EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep

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In 2003, the EFNS Task Force was set up for putting forth guidelines for the management of the Restless Legs Syndrome (RLS) and the Periodic Limb Movement Disorder (PLMD). After determining the objectives for management and the search strategy for primary and secondary RLS and for PLMD, a review of the scientific literature up to 2004 was performed for the drug classes and interventions employed in treatment (drugs acting on the adrenoreceptor, antiepileptic drugs, benzodiazepines/hypnotics, dopaminergic agents, opioids, other treatments). Previous guidelines were consulted. All trials were analysed according to class of evidence, and recommendations formed according to the 2004 EFNS criteria for rating. Dopaminergic agents came out as having the best evidence for efficacy in primary RLS. Reported adverse events were usually mild and reversible; augmentation was a feature with dopaminergic agents. No controlled trials were available for RLS in children and for RLS during pregnancy. The following level A recommendations can be offered: for primary RLS, cabergoline, gabapentin, pergolide, ropinirole, levodopa and rotigotine by transdermal delivery (the latter two for short-term use) are effective in relieving the symptoms. Transdermal oestradiol is ineffective for PLMD.

Background

Restless Legs Syndrome (RLS) was first identified by Willis [1] and reviewed in full monographic form by Ekbom [2]. Accordingly, it is also termed ‘Ekbom syndrome’. RLS is also known as ‘anxietas tibiarum’ and by the colloquial term ‘leg jitters’. RLS has a significant motor counterpart in the form of recurrent jerking movements termed ‘periodic limb movements in sleep’ (PLMS, formerly ‘nocturnal myoclonus’ and ‘periodic leg movements in sleep’). Even though PLMS may occur independently from RLS as an incidental polysomnographic finding, the International Classification of Sleep Disorders recognizes the ‘Periodic Limb Movement Disorder’ (PLMD) because of its potential impact on sleep quality and a possible source of excessive daytime sleepiness, particularly when PLMS are associated with arousals (PLMS-A) [3]. PLMS/PLMD severity is assessed by the PLMS Index (PLMS-I: PLMS per hour of polysomnographic recording).

The International Restless Legs Syndrome Study Group has proposed four minimal clinical diagnostic criteria for RLS [4] revised in 2003 [5]: (i) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (ii) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (iii) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (iv) the urge to move or unpleasant sensations are worse at night than during the day or only occur in the evening or night.

Severity is measured on the International RLS rating scale which has 10 questions for disease severity [6]. An RLS Quality of Life Instrument measuring quality of life has been recently validated [7]. RLS may be either primary or secondary [8]. Primary RLS often represents a familial disorder. RLS may also be secondary to other pathological conditions, in particular...
peripheral neuropathies, myelopathies, uraemia, rheumatoid arthritis, Parkinson’s disease, iron deficiency, attention-deficit hyperactivity disorder in children, and pregnancy. Dysfunction of the endogenous opioid and dopaminergic systems has been implicated in RLS principally based on the favourable effects of pharmacological interventions. The evidence for a central dopaminergic defect is still controversial. A role for iron and iron storage in the pathophysiology has also been derived from studies on iron metabolism in RLS.

The goal of therapy for RLS and PLMD is to control the symptoms. The aim of this guideline is to examine the best evidence available on the effectiveness of any treatment in these disorders.

Objectives

To determine the effectiveness and maintained effect of drugs and physical interventions in the treatment of RLS and PLMD, the following hypotheses were tested:

1. Any drugs are more effective than no treatment or treatment with placebo:
   a. in abolishing or reducing the occurrence of RLS and PLMD;
   b. in improving the quality of life.
2. One class or one molecule is better than another.
3. Any physical intervention is more effective than no treatment or treatment with placebo:
   a. in abolishing or reducing the occurrence of RLS and PLMD;
   b. in improving the quality of life.
4. The side-effects of the class or molecules and of the physical treatments proved to be effective do not exceed the therapeutic effects.

Methods and search strategy

The best available evidence to address each question was sought, with the classification scheme by type of study design according to the EFNS Guidance document (Class I to Class IV evidence, [9]). If the highest class of evidence was not sufficient or required updating the literature search was extended to the lower adjacent class of evidence. Patients with RLS and/or PLMD, with any other comorbidity and co-treatment were considered. Explicit diagnostic criteria of RLS were not required for inclusion. Therapies with any kind of drugs (any dose, any regimen) and with any kind of physical intervention were included. The following classes of drugs were considered: drugs acting on the adrenoreceptor, antiepileptic drugs, benzodiazepines/hypnotics, dopaminergic agents (levodopa, ergot- and non-ergot-derived dopaminergics), opioids, other treatments. The duration of treatment in every study was divided into short term (≤30 days) or long term (> 30 days).

For RLS, types of outcome measures were the following domains:
1. paraesthesia/dysaesthesia, or pain (by simple subjective report or subjective validated scales/questionnaires).
2. Polysomnographic indexes of sleep dysfunction (mean PLMS-I in sleep, mean 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.

For PLMD, the outcomes belonged to the following domains:
1. Polysomnographic indexes of sleep dysfunction.
2. Quality of life.
3. Adverse events.
4. Drop-outs.

In the strategy for identification of studies, search terms were generated for searching the following electronic databases (see Table S1 on the website): Cochrane Library, National Library of Medicine’s MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1982). Existing guidelines were also sought and taken into consideration.

All references until the end of 2004 were reviewed to assess potentially relevant studies for inclusion, and data extraction performed. For every key question, an evidence table was created listing the design and methodological classification of each study. For forming guideline recommendations, the volume of evidence, applicability, generalizability, consistency and clinical impact, were summarized by every member of the Task Force. Classes of evidence and rating levels of recommendations were attributed according to the EFNS Task Force Guidance [9]. Disagreement was resolved by discussion. Finally, every member of the guideline group had to declare a potential conflict of interest, if any.

Results

Class I to III studies are reported here, and are referenced in Table S2 (placed on the website). Class IV studies were also considered, but are only referenced in Table S3 (placed on the website).
Drugs acting on the adrenoreceptor

Fifteen reports concerned the use of drugs acting on the adrenoreceptor (clonidine, phenoxybenzamine, propranolol, talipexole). In primary RLS, in a class II study [10], clonidine (mean dosage 0.5 mg 2 h before onset of symptoms) for 2–3 weeks, improved paraesthesia and motor restlessness (1.6 and 1.7 points respectively of a non-validated scale) and sleep latency (35.5 min) but PLMS-I, PLMS-A, actigraphy and sleep efficiency were left unchanged. Adverse events (dry mouth, decreased cognition, constipation, decreased libido, lightheadedness, sleepiness, headache) during clonidine did not lead to drop-outs. There is a class III evidence [11] that talipexole (an agonist both at dopamine D2 and adrenergic z-2 autoreceptors) 0.4–0.8 mg at bedtime improved symptoms and sleep efficiency and reduced PLMS-I and PLMS-A.

In secondary RLS there is a class III evidence [12] that 0.075 mg clonidine twice daily, showed decrease/relief of symptoms in nine of 10 compared with one of 10 patients treated with placebo, at 3 days, in chronic uraemia.

Recommendations

Clonidine is probably effective in reducing symptoms and sleep latency in primary RLS at short term (level B rating). Clonidine had several but tolerated adverse events (dry mouth, decreased cognition and libido, lightheadedness, sleepiness, headache) (level B). There is no sufficient evidence to make a recommendation about talipexole, propranolol and phenoxybenzamine, and about clonidine in secondary RLS.

Antiepileptic drugs

Twenty-two reports concerned the use of antiepileptic drugs (carbamazepine, gabapentin, lamotrigine, topiramate, valproate). In primary RLS, there is class II evidence [13] that carbamazepine 100–300 mg (median dose 236 mg) at bedtime improved the frequency of RLS symptoms reducing attacks from a mean of 2.9 to 1.5 per week in a long-term (5 weeks) trial. Adverse events were reported as ‘not serious’ in 34 of 84 patients versus 20 of 90 patients with placebo. Another class II evidence [14] reported a beneficial effect of carbamazepine with respect to placebo, but without calculation of statistical significance. There is class I evidence [15] that gabapentin at the dose of 1800 mg daily (one-third of total dosage at 12.00 hours and two-thirds at 20.00 hours) versus placebo reduced RLS symptoms by 8.4 points according to the RLS Rating Scale, improved sleep efficiency by 9.8% and reduced PLMS-I by 9.8 events, at 6 weeks. Adverse events were more frequent with gabapentin (48% vs. 20.8%), and commonly included malaise, somnolence, and gastrointestinal symptoms. No adverse events lead to discontinuation of treatment. Class III evidence trials with gabapentin [16–19] reported an improvement in RLS symptoms at long-term follow-up (6–18 months) with minor adverse events (dizziness, drowsiness, enhanced alcohol effect and headache).

In a class II evidence trial with 20 patients [20], valproate slow release at an average dose of 600 mg versus placebo significantly reduced RLS symptom intensity by 1.7 points according to a non-validated scale, and RLS symptom duration by 92.3 min/24 h, but not PLMS-I and PLMS-A, at 3 weeks. Most commonly reported adverse event was drowsiness.

In secondary RLS in haemodialysis patients, there is class II evidence [21] that gabapentin at a dose of 200/300 mg after each haemodialysis session versus placebo reduced RLS symptoms by 2.8 points, according to a non-validated scale, at 6 weeks. Two patients dropped out for somnolence and lethargy under gabapentin. In a class III study [22], subjects with secondary RLS and heroin abuse during rapid opiate detoxification had symptoms reduced by 2.0 points in a non-validated scale at 1 h, after taking gabapentin at the dose of 1200 mg.

Recommendations

Gabapentin, at 800–1800 mg/day can be considered effective in primary RLS (level A rating) and probably effective in secondary RLS after haemodialysis (level B). Adverse events were usually mild and reversible. Carbamazepine 100–300 mg and valproate slow release at 600 mg/day can be recommended as probably effective in primary RLS (level B). There is insufficient evidence to make a recommendation about topiramate and lamotrigine, and about the use of antiepileptic drugs in PLMD.

Benzodiazepines/hypnotics

A total of 36 reports concern the use of benzodiazepines/hypnotics (alprazolam, clonazepam, diazepam, nitrazepam, oxazepam, temazepam, triazolam and zolpidem).

For primary RLS, there is conflicting class II evidence [23,24] that clonazepam 0.5–2 mg did or did not significantly eliminate/reduce paraesthesia/dysaesthesia compared with placebo (a discrepancy possibly related to different administration schedules: before bedtime versus four doses/throughout the day). As for polysomnographic indices, only a 14% improvement in sleep efficiency was reported in a class III short-term trial with clonazepam 1 mg at bedtime [25]. In a class II
trial [23], clonazepam 1 mg at bedtime improved subjective sleep quality. Adverse events were absent in one class II study but daily sleepiness was found in three patients (out of six) versus one on placebo in another class II study of clonazepam 0.5–2 mg four doses throughout the day [24].

For PLMD, there is class II evidence that clonazepam, 1 mg was not more effective than temazepam 30 mg [26] and that clonazepam 0.5–1.5 mg was not more effective than cognitive-behavioural therapy [27]. Several class III trials show that clonazepam 0.5–2 mg at bedtime decreased the PLMS-I and sometimes the PLMS-A [26,28–31]. Adverse events with clonazepam 0.5 mg at bedtime were increased anxiety leading to drop-out in one of six patient ([27], class II trial), and somnolence or dizziness in two with one drop-out of 10 patients ([29], class III trial). There are two class II studies that triazolam (0.125–0.50 mg) improved sleep efficiency and daytime sleepiness without any effect on PLMS at short-term follow-up [32,33]. There are single class III trials that temazepam (30 mg) [26] and nitrazepam (2.5–10 mg) [34] improved sleep efficiency, sleep latency, and PLMS-I.

Recommendations
Clonazepam should be considered as probably effective for improving symptoms in primary RLS when given at 1 mg before bedtime, but also probably ineffective when given at four doses throughout the day (level B rating). In PLMD, clonazepam at 0.5–2 mg/daily is probably effective in ameliorating PLMS-I and PLMS-A (level B) and triazolam (0.125–0.50 mg/day) is probably effective in ameliorating sleep efficiency and probably ineffective in reducing PLMS (level B). Adverse events with benzodiazepines (morning sedation, memory dysfunction, daytime somnolence and muscle weakness) were usually mild, dose dependent and reversible. There is insufficient evidence to make a recommendation about alprazolam, nitrazepam, temazepam and zolpidem. Likewise no recommendation can be offered for benzodiazepines/hypnotics in secondary RLS.

Dopaminergic agents

Levodopa
Fifty-two reports concerned the use of levodopa. For primary RLS, at 4 weeks, there is class I evidence [35] that levodopa/benserazide in a single bedtime dose (mean: 159/40 mg) versus placebo improved quality of sleep by 0.7 points on a 1–5 point scale, reduced sleep latency by 26 min, improved quality of life, and reduced PLMS-I by 27.8 events per hour. This study did not consider improvement in RLS symptoms as outcome. There are class II studies [20,36–41] that short-term (1 night/4 weeks) levodopa/benserazide in a single bedtime dose (100–200 mg) without or with an extra 100 mg dose 3 h after bedtime reduced RLS symptoms moderately, by 0.5 points on a 4-point scale, 1.9 points on a 10-point scale, and 29.3 points on a Visual Analogue Scale (VAS). The same was not demonstrated in another study. In a class II study of selected RLS patients of rapid release levodopa/benserazide (from 100/25 to 200/50 mg) versus rapid release levodopa/benserazide plus slow release levodopa/benserazide (100/25 mg) at bedtime, the latter was shown to reduce RLS symptoms in the second half of the night, improve subjective sleep quality and reduce sleep latency [40]. Commonly reported adverse events in these studies were diarrhoea, nausea, dyspepsia, reduced general drive, muscle weakness, somnolence and headache. Worsening or augmentation of RLS were reported in two of 37 and four of 20 patients, or 16.7–26.7% of patients.

For secondary RLS, at short-term follow-up, two class II studies [38,42] evaluated levodopa (plus benserazide or carbidopa) in a single bedtime dose (100–200 mg) versus placebo in uraemic patients. In one study, RLS symptoms were reduced (0.9 points improvement on a 0- to 10-point scale). PLMS-I and PLMS-A were also reduced and quality of life improved. However, in the study of Walker et al. [42], only PLMS indexes but not RLS symptoms were improved.

For PLMD, there are class II studies of levodopa (plus benserazide or carbidopa; 200 mg at bedtime or 100 mg five times a day) versus placebo in PLMD with or without RLS [43], PLMD with narcolepsy [44] and PLMD in complete spinal lesion patients [45]: PLMS-I and PLMS-A were reduced.

Recommendations
In primary RLS and at short-term follow-up, levodopa was effective in reducing symptoms of RLS and in improving sleep quality and quality of life and reducing PLMS (level A rating). Adverse events were minor but more frequent than placebo (level A). In long-term follow-up, levodopa was possibly still effective, but 30–70% of patients dropped out because of adverse events or lack of efficacy (level C). Augmentation
probably occurred in 20–82% of treated patients, in a still uncertain number of them leading to treatment discontinuation. In RLS secondary to uraemia, at short-term follow-up, levodopa was probably effective in reducing symptoms, improving quality of life and reducing PLMS-I and PLMS-A (level B). In PLMD, at short-term follow-up, levodopa was probably effective in improving PLMS-I and PLMS-A (level B).

**Ergot derivatives**

Thirty-nine reports concerned the use of ergot derivatives (a-dihydroergocryiptine, bromocriptine, cabergoline, lisuride, pergolide and terguride).

In primary RLS, a-dihydroergocryptine 10–40 mg gave subjective reduction of RLS symptoms in a class III study; subjective sleep patterns also improved [46]. Bromocriptine 7.5 mg in a class II study [47] gave partial subjective improvement in restlessness and paraesthesia in five of six patients, without relevant adverse side-effects. For cabergoline (0.5, 1 and 2 mg once daily), a class I trial in 86 patients [48] showed a change from baseline respectively of −13.1, −13.5 and −15.7 points on the International RLS scale score with respect to −3.3 with placebo at 5 weeks. Abolition of symptoms was observed in 36.4% of the 2 mg cabergoline group with respect to 4.4% with placebo. Long-term (1 year) open label treatment at mean doses of 2.2 mg/day or at 1.5 mg/day for 26 weeks [49] remained effective (class III). During long-term treatment, adverse events led to drop-outs in 11 of 85; in particular, augmentation was found in 11% of patients. For pergolide, there are six short-term and five long-term studies. In a class I evidence trial (total number of patients involved was 100) pergolide at dosages from 0.05 mg upwards to 1.5 mg and at mean dosages of 0.4–0.55 mg daily significantly improved RLS severity, significantly ameliorated subjective quality of sleep and significantly decreased PLMS-I and PLMS-A [50]. The rate of responders (‘much improved’ or ‘very much improved’ to Patient Global Impression Scale) at 6 weeks was 68% in the pergolide versus 15% in the placebo group. Maintenance for 12 months resulted in a significant reduction of PLMS-I and PLMS-A at a mean dosage of 0.52 mg daily (class III evidence). Adverse events were reported in 40–70% of patients as mild: nausea, headache, nasal congestion, dizziness, orthostatic hypotension, easily controlled in one study with domperidone 20 mg. No rebound or augmentation phenomenon was observed in class I and II trials. A class II comparative trial of pergolide versus levodopa [51] pointed out the better outcome with pergolide treatment: pergolide 0.125 mg daily gave complete relief in 82% of patients when compared with 9% with levodopa 250 mg; moreover, pergolide caused a 79% reduction in PLMS-I when compared with 45% with levodopa. Terguride 0.25–0.5 mg/day improved subjective RLS symptoms in a class III trial.

In RLS secondary to uraemia undergoing haemodialysis, pergolide 0.05–0.25 mg in short term (10 nights) did not modify time to sleep onset, number of awakenings and actigraphy for PLMS. Subjective improvement in sleep quality and RLS symptoms in five of eight patients was not validated by statistical analysis against the placebo (class II study) [52]. Adverse events were nausea in one subject and nightmares in another. In PLMD in narcolepsy, there is class II evidence [53] that bromocriptine (7.5 mg) was effective.

**Recommendations**

In primary RLS, pergolide is established as effective at mean dosages of 0.4–0.55 mg/day (level A rating) and possibly effective in the long term (level C). PLMS-I and PLMS-A are also improved. Cabergoline is also effective at 0.5–2 mg/day (level A) and possibly effective in the long term (level C). Bromocriptine 7.5 mg can be recommended as probably effective (level B). In secondary RLS associated with chronic haemodialysis, pergolide in short-term administration is probably ineffective at 0.25 mg/day (level B). In PLMD associated with narcolepsy, bromocriptine is probably effective (level B). Most frequent adverse events of ergot-derived dopamine agonists (nausea, headache, nasal congestion, dizziness and orthostatic hypotension) were controlled by domperidone. Augmentation was not assessed with pergolide in class I studies. There is insufficient evidence to make a recommendation about a-dihydroergocryiptine, lisuride and terguride.

**Non-ergot derivatives**

Thirty-nine reports concerned the use of non-ergot derivatives (pramipexole, ropinirole, rotigotine). At the time of writing ropinirole was the most extensively studied drug for RLS in class I studies. For primary RLS, in a class I trial of 284 patients [54] treatment with ropinirole at a mean effective dose of 1.9 mg/daily caused a significant reduction in the International RLS scale score (11.04 points vs. 8.03 under placebo) and quality of life after 12 weeks. Similar results obtained in two other class I trials, one of 266 patients with ropinirole at 1.5 mg/day mean effective dose (11.2 points reduced International RLS scale score versus 8.7 under placebo) [55] and another of 22 patients with ropinirole at a mean dosage of 4.6 mg daily [56]. Mild and transient adverse events included nausea, headache, fatigue and dizziness. As for polysomnographic indices of sleep disruption, in a class I study with polysomnography [57], ropinirole at a mean dose of 1.8 mg/day
significantly improved PLMS-I (by 76.2% vs. 14% on placebo), PLMS-A and sleep latency. Adverse events were headache and nausea, less commonly dizziness. Worsening of RLS possibly because of augmentation was observed in four of 59 (7%) patients.

As for pramipexole, a class II trial of pramipexole (0.75–1.5 mg 1 h before bedtime) in 10 patients [58] demonstrated significantly reduced RLS subjective scores and significant improvements in PLMS-I. Adverse events (nausea, constipation, loss of appetite in 90% of patients; dizziness in 40%, daytime fatigue in 30%) were reported as mild and transient, but persistent nausea was observed in 33% at 1.5 mg/day. Long-term use of pramipexole was effective in class III trials.

Rotigotine (continuous transdermal patch delivery at 1.125, 2.25 and 4.5 mg/day) improved RLS symptoms (by 10.5–15.7 points compared with 8 on placebo) in a short-term class I trial of 63 patients, significantly so at the 4.5 mg dose [59]. Adverse events and skin tolerability were similar with placebo. As these data were obtained over a 1-week study period, the mid- and long-term efficacy of rotigotine remains to be seen.

For RLS secondary to uraemia undergoing haemodialysis, there is one class II study in 11 patients whereby ropinirole 1.45 mg/day gave better improvement of symptoms than levodopa 190 mg/daily [60].

Recommendations

In primary RLS, ropinirole at 1.5–4.6 mg/day has a level A rating of efficacy. Rotigotine by transdermal patch delivery is also effective in the short term (level A), and pramipexole is probably effective (level B). In RLS secondary to uraemia ropinirole is probably effective (level B). Adverse events were those common to all dopaminergic agents. Augmentation has not been well studied for any of these drugs, and has been reported by 7% of patients with ropinirole (class I evidence). There is insufficient evidence to make recommendations about the use of non-ergot derivatives in PLMD.

Opioids

Twenty-two reports concerned the use of opioids (codeine and dihydrocodeine, dextromorphan, methadone, morphine, oxycodeone, propoxyphene, tilidine and tramadol). For primary RLS, there is class II evidence [61] that short-term oxycodone at a mean dose of 11.4 mg daily gave a 52% improvement in subjective rating scales on RLS symptoms. In this study, oxycodone also significantly reduced PLMS-I (by 34%) and PLMS-A (by 23%), whilst improving sleep efficiency (by 25%). Adverse events were minimal constipation in two of 11 and daytime lethargy in one of 11 patients.

For PLMD, there is class II evidence [43] that short-term propoxyphene 100–200 mg before bedtime did not improve sleep latency, sleep efficiency and PLMS-I, but reduced PLMS-A by 28.6 events per hour versus placebo. Adverse events were mild depression, dizziness, nausea and one of six patients dropped out because of urticaria and tongue swelling.

Recommendations

For primary RLS, oxycodone at a mean dosage of 11.4 mg can be considered as probably effective in improving RLS symptoms and PLMS-I, PLMS-A and sleep efficiency on a short-term basis (level B rating). Adverse events (mild sedation and rare nocturnal respiratory disturbances on long-term use) were usually mild and reversible, problems of addiction being observed only rarely. For PLMD, short-term propoxyphene is probably ineffective in improving sleep quality and PLMS-I (level B). There is insufficient evidence to make a recommendation about morphine, tramadol, codeine and dihydrocodeine, tilidine, and methadone and about the intrathecal route of administration. There is insufficient evidence to make a recommendation about the use of opioids in secondary RLS.

Other treatments

Eighty-two reports concerned the use of other treatments. Non-pharmacological cognitive or physical agent interventions, and drug treatments with muscle relaxants, vitamins/minerals, hormones (estrogens, melatonin, erythropoietin) and antidepressants were the subjects of these trials. Surgical interventions with deep brain stimulation in Parkinson’s disease, venous sclerosis and kidney transplant were also available.

For primary RLS, one class II trial of iron sulphate 325 mg given in liquid form per os over 12 weeks (concurrently with other treatments) did not show any significant effect either on RLS symptoms or sleep quality; seven of 28 patients dropped out and relevant adverse events were nausea, constipation, tooth discoloration, dark stools, vertebral fracture and RLS worsening [62]. No effect was noted with vibration in a class II trial [23]. Improved RLS severity, sleep efficiency or decreased PLMS-I were reported in class III single trials of iron dextran given intravenously in a single dose of 1000 mg [63], magnesium oxide 12.4 mmol [64] and amantadine 100–300 mg/day [65].

For RLS secondary to uraemia, there is class II evidence [66] for improved RLS symptoms with intravenous iron dextran 1000 mg: efficacy waned however 4 weeks after treatment. In a class III study, kidney transplantation abolished RLS symptoms at short term in all of 11 patients, and in four patients of the 11 at long term [67].
In PLMD, a class I trial with transdermal oestradiol 2.5 g/day gel (or 50 μg/24 h for patients older than 55 years) showed no effect on PLMS-I and PLMS-A at 3 months [68]. Single class II trials showed that modafinil 200–440 mg/day in PLMD associated with narcolepsy [69] and 1-day nocturnal haemodialysis [70] were ineffective. In PLMD associated with insomnia, a class II trial of cognitive-behavioural therapy (sleep education, stimulus control, sleep restriction) found no difference with clonazepam 0.5–1.5 mg/day [27]. Several class III trials with nasal continuous airway positive pressure in patients with obstructive sleep apnoeas resulted in conflicting findings of either unchanged, increased or decreased PLMS-I. In PLMD associated with depressive insomnia, a class III trial of trazodone 100 mg did not modify sleep quality or PLMS-I, or on the contrary reduced PLMS-I by 10.8 (two 1-night only class III studies [71,72]. In class III studies, 5-OH-tryptophan 500 mg did not modify PLMS-I/PLMS-A [73], whilst apomorphine, either 0.5 mg single dose subcutaneously or transdermal [74,75] and physical exercise in PLMD patients with complete spinal lesion [76–78] reduced the PLMS-I.

Recommendations
In primary RLS, both iron sulphate and vibration are probably ineffective (level B rating). There is insufficient evidence to make any recommendation about the use of intravenous iron dextran, magnesium oxide and amantadine. In RLS secondary to uraemia, iron dextran 1000 mg in a single intravenous dose is probably effective in the short term (<1 month) (level B). In PLMD, transdermal oestradiol is established as ineffective (level A rating) and modafinil and 1-day nocturnal haemodialysis as probably ineffective, whilst cognitive-behavioural therapy is no different than clonazepam (level B). 5-OH-tryptophan and trazodone are possibly ineffective and apomorphine and physical exercise (in myelopathy) possibly effective (level C rating).

Discussion
Before offering final comments, we wish to emphasize that dopaminergic agents are the best-studied drugs to date because of the increasing interest of pharmaceutical companies in achieving an official treatment indication for RLS. However, as only few and small studies have been carried out on non-dopaminergic compounds, and some have shown promising therapeutic effects, it is to be hoped that an increased effort from both industry and investigators to develop further alternatives will be carried out. Accordingly, lack of controlled trials for many drug classes should not be construed as implying negative evidence of efficacy. The most frequently observed weak points of the above-cited randomized controlled trials were flaws in allocation concealment procedures, the absence of a predefined primary endpoint, the overuse of non-validated or surrogate endpoints instead of clinically relevant patient oriented endpoints (e.g. rate of remission, quality of life). Such problems are generally, but not only, shared by studies predating the year 2000. The recently validated international scales of disease severity and disease-specific quality of life [6,7] will represent valuable tools to design future trials with clinically relevant primary endpoints. Furthermore, augmentation has not been assessed adequately for most drugs (both dopaminergic and not-dopaminergic) and it is hoped that, as more specific and reliable tools are being developed, they will allow a better assessment of both the long-term efficacy and augmentation.

Recommendations
For primary RLS, ropinirole given at mean dosages of 1.5–4.6 mg/day, and pergolide at 0.4–0.55 mg/day have confirmed level A rating efficacy for relieving paraesthesia and motor restlessness. Cabergoline, levodopa and transdermal delivery rotigotine are also established as effective, the latter two so far only for short-term use (level A rating). Amongst the antiepileptic drugs, gabapentin should be considered as effective in primary RLS (level A rating).

For other dopaminergics (pramipexole, bromocriptine) and for valproate, carbamazepine, clonidine and oxycodone there is evidence to consider these drugs as probably effective (level B rating), whilst for clonazepam evidence for probable efficacy (at 1 mg at bedtime) and probable inefficacy (at 4 doses/day), according to dosage schedule (level B rating). Iron sulphate and vibration are probably ineffective (level B rating). In long-term use, levodopa is possibly effective (level C rating).

For RLS secondary to uraemia, levodopa, ropinirole 1.45 mg/day, gabapentin 200–300 mg/day and iron dextran 1000 mg i.v. are probably effective, the latter on short-term use (level B rating). For PLMD, transdermal oestradiol is ineffective (level A rating). Clonazepam and levodopa are probably effective whilst propoxyphene, triazolam, modafinil and one-night haemodialysis probably ineffective (level B rating). Bromocriptine is probably effective in PLMD associated with narcolepsy (level B). 5-OH-tryptophan and trazodone are possibly ineffective and apomorphine and physical exercise possibly effective (level C rating).

As for adverse events, these were reported as usually mild and reversible upon discontinuation of treatment in the generality of the trials. In particular the peripheral adverse events of dopaminergics were easily...
relieved by domperidone. For this class of drugs, augmentation represents a troublesome adverse event: even though reported particularly with levodopa, it is hard to get reliable comparative data, especially in the absence of an augmentation rating scale. Recently, concern with the ergot derivatives was raised by the discovery of severe multivalvular heart defects and constrictive pericarditis and pleuropulmonary fibrosis after long-term use in Parkinson’s disease (reported with cabergoline, pergolide and bromocriptine). Daily dosages in these cases were equal or greater than 4 mg pergolide for several months. Spontaneous echocardiographic regression of valvular insufficiency along with marked clinical improvement was reported after cessation of the ergot derivatives in some case reports. It was suggested that high doses should be avoided and that patients under dopamine agonists receive a clinical cardiac assessment at 3–6 months intervals and if any doubt, obtain an echocardiogram. However, the cardiopulmonary fibrosis side-effects of the ergot derivatives have been described too recently for a meaningful analysis across the different compounds.

Comparison of these versus guidelines already published [79–81] demonstrates minor differences in judgement, in part related to the different sets of evidence utilized. In all guidelines, dopaminergic agents come out as the best-recommended agents for the treatment of RLS. Opioids have not been here considered as established, and for iron supplementation we found only class II favourable trials (short term) or even evidence of inefficacy. Iron has been reported as more effective in low-ferritin patients. Unfortunately, still partial evidence is overall available for secondary RLS, almost all in RLS secondary to uraemia, and for PLMD. In particular, recommendations cannot be offered for RLS during pregnancy or during childhood, where quality trials are needed.

Finally, it is useful to underline that these guidelines should not be considered as exhausting all methods of care for RLS or PLMD. In consideration of the circumstances presented by any particular patient, the ultimate judgement regarding the type of care need always rest with the attending physician.

**Final level A recommendations**

For primary RLS:
- Cabergoline (0.5–2 mg once daily) improves RLS scores.
- Gabapentin (dosage 800–1800 mg/daily) reduces RLS scores and improves sleep efficiency and PLMS-I.
- Levodopa/benserazide (mean dose 159/40 mg at bedtime) improves RLS symptoms, quality of sleep, sleep latency, PLMS-I and quality of life.
- Pergolide (mean doses 0.4–0.55 mg/day) is effective in improving RLS severity and ameliorating subjective quality of sleep.
- Ropinirole (mean doses 1.5–4.6 mg/day) is effective in ameliorating RLS scale scores and quality of life, and in improving sleep latency and PLMS-I/PLMS-A.
- Rotigotine by transdermal patch delivery (4.5 mg) and in short-term use improves RLS symptoms.

For PLMD:
- Transdermal oestradiol is ineffective.

**Conflicts of interest**

Dr Billiard received continuing medical education honoraria from GlaxoSmithKline. Dr Clarenbach was involved in a trial with Schwarz Pharma, and Dr Montagna was involved in trials with GlaxoSmithKline, Schwarz Pharma and received consultant honoraria from Boehringer-Ingelheim. Dr Trenkwalder received grants/research support from GlaxoSmithKline, is a consultant for Boehringer-Ingelheim, GlaxoSmithKline and Novartis, and received speakers honoraria for educational symposia from GlaxoSmithKline, Hoffmann La Roche and Pfizer. Dr Garcia-Borreguero received research grants from Pfizer and is a consultant for Pfizer, GlaxoSmithKline, Schwarz Pharma and Boehringer-Ingelheim.

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**Supplementary material**

The following supplementary material can be found at http://www.blackwell-synergy.com/toc/ene/13/10:
- Table S1. Search strategy for identifications of studies.
- Table S2. Class I, II and III evidence studies.
- Table S3. Class IV evidence studies.

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