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EFNS/ENS/ESRS GUIDELINES

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

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Background: Since the publication of the first European Federation of Neurological Societies (EFNS) guidelines in 2005 on the management of restless legs syndrome (RLS; also known as Willis-Ekbom disease), there have been major therapeutic advances in the field. Furthermore, the management of RLS is now a part of routine neurological practice in Europe. New drugs have also become available, and further randomized controlled trials have been undertaken. These guidelines were undertaken by the EFNS in collaboration with the European Neurological Society and the European Sleep Research Society.

Objectives: To provide an evidence-based update of new treatments published since 2005 for the management of RLS.

Methods: First, we determined what the objectives of management of primary and secondary RLS should be. We developed the search strategy and conducted a review of the scientific literature up to 31 December 2011 (print and electronic publications) for the drug classes and interventions employed in RLS treatment. Previous guidelines were consulted. All trials were analysed according to class of evidence, and recommendations made according to the 2004 EFNS criteria for rating.

Recommendations: Level A recommendations can be made for rotigotine, ropinirole, pramipexole, gabapentin enacarbil, gabapentin and pregabalin, which are all considered effective for the short-term treatment for RLS. However, for the long-term

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treatment for RLS, rotigotine is considered effective, gabapentin enacarbil is probably effective, and ropinirole, pramipexole and gabapentin are considered possibly effective. Cabergoline has according to our criteria a level A recommendation, but the taskforce cannot recommend this drug because of its serious adverse events.

Background

In the last 5 years, a number of controlled studies have been undertaken to examine both existing and new drugs for the management of restless legs syndrome (RLS). During this period, major changes have taken place in RLS practice, with the approval of three new drugs in Europe (ropinirole, pramipexole and rotigotine). Also, major developments have been made in our understanding of the causes of the disease: we now know that iron plays a major role in the pathophysiology of RLS, likely both as a forewarning of a newly developing metabolic pathology and as a direct effect of iron deficiency. Studies have detected brain iron metabolism changes in patients with RLS using imaging, and in cerebrospinal fluid with reduced ferritin and aberrant circadian rhythm of dopamine metabolites, suggesting decreased brain iron stores [1–3] with the probable consequence of altered function of the dopamine system [4]. Data from neuropathological studies show that there is less iron in neuromelanin cells [5], and several MRI studies have detected low brain iron *in vivo* [6,7], a finding confirmed by transcranial ultrasound that has detected hypoechogenic substantia nigra indicating low iron stores [8–10]. Major advances have also taken place in genetics, where risk polymorphisms – that is, genetic variants that increase the risk of having RLS – have been identified in five chromosomal regions [11–13].

In light of the new evidence for treatment, and the changes in routine clinical care introduced by the approval of new drugs in Europe, the European Federation of Neurological Societies (EFNS) deemed it necessary for a task force to re-examine the data and revise the first RLS guidelines [14]. It should be noted that periodic limb movement disorder (PLMD) has been deleted from the current guidelines as there are no new studies concerning PLMD and therefore no new recommendations.

Objectives

These guidelines seek to provide revised evidence-based recommendations for the treatment for RLS. This current revision uses the same definition of RLS that was used in the previous guidelines. However, only studies that clearly diagnosed RLS according to the essential criteria were included [15]. The previous guidelines divided treatment into short-term and long-term, defined as <30 days and >30 days, respectively. However, such a classification does not take into account the fact that augmentation, a paradoxical worsening of symptoms caused by treatment [16], manifests after several months of treatment. Furthermore, studies performed after the last guidelines [14] tended to have a longer duration of treatment. Therefore, we considered trials <6 months to be short-term and those ≥6 months to be long-term.

To determine the effectiveness of drugs and physical interventions in the treatment for RLS, the following hypotheses were assessed.

1 Any drugs are more effective than no treatment or treatment with placebo:
   - **a** in abolishing or reducing the occurrence of RLS symptoms;
   - **b** in improving quality of life.
2 One class (see Table 1) or one agent is better than another.
3 Physical intervention is more effective than no treatment or treatment with placebo:
   - **a** in abolishing or reducing the occurrence of RLS symptoms;
   - **b** in improving the quality of life (QoL).
4 The risk/benefit ratio of any treatment is positive for the patient.

Methods and search strategy

A literature search was performed using the same strategy as the previous guidelines (Table 2); all terms were searched as free text and standardized search items in electronic databases (Cochrane Library, National Library of Medicine's MEDLINE, EMBASE, CINAHL). Existing guidelines and meta-analyses were also taken into consideration. All articles published (including those available online before going to print) in English between 1 January 2005 and 31 December 2011 were assessed for inclusion, and data extraction performed. In addition, task force members performed an independent literature search. Each working group task force member was allocated to cover two drugs or class of drugs, and each allocated topic was reviewed independently by two members to reduce reviewer error and bias. Dropout rates because of

Table 1 Evidence classification scheme for a therapeutic intervention [17]

Class I: An adequately powered prospective, randomized, controlled, double-blind clinical trial 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 are required:
a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent amongst treatment groups or there is appropriate statistical adjustment for differences.
Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e.
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion
Rating of recommendations
Level A rating (established as effective, ineffective, or harmful) requires at least one convincing Class I study or at least two consistent, convincing Class II studies.
Level B rating (probably effective, ineffective, or harmful) requires at least one convincing Class II study or overwhelming Class III evidence.
Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing Class III studies.
Good practice points Where there was a lack of evidence but consensus was clear, the task force has stated their opinion as good practice points.

adverse events were noted, and risk of bias was assessed. Full text copies of the relevant studies were obtained, and task force members assessed them for inclusion and extracted the relevant data into evidence tables.

The methodological limitations of this review concern language and publication bias: the task force only included studies published in English peer-reviewed journals available in electronic format. Language and publication bias are considered to lead to an inflation of positive results in reviews and meta-analyses. The positive, level A recommendations made by the task force are only made for drugs where large-scale studies have been published, therefore limiting positive result bias.

As established by EFNS methodology, the studies were classified according to type of study design (Class I–Class IV evidence) (Table 1) [17]. If the highest level of evidence was not sufficient, the literature search was extended to the lower adjacent level of evidence. Patients with RLS (defined using explicit diagnostic criteria), with any other co-morbidity and co-treatment, were considered. Guideline recommendations were made by assessing the volume of evidence, applicability, consistency and clinical impact. Class of evidence and rating of recommendations were attributed according to the EFNS Task Force Recommendations (Table 2) [17].

As in the previous guidelines, types of outcome measures were the following,

1 Paraesthesia/dysaesthesia or pain (by simple subjective report or subjective validated scales/questionnaires).
2 Polysomnographic indexes of sleep dysfunction [mean periodic limb movements in sleep index (PLMS-I), and while awake PLMS-A, sleep efficiency, sleep latency, actigraphic activity in sleep].
3 Quality of life.
4 Adverse events; augmentation effect, defined as markedly augmented RLS symptoms occurring in the afternoon and the evening prior to the taking the next nightly dose, was rated amongst adverse events at the latest follow-up.
5 Drop-outs.
6 Rate of patients choosing to remain in treatment after completion of trial.

Any discrepancies in the reviews were resolved by consensus amongst the two reviewers. The first draft of the manuscript was written and directly supervised by the task force chairman (DGB). All members of the task force read the first draft and discussed it by email. Subsequent drafts were circulated, finalized and discussed by email. When there were no new studies, the previous EFNS recommendations were not modified.

The GRADE.com system was simultaneously used for the evaluation of Level A recommendations. According to this new and more sensitive tool, overall quality of evidence is classified as high, moderate, low and very low. According to the available studies, the overall quality of evidence is rated between high and low.

Results

For each agent, the studies with the highest class of evidence are reported here. For certain agents, no

Table 2 Search strategy for identification of studies

Published papers (systematic reviews, meta-analysis, randomized trials, cohort studies, case–control studies, observational studies) were identified from the following sources published between 1 January 2005 and 31 December 2011
Cochrane Database of Systematic Reviews (CSDR) in the Cochrane Library
Database of Abstract of Reviews of Effects (DARE) in the Cochrane Library
CENTRAL (Cochrane Central Register of Controlled Trial) in the Cochrane Library
National Library of Medicine's MEDLINE database
EMBASE database
CINAHL database
Checking reference lists: bibliographies of identified articles reviewed to find additional references
Search terms
All the electronic databases considered were checked with terms focusing only on the condition. With regard to Restless Legs Syndrome the following search was performed:
(restless* OR jitter* OR anxiet*) AND (limb* OR leg* OR tibia*) OR ekbom* OR "restless legs syndrome"
For the search with MeSH terms: Restless Legs Syndrome (MeSH)
With regard to PLMD the following search was performed:
(myoclon* OR movement* OR periodic*) AND (limb* OR leg* OR tibia*) AND (noct* OR sleep*)
For the search with MeSH terms: Nocturnal Myoclonus Syndrome (MeSH)
The search strategy identified 3309 references (possible duplicates) for RLS and/or PLMD. After assessing from title, abstract or full text of articles, a total of 54 articles for RLS were eligible for inclusion in the above review.
According to each treatment category the following articles were included:
Dopaminergic agents: 25
Non-ergot derivatives: 18
Rotigotine: 4, Ropinirole: 3, Pramipexole: 10, Sumanirole: 1
Ergot derivatives: 5
Cabergoline: 2, Lisuride: 2, Terguride: 1
Levodopa: 2 (one comparative study with cabergoline, another with pramipexole)
Antiepileptic drugs: 15
Alpha-2-delta ligands: 11
Gabapentin anacarbil: 7, Pregabalin: 2, Gabapentin: 2
Oxcarbazepine: 2
Lamotrigine: 1
Levetiracetam: 1
Adrenergic agents: 0
Benzodiazepines/hypnotics: 1
Clonazepam: 1
Opioids: 3
Other: 12
Iron: 4
Botox onabotulinumtoxinA: 1
Bupropion: 1
Infrared light: 2
Aerobic training: 2
Magnesium: 1
Valerian: 1

Class I–III studies were available and, therefore, in these cases Class IV studies have been included. Very few studies have been performed on secondary RLS, none of which was Class I; therefore, these guidelines effectively concern the treatment of primary RLS (see Table S1 for all results).

Dopaminergic agents

Dopaminergic agents are the class of drugs for which the most studies have been published since the previous guidelines.

Non-ergot derivatives

Eighteen reports were retrieved for the non-ergot derivatives (rotigotine, ropinirole, pramipexole and sumanirole).

Rotigotine (two short-term and two long-term studies, Class I evidence, new conclusion: 'effective' for the short- and long-term treatment of primary RLS)

The short-term efficacy of rotigotine transdermal patch for the treatment for RLS has been established by the previous guidelines. However, data on mid- and long-term efficacy were lacking at the time. Four new reports provide high-quality evidence of the efficacy of rotigotine for the treatment of primary RLS [18–21]. A 6-week dose-finding trial [18] found rotigotine to be efficacious in improving RLS symptoms [International RLS severity scale (IRLS) total score] compared with placebo at doses of 4 mg/24 h, 3 mg/24 h, 2 mg/24 h and 1 mg/24 h ($P = 0.0013$, $P < 0.0001$, $P = 0.0003$ and $P = 0.0004$, respectively). The 0.5 mg/24 h dose was not found to be efficacious ($P = 0.2338$). The mean change in the RLS-QoL from baseline was 16.82 (SD ± 12.85) vs. 12.4 (SD ± 15.5) for placebo. A 6-month European study [19] found rotigotine to be efficacious at all doses from 1 to 3 mg in improving IRLS total score and Clinical Global Impression (CGI), item 1 (all $P < 0.0001$), overall QoL improvements were dose-dependent, and the mean change in RLS-QoL from baseline was 15.43 (SD ± 14.04) vs. 7.3 (SD ± 13.5) for placebo. A 6-month fixed dose (0.5–3 mg/24 h) maintenance study performed in the United States [20] found rotigotine 2 and 3 mg/24 h to be efficacious, and a 4-week polysomnographic study reported the efficacy of an average dose of 2.09 mg/24 h (±0.78) in improving RLS symptoms according to IRLS, CGI-I and the periodic limb movement index (PLMI), as well as QoL [21]. In addition to the Class I evidence, there is Class III evidence consisting of a well-designed 5-year prospective open-label study, with an average rotigotine dose of 3.1 mg/24 h at the end of the maintenance period. There was an improvement in severe RLS symptoms as shown by a change in the total IRLS score from 27.7 (SD 6.0) at baseline to 9.0 (SD 9.2) at study end; 39% of completers were symptom free at the end of

the trial; 30% of patients dropped out because of adverse events and 11% because of lack of efficacy, the majority of these drop-outs occurred in the first year. The most common adverse events were adverse application site reactions affecting 58% of all patients treated in this study at least once and accounting for 19% of patients dropping-out. The incidence of adverse site reactions was 37% in year 1 and <6% in years 4 and 5. The overall 5-year incidence of clinically significant augmentation was 13.2% (39/295); for 5.1% of patients, this occurred at 1–3 mg/24 h, whilst 8.1% were receiving 4 mg/24 h [22].

Ropinirole (three short-term studies and one long-term study, Class I evidence, no change to previous recommendation: 'effective' for the short-term and 'possibly effective' for the long-term treatment of primary RLS)

Of six reports on ropinirole, there are three short-term [23–25] and one long-term [26] RCTs that confirm the recommendations of the earlier guidelines. These studies report that ropinirole at a mean dose between 2.1 and 3.1 mg/day is efficacious for the treatment of primary RLS as measured on the IRLS, CGI-I, Patient Global Impression of Improvement and the PLMI [23–26]. A significant improvement in QoL compared with baseline, as measured using the RLS-QoL questionnaire, is reported in one study [24] [ropinirole vs. placebo: 16.9 (SE ± 2.14) vs. 12.4 (SE ± 2.08), respectively, $P = 0.003$]. The same study also found ropinirole to improve anxiety in those with anxiety ($n = 62$) as measured on the Hospital Anxiety and Depression rating scale (HADS) ($P = 0.04$). Ropinirole is also associated with significantly greater improvements in subjective measures of sleep disturbance, quantity and adequacy [24,26]. Main side effects included nausea, somnolence, fatigue and depression. Augmentation was not assessed using established criteria, but the 36-week study [26] indicated a possible 1.5% rate of augmentation in this period. For long-term treatment, there is one open-label trial (52 weeks) available [27]. In this study, the efficacy was similar to the aforementioned trials, augmentation was assessed as an adverse event using the verbatim term 'RLS', this gave a possible rate of 9.1%, and 2.3% of patients stopped or reduced the dose because of the adverse event 'RLS'. A recent prospective multicentre study [28] provides new data on augmentation: this two-phase study with ropinirole (median total daily dose of 1.8 mg; range 0.4–3.6 mg) reported a 4% augmentation rate, with 3% being clinically significant (vs. <1% for placebo) over the 6-month double-blind phase, and a 3% augmentation rate (2% clinically significant) during the open-label 6-month follow-up phase. Mean time to first episode of augmentation was longer for ropinirole (116 days; range: 62–183; $n = 7$) than placebo (30 days; $n = 1$), confirming that episodes of true augmentation are usually not seen during the first 2 months of treatment [28]. Differences in efficacy over the 6-month double-blind period between ropinirole and placebo were mild [treatment difference in IRLS score −2.5 (−4.6, −0.3), but still statistically significant ($P < 0.05$)] [28].

Pramipexole (eight short-term and two long-term studies, Class I evidence, change to previous recommendation: 'effective' for the short-term and 'possibly effective' for the long-term treatment of primary RLS)

Seventeen reports concern the use of pramipexole; of these, there are 10 new RCTs including over 1500 patients [29–38]. For primary RLS, pramipexole (0.25–0.75 mg) improves RLS symptoms in both the short- and long-term, as measured using the IRLS, and PSG measures significantly improve. As far as sleep is concerned, pramipexole 0.5–0.75 mg was shown to improve sleep latency, but not sleep efficiency or total sleep time [39]. Pramipexole 0.25–0.75 mg significantly improved QoL as measured with the SF-36 and the RLS-QoL [32,34,35,37,39]; non-significant improvements in depression (Beck Depression Inventory) and anxiety [HADS-Anxiety subscale (HADS-A)] were also reported [37]. The most common adverse events to be described are nausea, headache, insomnia, somnolence and dizziness. Only one of the RCTs reported Augmentation Severity Rating Scale data on augmentation; this was a 6-month study by Högl *et al*. that reported a 9.2% rate of augmentation for pramipexole, compared with 6% for placebo [36]. IRLS score decreased by an adjusted mean of −13.7 in the pramipexole group compared with −11.1 in placebo ($P = 0.0077$). Two short-term studies reported a worsening of RLS: of 3.7% in one study [39], whilst no figures were given in the second study [34]. One open-label 46-week study [40], and a retrospective study lasting a mean 30.5 months [41] reported possible augmentation rates of 4.3% and 22.4%, respectively.

Sumanirole (one short-term study, Class I evidence, new conclusion 'non-effective' for the treatment of primary RLS)

There is only one published Class I study on sumanirole for the treatment for RLS [42]. This double-blind study failed to find sumanirole at doses of 0.5–4 mg to be efficacious in improving IRLS scores in patients with primary RLS. An improvement was seen in PLMSI scores at doses of 2 and 4 mg. A dose-finding study was not undertaken prior to this study, and the dosages used are thought to have been too low. Five patients dropped out of the study because of adverse events. At a dose of 0.5–4 mg, sumanirole is non-efficacious for the treatment for RLS. Sumanirole is not on the market

and has not been approved in Europe or elsewhere for the treatment for RLS.

Recommendations for non-ergot derivatives

Rotigotine transdermal patch (1–3 mg/24 h) is effective (level A) for the short- and long-term treatment of primary RLS. Ropinirole is effective (level A) for improving symptoms in primary RLS when given at a mean dose of between 2.1 and 3.1 mg/day over the short-term and possibly over the long-term. Pramipexole is considered effective in the short-term (level A) and possibly effective (level B) for the long-term treatment for RLS at doses between 0.25 and 0.75 mg. Sumanirole at the investigated doses (0.5–4 mg) is ineffective (level A) for the treatment of primary RLS. There were no new studies with this class of drugs for the treatment for secondary RLS.

Ergot derivatives

A total of five new reports concern the ergot derivatives (cabergoline and lisuride). There were no new studies meeting inclusion criteria for pergolide, bromocriptine, a-dihydroergocryptine.

Cabergoline (one short-term and one long-term study, Class I evidence, new conclusion: not generally recommended for the treatment of primary RLS because of adverse events)

One short-term study confirmed the previous conclusion that cabergoline 0.5–2 mg is efficacious for the treatment of primary RLS over the short-term as measured with the PLMS-AI ($P = 0.0024$) and the IRLS ($P = 0.0002$), and improves RLS-QoL scores ($P = 0.0247$) [43]. A longer, 30-week study found cabergoline 2 and 3 mg to be efficacious for primary RLS, and with significantly improve RLS-QoL compared with baseline ($P = 0.0001$). Augmentation was reported in 5.6% of patients on cabergoline compared with 14.2% for levodopa, which was used as a control [44]. In countries where cabergoline is licensed for use in Parkinson's disease, a boxed warning has been added to product labelling concerning the increased risk of developing cardiac valvular disease with dosages higher than 3 mg. Cabergoline, as any of the ergoline derivatives, is therefore contraindicated in patients with a history of cardiac, pulmonary or retroperitoneal fibrosis or signs of cardiac valve abnormalities. Owing to the increased risk of severe side-effects despite the good study evidence for efficacy, cabergoline is not currently used for the treatment of new patients with RLS. If patients on long-term treatment for RLS with cabergoline prefer to stay on their treatment, they should at least undergo echocardiographic and X-ray-thorax monitoring periodically to detect any fibrosis valve abnormalities and fibrosis early enough.

Lisuride (two short-term studies, Class III evidence, no change to previous recommendation: insufficient evidence)

Two small pilot studies [45,46] providing Class III evidence found lisuride transdermal patch 3 and 6 mg to improve IRLS scores and to improve PLMI as measured using actigraphy. Lisuride is not currently on the market for the treatment for RLS.

Terguride (one short-term study, Class III evidence, no change to previous recommendation: insufficient evidence)

There is Class III evidence [47] that terguride (0.25 mg/day) administered for at least 2 weeks improves RLS symptoms as measured using the IRLSS ($P = 0.014$). In this short-term study, there was no significant change in subjective nocturnal sleep duration as measured with the Epworth Sleepiness Scale. Augmentation was seen in one of the seven patients following dose doubling.

Pergolide (no new studies, new conclusion: not recommended for the treatment of primary RLS due to adverse events)

Similarly to cabergoline, the use of pergolide has been associated in Parkinson's disease to an increased risk of valvulopathy and fibrosis. Furthermore, pergolide has been withdrawn from the market in EU and in the USA.

Bromocriptine (no new studies, no change to previous recommendation: probably effective for the short-term treatment of primary RLS)

Recommendations for ergot derivatives

In primary RLS, no new studies have been published on pergolide. Although the previous conclusion of effectiveness at mean dosages of 0.4–0.55 mg/day (level A) and possible effectiveness in the long-term (level C) remains, the possible toxicity because of an increased, although low incidence of valvular fibrosis and other fibrotic side-effects, outweigh the benefits [48]. Furthermore, at the time of writing, pergolide was no longer available in many European countries. For cabergoline, the same precaution as for pergolide applies. There is insufficient evidence to make any recommendations on terguride. There are no new studies on bromocriptine and, therefore, the previous conclusion of probably effective at 7.5 mg for primary RLS (level B) remains. The most frequent adverse events of ergot-derived dopamine agonists are nausea, headache, nasal congestion, dizziness and orthostatic hypotension. Augmentation remains an open issue for all ergot derivatives and requires further extensive investigation. Furthermore, owing to the negative

side-effect profile, especially the potential to induce fibrosis, ergot derivatives cannot be recommended for the first-line treatment for RLS and, if used, necessitate cardiopulmonary monitoring for fibrosis.

Levodopa (one long-term and one short-term study, Class I evidence, no change to previous recommendations: effective for the short-term treatment and possibly effective for the long-term treatment of primary RLS)

A large, Class I, 30-week double-blind, RCT comparing cabergoline to levodopa 200 and 300 mg was found to be efficacious for the treatment of primary RLS; however, 14.2% of patients discontinued owing to lack of efficacy and 9.8% discontinued owing to augmentation [44]. RLS-QoL significantly improved in both treatment groups compared with baseline (both $P = 0.0001$). A short-term study [38] compared the efficacy and safety of levodopa (125–375 mg) with pramipexole (0.25–0.75 mg) in *de novo* patients with primary RLS. Both drugs were effective in reducing RLS symptoms. However, given the important risk of augmentation, levodopa should not be given at a dosage higher than 200 mg [49]. In clinical practice, levodopa is now better established as a diagnostic test for RLS and as an on-demand treatment in sporadic RLS; however, in countries like Germany, it is the most frequently prescribed first-line therapy.

Antiepileptic drugs

Fifteen reports concerned the use of antiepileptic drugs (pregabalin, gabapentin, gabapentin enacarbil, oxcarbazepine, lamotrigine and levetiracetam).

Alpha-2-delta ligands

Gabapentin enacarbil (five short-term studies, Class I evidence, and two long-term studies, Class II and III evidence; new recommendations: effective for the short-term and probably effective for the long-term treatment of primary RLS)

Gabapentin enacarbil did not figure in the previous guidelines; three Class I studies now report efficacy for the treatment of primary RLS [50–54]. One short-term study (14 days) demonstrated efficacy (improvement in IRLS, CGI-I investigator and patient scores, all $P < 0.0001$) at 1200 mg/day but not at 600 mg/day [50]. Sleep quality as measured on the post-sleep questionnaire also improved ($P = 0.003$) [50]. Adverse effects, of which somnolence and dizziness were the most common, were reported in 82% of patients receiving 1200 mg, vs. 59% receiving 600 mg gabapentin enacarbil and 42% of those on placebo. Another 14-day trial [51] reported a significant improvement in IRLS score and in CGI-I investigator and patient scores (all $P = 0.0001$), as well as a reduction in RLS pain score in patients with a baseline RLS pain score ≥ 4 (-3.7 vs. -1.9 with placebo $P < 0.0001$).

Gabapentin enacarbil significantly improved scores on all post-sleep questions except the ability to 'function' on the investigator-designed questionnaire. Improvement was seen in wake after sleep onset and the number of awakenings, and there was an increase in sleep stages 3 and 4, and a decrease in stage 1 [51]. Improvements in sleep outcomes were confirmed in two more recent trials [52,53]. The improvement in PLMS indices was not significant in this 14-day study. However, a polysomnography crossover study found a dose of 1200 mg/day to significantly reduce the PLMS-A at week 4 compared with placebo ($P = 0.002$) [52]. A longer study [54] (12 weeks) found 1200 mg/day gabapentin enacarbil to be efficacious as early as week 1 as seen on CGI-I, MOS scales, PSQ and RLS-QoL scores (all $P = 0.0001$). Only one study finds gabapentin enacarbil to be efficacious at doses of 600 and 1200 mg/day [53]. In this study, gabapentin enacarbil 600 and 1200 mg/day significantly improved IRLS total scores at week 12 compared with placebo [mean treatment difference (AMTD): 600 mg/day -4.3; $P < 0.0001$; 1200 mg/day -3.5; $P = 0.0015$], and significantly more patients in both treatment arms were CGI-I responders compared with placebo (72.8%, 600 mg/day; 1200 mg/day, 77.5% vs. 44.8% for placebo). The most commonly reported adverse events were somnolence (600 mg = 21.7%; 1200 mg = 18.0%; placebo = 2.1%) and dizziness (600 mg/day = 10.4%; 1200 mg/day = 24.3%; placebo = 5.2%). Dizziness increased with dose and led to discontinuation in two subjects (one in each active treatment arm). Somnolence led to discontinuation in three subjects in the 600 mg/day treatment arm. In all the above studies, the most common reported adverse events were somnolence and dizziness.

In addition to the above, there are three long-term, open-label studies [55–57] providing Class II and III evidence. These studies found gabapentin enacarbil 1200 mg/day to be efficacious in improving primary RLS symptoms. In the 64-week study, treatment-emergent adverse events caused 10.3% of subjects to withdraw from the trial, and the most common side-effects were somnolence and dizziness (19.7% and 11.5% of subjects) [55]. No specific data on augmentation were provided, although Ellenbogen did not find early markers of augmentation (e.g. an earlier onset of symptoms in the afternoon) [55]. Gabapentin enacarbil can be considered an effective treatment for the short-term and probably effective for the long-term treatment of RLS at a dose of 1200 mg/day, and arguably at 600 mg/day.

Pregabalin (two short-term studies, Class I evidence, new conclusion: effective for the short-term treatment of primary RLS; insufficient evidence for the long-term)

Pregabalin did not figure in the previous guidelines. In primary RLS, two Class I studies [58,59] have found this drug to be an efficacious treatment. In a 12-week study [58], pregabalin 150–450 mg/day (mean dose 337.50 mg/day) was found to significantly improve IRLS total score ($P = 0.005$), CGI ($P = 0.035$), RLS-6 sleep measures and MOS scale for sleep disturbance, sleep adequacy and sleep quantity (all $P = 0.001$). In addition, there was an improvement in PLMI, PLM-AI and PLM-W ($P = 0.001$, 0.05, 0.05), and increased sleep stages 1 and 2 and slow-wave sleep. A 6-week study [59] found that pregabalin (at least 150 mg/day) significantly reduced IRLS scores ($P = 0.04$). An improvement in CGI-I and SF-36 scores was only significant at a daily dose of 450 mg (both $P = 0.05$). There was an improvement in RLS-QoL, but this was not statistically significant at week 6 compared with placebo [59].

In secondary RLS, there is only one open-label case series providing Class IV evidence of pregabalin in RLS patients with polyneuropathy [60]. In this study, a mean dose of 305 mg/day was found efficacious in improving symptoms as measured by subjective clinical impression.

Gabapentin (two short-term studies, Class III and IV evidence, no change to previous recommendations: effective for the short-term treatment of primary RLS and probably effective in secondary RLS after haemodialysis)

No new studies providing Class I evidence have been published for gabapentin and, therefore, the previous recommendations based on Class I evidence remain unchanged.

Oxcarbazepine (two studies, Class IV evidence, new conclusion: insufficient evidence)

Oxcarbazepine did not figure in the previous guidelines; and only Class IV studies have been published since. In primary RLS, complete remission was reported with a daily dose of 600 mg as rated by subjective clinical impression [61]. In secondary RLS, a single case report found a daily dose of 300 mg and paroxetine to improve IRLS score [62].

Recommendations

Pregabalin and gabapentin enacarbil can be considered effective for the short-term treatment of primary RLS (both level A). In addition, gabapentin enacarbil can be considered probably effective for the long-term treatment of RLS. Gabapentin continues to be considered effective in the short-term treatment of primary RLS (level A) and probably effective in secondary RLS after haemodialysis (level B). There is insufficient evidence to make any efficacy conclusions on oxcarbazepine.

Other antiepileptic drugs

Lamotrigine (one study, Class IV evidence, new conclusion: insufficient evidence)

Lamotrigine did not figure in the previous guidelines, and there is only Class IV evidence concerning treatment for RLS. A case series found lamotrigine at a mean dose of 360 mg/day to subjectively improve symptoms, but did not improve actigraphy or SIT scores [63]. Side-effects included pruritus, dizziness (one withdrawal) and chest pain.

Levetiracetam (one study, Class IV evidence, new conclusion: insufficient evidence)

There is evidence from two case reports [64] that levetiracetam 1000 mg/day given at bedtime improves the symptoms of primary RLS and RLS secondary to iron deficiency. In addition, it reduced sleep latency, increased sleep efficiency and reduced daytime sleepiness.

Recommendations

There is insufficient evidence to conclude on the efficacy of lamotrigine or levetiracetam for the treatment of RLS.

Adrenergic agents

No new reports concern the use of drugs acting primarily on adrenoceptors. Therefore, the previous recommendations remain unchanged.

Recommendations

Clonidine is probably effective in reducing symptoms and sleep latency in primary RLS at short-term (level B). Clonidine had several but tolerated adverse events (dry mouth, decreased cognition and libido, lightheadedness, sleepiness, headache). There is not sufficient evidence to recommend talipexole (primary RLS).

Benzodiazepines/hypnotics

Since the publication of the previous guidelines, only one report concerns the use of benzodiazepines (clonazepam).

Clonazepam (one study, Class III evidence, no change to previous recommendation: probably effective for primary RLS)

There is Class III evidence from an open-label, prospective switch study [65] whereby patients with an improved outcome after the switch to pramipexole.

Recommendations

Owing to the lack of new studies of sufficient quality evidence, the task force is not able to make any further recommendations for benzodiazepines.

Opioids (no change to previous recommendations)

Only three studies with low evidence classes have been published since the previous guidelines concerning opioids [66–68]. A case report on tramadol reports the first case of augmentation in this class of drugs [68].

Recommendations

Owing to the lack of new studies of sufficient quality, the task force is not able to make any further recommendations for opioids.

Iron

Whilst there is evidence that patients with low ferritin plasma levels (<45 μg/l) benefit most from iron supplementation [69–71], it remains controversial whether patients with normal ferritin levels benefit to the same degree [72]. Ferritin levels have been implicated in the pathophysiology of RLS, and a recent study has suggested that ferritin may be a biomarker for the development of RLS augmentation [73].

Iron sucrose (two studies, Class I evidence, new conclusion: not effective for the treatment of primary RLS)

Two RCTs examining the efficacy of 1000 mg (total dose) intravenous iron sucrose for the treatment of primary RLS found no clinical or statistically significant benefit on IRLS or in sleep parameters compared with placebo [74,75].

Oral ferrous sulphate (one study, Class I evidence, new conclusion: probably effective for the short-term treatment of primary RLS)

A 12-week, Class I study [76] found ferrous sulphate to significantly improve IRLS scores ($P = 0.01$), and there was a non-significant improvement in subjective quality of life.

IV ferric carboxymaltose (one study, Class I evidence, new conclusion: probably effective for the short-term treatment of primary RLS)

A recent randomized study on IV ferric carboxymaltose (500 mg given in two doses, 5 days apart) found a response rate of 45% in patients with RLS, and remission in 29%. The response continued for up to 24 weeks following initial treatment [77]. Improvements were seen on the IRLS ($P = 0.040$), the CGI-I ($P = 0.004$) and QoL improved significantly more with ferric carboxymaltose than placebo compared with baseline ($P = 0.024$).

Other

Botox onabotulinumtoxinA: insufficient evidence

There is Class III evidence that botox onabotulinumtoxin A improves RLS symptoms during the first 4 weeks after treatment [78].

Bupropion: insufficient evidence

One study [79] providing Class I evidence failed to find bupropion (150 mg) to provide a statistically significant reduction in RLS symptoms at 6 weeks compared with placebo, although a benefit at 3 weeks was reported.

Infrared light: insufficient evidence

There is Class III evidence concerning the use of infrared light in alleviating RLS symptoms [80,81]. Twelve 30-min treatments to lower legs with near-infrared light were shown to improve IRLS scores ($P < 0.001$).

Aerobic training: insufficient evidence

There is only Class III evidence that aerobic and lower-body resistance training 3 days per week is effective in improving mild primary RLS symptoms as measured on the IRLS ($P = 0.001$) [82]. There is also Class III evidence that shows that interdialytic aerobic training reduced secondary RLS symptoms in a case series of patients on haemodialysis [83].

Folate: insufficient evidence

There are no specific studies regarding the effect of folate for the treatment for RLS.

B12: insufficient evidence

No studies have evaluated the effect of vitamin B12 on RLS symptoms.

Magnesium: insufficient evidence

There are no available studies providing Class I evidence for magnesium. There is Class IV evidence that shows magnesium relieves symptoms in isolated cases of RLS secondary to pregnancy [84]. However, magnesium is not likely to play a major role in treatment of primary RLS [85]. In patients with renal failure, magnesium can accumulate and lead to neuromuscular blockade.

Vitamin E: insufficient evidence

No studies reported the effect of vitamin E on RLS symptoms.

Physiotherapy: insufficient evidence

No studies reported the effect of physiotherapy on RLS symptoms.

Valerian: ineffective

One study with valerian (Class III evidence) failed to find it efficacious for treating RLS symptoms or improving sleep [66].

Recommendations

In light of new evidence, oral ferrous sulphate and intravenous ferric carboxymaltose are considered possibly effective for the short-term treatment of primary RLS. Valerian is considered ineffective. There is insufficient evidence to conclude on the efficacy of folate, B12, magnesium, vitamin E, botox, bupropion, physiotherapy, infrared light and aerobic training.

Final level A recommendations

Strong recommendations

- Rotigotine transdermal patch (1–3 mg) is effective for the short- and long-term treatment of primary RLS.
- Ropinirole is effective for improving symptoms in primary RLS when given at a mean dose of between 2.1 and 3.1 mg/day over the short-term.
- Pramipexole is considered effective in the short-term at doses between 0.25 and 0.75 mg.
- Gabapentin enacarbil (1200 mg daily) is effective for the short-term treatment of primary RLS.
- Pregabalin (150–450 mg daily) is effective for the short-term treatment of primary RLS.
- Gabapentin is effective for the short-term treatment of primary RLS.

Weak recommendations

- There is high-quality evidence that shows that cabergoline (0.5–3 mg/day) improves RLS symptoms; however, cabergoline cannot be recommended because of serious adverse risks (see above).
- There is high-quality evidence that shows that levodopa (up to 300 mg/day) improves RLS symptoms. However, given the higher risk of augmentation compared with dopamine agonists, levodopa should not be given at a dosage higher than 200 mg/day [49]. In clinical practice, levodopa is now better established as a diagnostic test for RLS and as on-demand treatment in sporadic RLS. Consequently the task force can only make a low recommendation for levodopa.

Discussion

In the previous guidelines [14] dopaminergic agents had been established as the first-line treatment of primary RLS. We consider that overall, this conclusion is still valid, particularly since gabapentin enacarbil is, at the time of writing, not available in Europe. Furthermore, the results of a preliminary report comparing a dopamine agonist (pramipexole) and an alpha-2 delta ligand (pregabalin) over 52 weeks have shown lower rates of augmentation for pregabalin, with similar or better long-term efficacy. Thus, the task force considers that the overall recommendation to use dopamine agonists as a first-line treatment could change in the future if supported by such studies.

Amongst the non-ergot derivatives, three substances provide Class I evidence that enables level A/strong recommendations to be made on their therapeutic efficacy in treating sensory symptoms and periodic leg movements. The largest number of new studies concerns pramipexole and rotigotine. Rotigotine appears to be superior to ropinirole and pramipexole; however, most of the studies with ropinirole and pramipexole have been performed with the standard preparations and not the extended release versions. It is possible that the extended release versions are more efficacious, but studies are lacking. For rotigotine, long-term studies have reached 5 years duration, showing maintained efficacy and relatively low rates of augmentation. As for the ergot derivatives, new studies place cabergoline as one of the best-studied and probably most effective substances. However, the use of ergot derivatives is limited by the fact that this drug class (particularly pergolide) has been associated with valvular heart disease when used in Parkinson's disease [86], although when used at lower doses, as in RLS, the risk seems less clear [87].

Despite some progress, the risk of augmentation with dopaminergic agents remains largely unstudied. During these years, new diagnostic criteria have been defined [16] and specific rating scales [49] have been developed. However, not all drugs have been investigated for a sufficiently long period of time for the augmentation rate to be accurately determined. Whilst a 6-month study on pramipexole [36] showed a surprisingly high rate for both the active substance (9.6%) and placebo (6%), the length of that study might have been too short to show the real differences. Furthermore, this study was not adequately powered to detect differences in augmentation rates. One of the main teachings of this study is the fact that differences between the active substance and placebo become evident mainly after 4 months of treatment. Something similar can be said regarding a recent study on ropinirole [28]. Therefore, the clinical utility of controlled studies evaluating augmentation with a duration of 6 months or less becomes questionable. Another important study recently published on rotigotine was an open study performed over 5 years. Whilst the augmentation rate was generally low and most of the new cases occurred within the first 2 years, the severity of the episodes generally worsened with time. Only 4.5% of the total sample discontinued because of augmentation [88]. Future long-term studies on augmentation will have to address questions such as the definition of clinical predictors for augmentation (in dose, length of treatment, severity at baseline), and whether all RLS patients are potentially vulnerable to augmentation.

As already mentioned above, there is an increasing tendency to investigate new non-dopaminergic drugs. In contrast to the previous guidelines where the lack of studies on non-dopaminergic drugs was highlighted, there has since been an increasing interest in these drugs, probably as a way to develop treatment

alternatives without the risk of augmentation. Such an interest is shown by the increasing number of studies on alpha-2 delta ligands (mainly gabapentin enacarbil and pregabalin). Amongst these substances, gabapentin is the drug for which we have the most data, although at the time of writing, it is not available in Europe. As stated above, gabapentin enacarbil markedly improves sensory symptoms and sleep architecture. The effects on painful RLS are still to be confirmed. At the time of completing these guidelines, only three studies have been performed on pregabalin, none of which was longer than 12 weeks. Only one study has been performed to date on augmentation under alpha-2 delta ligands, and the incidence rate under pregabalin was significantly lower than for pramipexole [89]. Overall, the increasing evidence of a therapeutic effect of alpha-2 delta ligands on RLS symptoms will likely lead to discussion on the potential role of glutamatergic mechanisms in the pathophysiology of RLS [90–92].

Compared with the studies in the previous guidelines, the pharmacological studies included here tend to be larger and have better defined inclusion and exclusion criteria, and standardized endpoints. There is an important placebo response in many trials. A recent meta-analysis has shown a pooled placebo response rate of 40.09% (95% CI: 31.99–48.19) when the following outcome measures were used: RLS severity, subjective sleep parameters, sleep parameters derived from nocturnal polysomnography, PLMS and daytime functioning. The greatest placebo effect was seen for the IRLS (−1.48, CI: −1.81 to −1.14); the effect was smaller for other RLS severity scales, moderate for daytime functioning, small to moderate for subjective and objective sleep parameters, very small for PLMS and absent for sleep efficiency [93]. Given the placebo response rates observed in most studies that used the IRLS scale, greater effort needs to be made to improve these endpoints or to use other objective, sleep-laboratory-based endpoints such as the suggested immobilization test [94] or the more recent multiple suggested immobilization test [95].

Given the development of tolerance observed in some studies, future studies should include recently published criteria on loss of efficacy [96] and have a duration of at least 1 year. Furthermore, future studies should include active comparators. Although dopamine agonists are still nowadays the recommended first-line treatment, this is largely due to the fact that these compounds have been investigated most extensively. Hence, future studies should enlarge the spectrum of treatment classes and include active comparators of different drug classes. To date, three main controlled studies have been performed using an active comparator: Trenkwalder *et al*. compared levodopa (200–300 mg/day) with cabergoline (2–3 mg/day) over a period of 30 weeks [44]. Cabergoline was shown to be more efficient than levodopa and also had a lower discontinuation rate; augmentation rates were higher for levodopa. Bassetti *et al*. found pramipexole to be more efficient than levodopa in a 4-week crossover trial [38]. Preliminary results on another trial [89] showed that 300 mg of the alpha-2 delta ligand pregabalin has greater efficacy over 52 weeks and a lower rate of augmentation than the dopamine agonist pramipexole. If confirmed, such studies will show the therapeutic relevance of drugs working on glutamatergic pathways as they might have a lower impact on augmentation. Further comparative, long-term trials are needed to assess such differences between drug classes, as some of the main differences in efficacy and augmentation rates can be shown when these studies are sufficiently long.

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Supporting Information

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

Table S1 Evidence table.

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A full list of references is available at wileyonlinelibrary.com/journal/ene; doi:10.1111/j.1468-1331.2012.03853.x