Winkelmann J, Trenkwalder C, Fry JM, Kataria V, Wagner M, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord 2001;16:1105–9.

[62] Ondo WG, Jia JJ. Effect of tetrabenazine use on restless legs syndrome. Sleep Med 2010;11:958–9.

[63] Earley CJ, Horska A, Mohamed MA, Barker PB, Beard JL, Allen RP. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. Sleep Med 2009;10:206–11.

[64] Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. Mov Disord 2009;24:1445–52.

[65] Allen RP, Adler CH, Du W, Butcher A, Bregman DB, Earley CJ. Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: a multi-centred, placebo-controlled preliminary clinical trial. Sleep Med 2011;12:906–13.

[66] Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. Am J Med 1996;100:333–7.

[67] Della Marca G, Vollono C, Mariotti P, Mazza M, Mennuni GF, Tonali P. Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases. J Neurol Neurosurg Psychiatry 2006;77:566–7.

[68] Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: a randomized, double-blind, placebo-controlled study. Sleep Med 2009;10:973–5.

[69] Silber MH, Ehrenberg BL, Allen RP, Earley CJ, Hening WA, Rye DB. Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004;79:916–22.

[70] Garcia-Borreguero D, Allen RP, Kohnen R, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. Sleep Med 2007;8:520–30.

[71] Garcia-Borreguero D, Allen R, Kohnen R, Benes H, Winkelman J, Högl B, et al. Loss of response during long-term treatment of restless legs syndrome: guidelines approved by the International Restless Legs Syndrome Study Group for use in clinical trials. Sleep Med 2010;11:956–7.

[72] Earley CJ, Allen RP. Restless legs syndrome augmentation associated with tramadol. Sleep Med 2006;7:592–3.

[73] Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep 2010;33:81–7.