European Journal of Neurology 2006, **13:** 1049–1065 doi:10.1111/j.1468-1331.2006.01410.x

EFNS TASK FORCE ARTICLE

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

L. Vignatelli[a], M. Billiard[b], P. Clarenbach[c], D. Garcia-Borreguero[d], D. Kaynak[e], V. Liesiene[f], C. Trenkwalder[g] and P. Montagna[a]

[a]*Department of Neurological Sciences, University of Bologna Medical School, Bologna, Italy;* [b]*Faculty of Medicine, Gui de Chauliac Hospital, Montpellier, France;* [c]*Neurologische Klinik, EV Johannes-Krankenhaus, Bielefeld, Germany;* [d]*Department of Neurology, Fundacion Jimenez Diaz, Sleep Disorders Unit, Universidad Autonoma de Madrid, Madrid, Spain;* [e]*Cerrahpasa Faculty of Medicine, Sleep Disorders Unit, Istanbul University, Istanbul, Turkey;* [f]*Faculty of Medicine, University of Kaunas, Kaunas, Lithuania; and* [g]*Department of Clinical Neurophysiology, University of Goettingen, Goettingen, Germany*

Keywords:
benzodiazepines, dopaminergics, drugs guidelines, periodic limb movement disorder, Restless legs syndrome

Received 30 September 2005
Accepted 3 October 2005

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 in the evening or 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

Correspondence: Prof. Pasquale Montagna, Dipartimento di Scienze Neurologiche, Università di Bologna, Via Ugo Foscolo 7, 40123 Bologna, Italy (tel.: + + 39 051 2092927; fax: + + 39 051 2092963; e-mail: pmontagn@neuro.unibo.it).

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 α-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.

On long-term (2–24 months), open phase (class III) trials levodopa proved still 'effective' in 70.2% of patients, showed satisfaction with therapy in 29–31% of patients and improved RLS symptoms by 6.0–6.5 points in a 7-point scale and reduced perceived sleep latency by 131 min. Drop-outs were many, 30–70% in these series, and augmentation ranged from 18.6% to 82%.

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 (α-dihydroergocryptine, bromocriptine, cabergoline, lisuride, pergolide and terguride).

In primary RLS, α-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 α-dihydroergocryptine, 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, dextrometorphan, methadone, morphine, oxycodone, 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 sclerotherapy 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 intravenous 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, 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.

Acknowledgements

We wish to acknowledge the help of Ms A. Laffi in typing the manuscript and Ms S. Muzzi for help with the bibliography. Supported by MURST ex 60% grants.

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.

References

1. Willis T. *The London Practice of Physice*, 1st edn. London: Thomas Bassett and William Crooke, 1685: 404.
2. Ekbom KA. Restless legs. *Acta Medica Scandinavica* 1945; **158:** 5–123.
3. American Academy of Sleep Medicine. Periodic limb movement disorder. *International Classification of Sleep*

Disorders. Diagnostic and Coding Manual, 2nd edn. Westchester, IL: American Academy of Sleep Medicine, 2005: 182–186.
4. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Movement Disorders* 1995; **10:** 634–642.
5. 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 Medicine* 2003; **4:** 101–119.
6. Walters AS, LeBrocq C, Dhar A, *et al*. International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Medicine* 2003; **4:** 121–132.
7. Atkinson MJ, Allen RP, Du Chane J, Murray C, Kushida C, Roth T. RLS Quality of Life Consortium. Validation of the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI): findings of a consortium of national experts and the RLS Foundation. *Quality Life Research* 2004; **13:** 679–693.
8. American Academy of Sleep Medicine. Restless legs syndrome. *International Classification of Sleep Disorders. Diagnostic and Coding Manual*, 2nd edn. Westchester, IL: American Academy of Sleep Medicine, 2005: 178–181.
9. Brainin M, Barnes M, Baron JC, *et al*. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *European Journal of Neurology* 2004; **11:** 577–581.
10. Wagner ML, Walters AS, Coleman RG, Hening WA, Grasing K, Chokroverty S. Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996; **19:** 52–58.
11. Inoue Y, Mitani H, Nanba K, Kawahara R. Treatment of periodic leg movement disorder and restless leg syndrome with talipexole. *Psychiatry and Clinical Neurosciences* 1999; **53:** 283–285.
12. Ausserwinkler M, Schmidt P. Erfolgreiche Behandlung des 'restless legs'-Syndroms bei chronischer Niereninsuffizienz mit Clonidin. *Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine* 1989; **119:** 184–186.
13. Telstad W, Sorensen O, Larsen S, Lillevold PE, Stensrud P, Hansen R. Treatment of the restless legs syndrome with carbamazepine: a double blind study. *British Medical Journal (Clinical Research Edition)* 1984; **288:** 444–446.
14. Lundvall O, Abom PE, Holm R. Carbamazepine in restless legs. A controlled pilot study. *European Journal of Clinical Pharmacology* 1983; **25:** 323–324.
15. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, crossover study. *Neurology* 2002; **59:** 1573–1579.
16. Mellick GA, Mellick LB. Management of restless legs syndrome with gabapentin (Neurontin). *Sleep* 1996; **19:** 224–226.
17. Happe S, Klosch G, Saletu B, Zeitlhofer J. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. *Neurology* 2001; **57:** 1717–1719.
18. Happe S, Sauter C, Klosch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology* 2003; **48:** 82–86.
19. Adler CH. Treatment of restless legs syndrome with gabapentin. *Clinical Neuropharmacology* 1997; **20:** 148–151.
20. Eisensehr I, Ehrenberg BL, Rogge-Solti S, Noachtar S. Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid. *Journal of Neurology* 2004; **251:** 579–583.
21. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among haemodialysis patients. *American Journal of Kidney Diseases* 2001; **38:** 104–108.
22. Freye E, Levy JV, Partecke L. Use of gabapentin for attenuation of symptoms following rapid opiate detoxification (ROD) – correlation with neurophysiological parameters. *Neurophysiologie Clinique* 2004; **34:** 81–89.
23. Montagna P, Sassoli-de-Bianchi L, Zucconi M, Cirignotta F, Lugaresi E. Clonazepam and vibration in restless legs syndrome. *Acta Neurologica Scandinavica* 1984; **69:** 428–430.
24. Boghen D, Lamothe L, Elie R, Godbout R, Montplaisir J. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. *Canadian Journal of Neurological Sciences* 1986; **13:** 245–247.
25. Saletu M, Anderer P, Saletu-Zyhlarz G, *et al*. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *European Neuropsychopharmacology* 2001a; **11:** 153–161.
26. Mitler MM, Browman CP, Menn SJ, Gujavarty K, Timms RM. Nocturnal myoclonus: treatment efficacy of clonazepam and temazepam. *Sleep* 1986; **9:** 385–392.
27. Edinger JD, Fins AI, Sullivan RJ, Marsh GR, Dailey DS, Young M. Comparison of cognitive-behavioral therapy and clonazepam for treating periodic limb movement disorder. *Sleep* 1996; **19:** 442–444.
28. Ohanna N, Peled R, Rubin AH, Zomer J, Lavie P. Periodic leg movements in sleep: effect of clonazepam treatment. *Neurology* 1985; **35:** 408–411.
29. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *Journal of Neurology, Neurosurgery, and Psychiatry* 1987; **50:** 1679–1681.
30. Inami Y, Horiguchi J, Nishimatsu O, *et al*. A polysomnographic study on periodic limb movements in patients with restless legs syndrome and neuroleptic-induced akathisia. *Hiroshima Journal of Medical Sciences* 1997; **46:** 133–141.
31. Arens R, Wright B, Elliott J, *et al*. Periodic limb movement in sleep in children with Williams syndrome. *Journal of Pediatrics* 1998; **133:** 670–674.
32. Doghramji K, Browman CP, Gaddy JR, Walsh JK. Triazolam diminishes daytime sleepiness and sleep fragmentation in patients with periodic leg movements in sleep. *Journal of Clinical Psychopharmacology* 1991; **11:** 284–290.
33. Bonnet MH, Arand DL. Chronic use of triazolam in patients with periodic leg movements, fragmented sleep and daytime sleepiness. *Aging* 1991; **3:** 313–324.
34. Moldofsky H, Tullis C, Quance G, Lue FA. Nitrazepam for periodic movements in sleep (sleep-related myoclonus). *Canadian Journal of Neurological Sciences* 1986; **13:** 52–54.

35. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep* 1999; **22:** 1073–1081.
36. Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. *Clinical Neuropharmacology* 1987; **10:** 69–79.
37. Brodeur C, Montplaisir J, Godbout R, Marinier R. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. *Neurology* 1988; **38:** 1845–1848.
38. Trenkwalder C, Stiasny K, Pollmacher T, *et al*. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep* 1995; **18:** 681–688.
39. Montplaisir J, Boucher S, Gosselin A, Poirier G, Lavigne G. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-DOPA. *Sleep* 1996; **19:** 196–199.
40. Collado-Seidel V, Kazenwadel J, Wetter TC, *et al*. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. *Neurology* 1999; **52:** 285–290.
41. Saletu M, Anderer P, Hogl B, *et al*. Acute double-blind, placebo-controlled sleep laboratory and clinical follow-up studies with a combination treatment of rr-L-dopa and sr-L-dopa in restless legs syndrome. *Journal of Neural Transmission* 2003; **110:** 611–626.
42. Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. *Sleep* 1996; **19:** 214–218.
43. Kaplan PW, Allen RP, Buchholz DW, Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993; **16:** 717–723.
44. Boivin DB, Montplaisir J, Poirier G. The effects of L-dopa on periodic leg movements and sleep organization in narcolepsy. *Clinical Neuropharmacology* 1989; **12:** 339–345.
45. de Mello MT, Poyares DL, Tufik S. Treatment of periodic leg movements with a dopaminergic agonist in subjects with total spinal cord lesions. *Spinal Cord* 1999; **37:** 634–637.
46. Tergau F, Wischer S, Wolf C, Paulus W. Treatment of restless legs syndrome with the dopamine agonist alpha-dihydroergocryptine. *Movement Disorders* 2001; **16:** 731–735.
47. Walters AS, Hening WA, Kavey N, Chokroverty S, Gidro-Frank S. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Annals of Neurology* 1988; **24:** 455–458.
48. Stiasny-Kolster K, Benes H, Peglau I, *et al*. Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology* 2004; **63:** 2272–2279.
49. Benes H, Heinrich CR, Ueberall MA, Kohnen R. Long-term safety and efficacy of cabergoline for the treatment of idiopathic restless legs syndrome: results from an open-label 6-month clinical trial. *Sleep* 2004; **27:** 674–682.
50. Trenkwalder C, Hundemer HP, Lledo A, *et al*. Efficacy of pergolide in treatment of restless legs syndrome: The PEARLS Study. *Neurology* 2004; **62:** 1391–1397.
51. Staedt J, Wassmuth F, Ziemann U, Hajak G, Ruther E, Stoppe G. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa. *Journal of Neural Transmission* 1997; **104:** 461–468.
52. Pieta J, Millar T, Zacharias J, Fine A, Kryger M. Effect of pergolide on restless legs and leg movements in sleep in uremic patients. *Sleep* 1998; **21:** 617–622.
53. Boivin DB, Lorrain D, Montplaisir J. Effects of bromocriptine on periodic limb movements in human narcolepsy. *Neurology* 1993; **43:** 2134–2136.
54. Trenkwalder C, Garcia-Borreguero D, Montagna P, *et al*. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *Journal of Neurology, Neurosurgery and Psychiatry* 2004a; **75:** 92–97.
55. Walters AS, Ondo W, Dreykluft T, Grunstein R, Lee D, Sethi K, TREAT RLS 2 Study Group. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Movement Disorders* 2004; **19:** 1414–1423.
56. Adler CH, Hauser RA, Sethi K, *et al*. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. *Neurology* 2004; **62:** 1405–1407.
57. Allen R, Becker PM, Bogan R, *et al*. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep* 2004; **27:** 907–914.
58. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 1999; **52:** 938–943.
59. Stiasny-Kolster K, Kohen R, Schollmayer E, Moller JC, Oertel WH, Rotigotine Sp 666 Study Group. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Movement Disorders* 2004; **19:** 1432–1438.
60. Pellecchia MT, Vitale C, Sabatini M, *et al*. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. *Clinical Neuropharmacology* 2004; **27:** 178–181.
61. Walters AS, Wagner ML, Hening WA, *et al*. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep* 1993; **16:** 327–332.
62. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. *European Neurology* 2000; **43:** 70–75.
63. Earley CJ, Heckler D, Allen RP. The treatment of restless legs syndrome with intravenous iron dextran. *Sleep Medicine* 2004; **5:** 231–235.
64. Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. *Sleep* 1998; **21:** 501–505.
65. Evidente VG, Adler CH, Caviness JN, Hentz JG, Gwinn-Hardy K. Amantadine is beneficial in restless legs syndrome. *Movement Disorders* 2000; **15:** 324–327.
66. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and

restless legs syndrome. *American Journal of Kidney Diseases* 2004; **43:** 663–670.
67. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. *Movement Disorders* 2002; **17:** 1072–1076.
68. Polo-Kantola P, Rauhala E, Erkkola R, Irjala K, Polo O. Estrogen replacement therapy and nocturnal periodic limb movements: a randomized controlled trial. *Obstetrics and Gynecology* 2001; **97:** 548–554.
69. Broughton RJ, Fleming JAE, George CFP, *et al*. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997; **49:** 444–451.
70. Hanly PJ, Gabor JY, Chan C, Pierratos A. Daytime sleepiness in patients with CRF: impact of nocturnal hemodialysis. *American Journal of Kidney Diseases* 2003; **41:** 403–410.
71. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, *et al*. Insomnia related to dysthymia: polysomnographic and psychometric: comparison with normal controls and acute therapeutic trials with trazodone. *Neuropsychobiology* 2001; **44:** 139–149.
72. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, *et al*. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2002; **26:** 249–260.
73. Guilleminault C, Mondini S, Montplaisir J, Mancuso J, Cobasko D, Dement WC. Periodic leg movement, L-dopa, 5-hydroxytryptophan, and L-tryptophan. *Sleep* 1987; **10:** 393–397.
74. Priano L, Albani G, Brioschi A, *et al*. Nocturnal anomalous movement reduction and sleep microstructure analysis in parkinsonian patients during 1-night transdermal apomorphine treatment. *Neurological Sciences* 2003; **24:** 207–208.
75. Haba-Rubio J, Staner L, Cornette F, *et al*. Acute low single dose of apomorphine reduces periodic limb movements but has no significant effect on sleep arousals: a preliminary report. *Neurophysiologie Clinique* 2003; **33:** 180–184.
76. de Mello MT, Lauro FAA, Silva AC, Tufik S. Incidence of periodic leg movements and of the restless legs syndrome during sleep following acute physical activity in spinal cord injury subjects. *Spinal Cord* 1996; **34:** 294–296.
77. de Mello MT, Silva AC, Rueda AD, Poyares D, Tufik S. Correlation between K complex, periodic leg movements (PLM), and myoclonus during sleep in paraplegic adults before and after an acute physical activity. *Spinal Cord* 1997; **35:** 248–252.
78. de Mello MT, Silva AC, Esteves AM, Tufik S. Reduction of periodic leg movement in individuals with paraplegia following aerobic physical exercise. *Spinal Cord* 2002; **40:** 646–649.
79. Chesson AL, Jr, Wise M, Davila D, *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:** 961–998.
80. Hening WA, 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:** 970–999.
81. 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:** 560–583.
82. Garcia-Borreguero D, Larrosa O, Verger K, Masramon X, Hernandez G. Effects of gabapentin on restless legs syndrome accompanied by nocturnal pain: results of a double-blind, crossover study with polysomnographic control in 24 patients. *European Journal of Neurology* 2002; **9:** 49–50.
83. Larsen S, Telstad W, Sorensen O, Thom E, Stensrud P, Nyberg-Hansen R. Carbamazepine therapy in restless legs. Discrimination between responders and non-responders. *Acta Medica Scandinavica* 1985; **218:** 223–227.
84. Zucconi M, Coccagna G, Petronelli R, Gerardi R, Mondini S, Cirignotta F. Nocturnal myoclonus in restless legs syndrome effect of carbamazepine treatment. *Functional Neurology* 1989; **4:** 263–271.
85. Perez-Bravo A. Utilidad del topiramato en el tratamiento del sindrome de piernas inquietas. *Actas Espanolas de Psiquiatria* 2004; **32:** 132–137.
86. Horiguchi J, Inami Y, Sasaki A, Nishimatsu O, Sukegawa T. Periodic leg movements in sleep with restless legs syndrome: effect of clonazepam treatment. *The Japanese Journal of Psychiatry and Neurology* 1992; **46:** 727–732.
87. Wetter TC, Trenkwalder C, Stiasny K, *et al*. Behandlung des idiopathischen und uramischen Restless-legs-Syndrom mit L-Dopa – Eine doppelblinde Cross-over-Studie. *Wiener Medizinische Wochenschrift* 1995; **145:** 525–527.
88. Collado-Seidel V. Treatment of the restless legs syndrome with a combination of standard and sustained release levodopa/benserazide (Madopar Depot): a double-blind controlled study. *Pharmacopsychiatry* 1997; **30:** 158.
89. Trenkwalder C, Seidel VC, Kazenwadel J, *et al*. Treatment of the restless legs syndrome with a combination of standard and sustained-release levodopa/benserazide (Madopar Depot(R)): a double-blind controlled study. *Journal of the Neurological Sciences* 1997; **150:** S204.
90. Montplaisir J, Godbout R, Poirier G, Bedard MA. Restless legs syndrome and periodic movements in sleep: physiopathology and treatment with L-dopa. *Clinical Neuropharmacology* 1986; **9:** 456–463.
91. von Scheele C. Levodopa in restless legs. *Lancet* 1986; **2:** 426–427.
92. Becker PM, Jamieson AO, Brown WD. Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: response and complications of extended treatment in 49 cases. *Sleep* 1993; **16:** 713–716.
93. Guilleminault C, Cetel M, Philip P. Dopaminergic treatment of restless legs and rebound phenomenon. *Neurology* 1993; **43:** 445.
94. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep* 1996; **19:** 205–213.
95. 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:** 801–810.
96. Trenkwalder C, Collado-Seidel V, Kazenwadel J, *et al*. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? *Movement Disorders* 2003; **18:** 1184–1189.

97. Garcia-Borreguero D, Serrano C, Larrosa O, Jose-Granizo J. Circadian effects of dopaminergic treatment in restless legs syndrome. *Sleep Medicine* 2004; **5:** 413–420.
98. Stiasny-Kolster K, Magerl W, Oertel WH, Moller JC, Treede RD. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. *Brain* 2004; **127:** 773–782.
99. Stiasny K, Moller JC, Bodenschatz R, *et al*. Rotigotine CDS in the treatment of moderate to advanced stages of restless legs syndrome: a double-blind placebo-controlled study. *Movement Disorders* 2002; **17:** S241.
100. Stiasny K, Uberall M, Oertel WH. Cabergoline in restless legs syndrome (RLS) – a double-blind placebo-controlled multicenter dose-finding trial. *European Journal of Neurology* 2002; **9:** 50.
101. Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome. An open label trial. *Neuropsychobiology* 2004; **50:** 65–70.
102. Stiasny K, Robbecke J, Schuler P, Oertel WH. Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline – an open clinical trial. *Sleep* 2000; **23:** 349–354.
103. Stiasny K. Clinical data on restless legs syndrome: a dose-finding study with cabergoline. *European Neurology* 2001; **46**(Suppl. 1)**:** 24–26.
104. Stiasny K. Handling the problem of augmentation in restless legs syndrome (RLS). *European Journal of Neurology* 2001; **8:** 15.
105. Zucconi M, Oldani A, Castronovo C, Ferini-Strambi L. Cabergoline is an effective single-drug treatment for restless legs syndrome: clinical and actigraphic evaluation. *Sleep* 2003; **26:** 815–818.
106. Trenkwalder C, Brandenburg U, Hundemer HP, *et al*. A randomized long-term placebo-controlled multicenter trial of pergolide in the treatment of restless legs syndrome with central evaluation of polysomnographic data. *Neurology* 2001; **56:** A5–A6.
107. Trenkwalder C, Brandenburg U, Hundemer HP, Lledo A, Quail D, Swieca J. A long-term controlled multicenter trial of pergolide in the treatment of restless legs syndrome with central evaluation of polysomnographic data. *Journal of the Neurological Sciences* 2001; **187:** S432.
108. Hundemer HP, Trenkwalder C, Lledo A, *et al*. The safety of pergolide in the treatment of restless legs syndrome (RLS): results of a randomized long-term multicenter trial of pergolide in the treatment of RLS. *Neurology* 2001; **56:** A20.
109. Wetter TC, Stiasny K, Winkelmann J, *et al*. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 1999; **52:** 944–950.
110. Tagaya H, Wetter TC, Winkelmann J, *et al*. Pergolide restores sleep maintenance but impairs sleep EEG synchronization in patients with restless legs syndrome. *Sleep Medicine* 2002; **3:** 49–54.
111. Staedt J, Hunerjager H, Ruther E, Stoppe G. Pergolide: treatment of choice in Restless Legs Syndrome (RLS) and Nocturnal Myoclonus Syndrome (NMS). Longterm follow up on pergolide. Short communication. *Journal of Neural Transmission* 1998; **105:** 265–268.
112. Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology* 1998; **51:** 1599–1602.
113. Stiasny K, Wetter TC, Winkelmann J, *et al*. Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 2001; **56:** 1399–1402.
114. Benes H, Deissler A, Clarenbach P, Rodenbeck A, Hajak G. Lisuride in the management of restless legs syndrome. *Movement Disorders* 2000; **15:** S134–S135.
115. Sonka K, Pretl M, Kranda K. Management of restless legs syndrome by the partial D2-agonist terguride. *Sleep Medicine* 2003; **4:** 455–457.
116. Estivill E, de la Fuente V. Uso de ropinirol como tratamiento del sindrome de piernas inquietas. *Revista de Neurologia* 1999; **28:** 962–963.
117. Estivill E, de la Fuente V. Eficacia del ropinirol como tratamiento del insomnio cronico secundario al sindrome de piernas inquietas: datos polisomnograficos. *Revista de Neurologia* 1999; **29:** 805–807.
118. Ondo W. Ropinirole for restless legs syndrome. *Movement Disorders* 1999; **14:** 138–140.
119. Saletu B, Gruber G, Saletu M, *et al*. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. *Neuropsychobiology* 2000; **41:** 181–189.
120. Saletu M, Anderer P, Saletu B, *et al*. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals and respiratory variables. *Neuropsychobiology* 2000; **41:** 190–199.
121. Watts RL, Freeman A, Rye DB, Bliwise DL, Krulewicz S. Ropinirole for restless legs syndrome. *Movement Disorders* 2000; **15:** S134.
122. Freeman A, Rye DB, Bliwise D, Chakravorty S, Krulewicz S, Watts RL. Ropinirole for restless legs syndrome (RLS): an open label and double blind placebo-controlled study. *Neurology* 2001; **56:** A5.
123. Ahmed I. Ropinirole in restless leg syndrome. *Missouri Medicine* 2002; **99:** 500–501.
124. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Pramipexole alleviates sensory and motor symptoms of restless legs syndrome. *Neurology* 1998; **51:** 311–312.
125. Becker PM, Ondo W, Sharon D. Encouraging initial response of restless legs syndrome to pramipexole. *Neurology* 1998; **51:** 1221–1223.
126. Lin SC, Kaplan J, Burger CD, Fredrickson PA. Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clinic Proceedings* 1998; **73:** 497–500.
127. Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. *European Journal of Neurology* 2000; **7**(Suppl. 1)**:** 27–31.
128. Saletu M, Anderer P, Saletu-Zyhlarz G, Hauer C, Saletu B. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *European Archives of Psychiatry and Clinical Neuroscience* 2002; **252:** 185–194.
129. Manconi M, Casetta I, Govoni V, Cesnik E, Ferini-Strambi L, Granieri E. Pramipexole in restless legs syndrome. Evaluation by suggested immobilization test. *Journal of Neurology* 2003; **250:** 1494–1495.
130. Hening W, Walters AS, Wagner ML, *et al*. Successful oxycodone therapy for the restless legs syndrome: a double-blind study. *Canadian Journal of Neurological Sciences* 1993; **20:** S212.

131. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. *Journal of Clinical Psychiatry* 1999; **60:** 241–244.
132. van Dijk JG, Bollen EL, Slootweg J, van der Meer CM, Durian FW, Zwinderman AH. Geen verschil in werkzaamheid tussen hydrokinine en placebo bij het 'restless legs'-syndroom. *Nederlands Tijdschrift voor Geneeskunde* 1991; **135:** 759–763.
133. Ausserwinkler M, Schmidt P. Clonidine is effective in the treatment of 'restless leg' syndrome in chronic uraemic patients. *Nephrology, Dialysis, Transplantation* 1988; **3:** 530.
134. Ausserwinkler M, Schmidt P. Clonidine is effective in the treatment of 'restless leg' syndrome in chronic uraemia patients. *Nephrology, Dialysis, Transplantation* 1989; **4:** 149.
135. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. *Renal Failure* 2004; **26:** 393–397.
136. Galvez-Jimenez N, Khan T. Ropinirole and restless legs syndrome. *Movement Disorders* 1999; **14:** 890–892.
137. Miranda M, Fabres L, Kagi M, *et al*. Tratamiento del sindrome de piernas inquietas en pacientes uremicos en dialisis con pramipexole: resultados preliminares. *Revista Medica de Chile* 2003; **131:** 700–701.
138. Miranda M, Kagi M, Fabres L, *et al*. Pramipexole for the treatment of uremic restless legs in patients undergoing hemodialysis. *Neurology* 2004; **62:** 831–832.
139. Holman AJ, Neiman RA, Ettlinger RE. Preliminary efficacy of the dopamine agonist, pramipexole, for fibromyalgia: the first, open label, multicenter experience. *Journal of Musculoskeletal Pain* 2004; **12:** 69–74.
140. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age and Ageing* 1994; **23:** 200–203.
141. Evidente VG. Piribedil for restless legs syndrome: a pilot study. *Movement Disorders* 2001; **16:** 579–581.
142. Ehrenberg BL, Eisensehr I, Corbett KE, Crowley PF, Walters AS. Valproate for sleep consolidation in periodic limb movement disorder. *Journal of Clinical Psychopharmacology* 2000; **20:** 574–578.
143. Nishimatsu O, Horiguchi J, Inami Y, Sukegawa T, Sasaki A. Periodic limb movement disorder in neuroleptic-induced akathisia. *Kobe Journal of Medical Sciences* 1997; **43:** 169–177.
144. Roehrs T, Zorick F, Wittig R, Roth T. Efficacy of a reduced triazolam dose in elderly insomniacs. *Neurobiology of Aging* 1985; **6:** 293–296.
145. Bonnet MH, Arand DL. The use of triazolam in older patients with periodic leg movements, fragmented sleep, and daytime sleepiness. *Journal of Gerontology* 1990; **45:** M139–M144.
146. Kaplan PW, Allen RP, Buchholz DW, Walters JK. Double-blind comparison of L-dopa versus propoxyphene in patients with periodic limb movements in sleep. *Electroencephalography and Clinical Neurophysiology* 1991; **79:** 32P.
147. Bedard MA, Montplaisir J, Godbout R. Effect of L-dopa on periodic movements in sleep in narcolepsy. *European Neurology* 1987; **27:** 35–38.
148. de Mello MT, Esteves AM, Tufik S. Comparison between dopaminergic agents and physical exercise as treatment for periodic limb movements in patients with spinal cord injury. *Spinal Cord* 2004; **42:** 218–221.
149. Boivin DB, Montplaisir J, Lambert C. Effects of bromocriptine in human narcolepsy. *Clinical Neuropharmacology* 1993; **16:** 120–126.
150. Hogl B, Rothdach A, Wetter TC, Trenkwalder C. The effect of cabergoline on sleep, periodic leg movements in sleep, and early morning motor function in patients with Parkinson's disease. *Neuropsychopharmacology* 2003; **28:** 1866–1870.
151. Saletu M, Anderer P, Saletu B, *et al*. Sleep laboratory studies in periodic limb movement disorder (PLMD) patients as compared with normals and acute effects of ropinirole. *Human Psychopharmacology* 2001; **16:** 177–187.
152. Fantini ML, Gagnon J, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. *Neurology* 2003; **61:** 1418–1420.
153. Buysse DJ, Reynolds CF, III, Hoch CC, *et al*. Longitudinal effects of nortriptyline on EEG sleep and the likelihood of recurrence in elderly depressed patients. *Neuropsychopharmacology* 1996; **14:** 243–252.
154. Nofzinger EA, Fasiczka A, Berman S, Thase ME. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. *Journal of Clinical Psychiatry* 2000; **61:** 858–862.
155. Grewal M, Hawa R, Shapiro C. Treatment of periodic limb movements in sleep with selegiline HCl. *Movement Disorders* 2002; **17:** 398–401.
156. Yamashiro Y, Kryger MH. Acute effect of nasal CPAP on periodic limb movements associated with breathing disorders during sleep. *Sleep* 1994; **17:** 172–175.
157. Briellmann RS, Mathis J, Bassetti C, Gugger M, Hess CW. Patterns of muscle activity in legs in sleep apnea patients before and during nCPAP therapy. *European Neurology* 1997; **38:** 113–118.
158. Kotterba S, Clarenbach P, Bommel W, Rasche K. Periodic leg movements in patients with obstructive sleep apnea syndrome during nCPAP therapy. *Somnologie* 2000; **4:** 93–95.
159. Scholle S, Scholle HC, Zwacka G. Periodic leg movements and sleep-disordered breathing in children. *Somnologie* 2001; **5:** 153–158.
160. Baran AS, Richert AC, Douglass AB, May W, Ansarin K. Change in periodic limb movement index during treatment of obstructive sleep apnea with continuous positive airway pressure. *Sleep* 2003; **26:** 717–720.
161. Guilleminault C, Flagg W. Effect of baclofen on sleep-related periodic leg movements. *Annals of Neurology* 1984; **15:** 234–239.
162. Bedard MA, Montplaisir J, Godbout R, Lapierre O. Nocturnal gamma-hydroxybutyrate. Effect on periodic leg movements and sleep organization of narcoleptic patients. *Clinical Neuropharmacology* 1989; **12:** 29–36.
163. Kovacevic-Ristanovic R, Cartwright RD, Lloyd S. Nonpharmacologic treatment of periodic leg movements in sleep. *Archives of Physical Medicine and Rehabilitation* 1991; **72:** 385–389.
164. Lavie P, Nahir M, Lorber M, Scharf Y. Nonsteroidal antiinflammatory drug therapy in rheumatoid arthritis patients: lack of association between clinical improvement and effects on sleep. *Arthritis and Rheumatism* 1991; **34:** 655–659.

165. Benz RL, Pressman MR, Hovick ET, Peterson DD. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (the SLEEPO study). *American Journal of Kidney Diseases* 1999; **34:** 1089–1095.
166. Kunz D, Bes F. Exogenous melatonin in periodic limb movement disorder: an open clinical trial and a hypothesis. *Sleep* 2001; **24:** 183–187.
167. Campos H, Tufik S, Bittencourt L, Haidar M, Baracat EC. Progeston reduces periodic leg movements in menopause. *Climacteric* 2002; **5:** 157 (abstract).
168. Saletu A, Gritsch F, Mailath-Pokorny G, Gruber G, Anderer P, Saletu B. Objektivierung der Therapieeffizienz eines neuartigen mandibularen Protrusionsbehelfs fur Schnarchen und schlafbezogene Atmungsstorungen mittels Polysomnographie. *Wiener Klinische Wochenschrift* 2002; **114:** 807–815.
169. Michalsen A, Schlegel F, Rodenbeck A, *et al*. Effects of short-term modified fasting on sleep patterns and daytime vigilance in non-obese subjects: results of a pilot study. *Annals of Nutrition and Metabolism* 2003; **47:** 194–200.
170. Simakajornboon N, Gozal D, Vlasic V, Mack C, Sharon D, McGinley BM. Periodic limb movements in sleep and iron status in children. *Sleep* 2003; **26:** 735–738.
171. Cicolin A, Lopiano L, Zibetti M, *et al*. Effects of deep brain stimulation of the subthalamic nucleus on sleep architecture in parkinsonian patients. *Sleep Medicine* 2004; **5:** 207–210.
172. Brenning R. Enantaldehydes and furaldehydes in molimina crurum nocturna including 'restless legs'. A comparative trial with carbacholine, inositolnicotinate, and placebo. *Nordisk Medicin* 1969; **81:** 528–534.
173. Christiansen I. Mesionositolhexanikotinat (Hexanicit) og pentaerytritoltetranikotinat (Bufon) ved restless legs. *Ugeskrift for Laeger* 1970; **132:** 1475–1476.
174. Hurlimann F. Restless legs and crampi in the night. Double blind study with circonyl in patients with defective peripheric arterial circulation. *Schweizerische Rundschau fur Medizin Praxis* 1974; **63:** 194–195.
175. Noseda A, Nouvelle M, Lanquart JR, *et al*. High leg motor activity in sleep apnea hypopnea patients: efficacy of clonazepam combined with nasal CPAP on polysomnographic variables. *Respiratory Medicine* 2002; **96:** 693–699.
176. Sorensen O, Telstad W. Carbamazepin (Tegretol) ved restless legs syndrom. *Tidsskrift for den Norske Laegeforening* 1984; **104:** 2093–2095.
177. Handwerker J-VJ, Palmer RF. Clonidine in the treatment of 'restless leg' syndrome. *New England Journal of Medicine* 1985; **313:** 1228–1229.
178. Bamford CR, Sandyk R. Failure of clonidine to ameliorate the symptoms of restless legs syndrome. *Sleep* 1987; **10:** 398–399.
179. Zoe A, Wagner ML, Walters AS. High-dose clonidine in a case of restless legs syndrome. *Annals of Pharmacotherapy* 1994; **28:** 878–881.
180. Riemann D, Gann H, Dressing H. Restless legs syndrome and periodic leg movements in sleep. *TW Neurologie Psychiatrie* 1995; **9:** 1951.
181. Merren MD. Gabapentin for treatment of pain and tremor: a large case series. *Southern Medical Journal* 1998; **91:** 739–744.
182. Morgan LK. Restless limbs: a commonly overlooked symptom controlled by 'Valium'. *Medical Journal of Australia* 1967; **2:** 589–594.
183. Matthews WB. Treatment of the restless legs syndrome with clonazepam. *British Medical Journal* 1979; **1:** 751.
184. Boghen D. Successful treatment of restless legs with clonazepam. *Annals of Neurology* 1980; **8:** 341.
185. Montplaisir J, Godbout R, Boghen D, DeChamplain J, Young SN, Lapierre G. Familial restless legs with periodic movements in sleep: electrophysiologic, biochemical, and pharmacologic study. *Neurology* 1985; **35:** 130–134.
186. Tollefson G, Erdman C. Triazolam in the restless legs syndrome. *Journal of Clinical Psychopharmacology* 1985; **5:** 361–362.
187. Scharf MB, Brown L, Hirschowitz J. Possible efficacy of alprazolam in restless leg syndrome. *The Hillside Journal of Clinical Psychiatry* 1986; **8:** 214–223.
188. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *American Journal of Medicine* 1996; **100:** 333–337.
189. Stautner A, Stiasny-Kolster K, Collado-Seidel V, Bucher SF, Oertel WH, Trenkwalder C. Comparison of idiopathic and uremic restless legs syndrome: results of data base of 134 patients. *Movement Disorders* 1996; **11:** S98.
190. Bezerra ML, Martinez JV. Zolpidem in restless legs syndrome. *European Neurology* 2002; **48:** 180–181.
191. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. *Archives of Neurology* 1982; **39:** 739.
192. von Scheele C, Kempi V. Long-term effect of dopaminergic drugs in restless legs. A 2-year follow-up. *Archives of Neurology* 1990; **47:** 1223–1224.
193. Lauerma H. Nocturnal wandering caused by restless legs and short-acting benzodiazepines. *Acta Psychiatrica Scandinavica* 1991; **83:** 492–493.
194. Oechsner M. Idiopathic restless legs syndrome: combination therapy with levodopa and ropinirole. *Aktuelle Neurologie* 1998; **25:** 190–192.
195. Kumar VG, Bhatia M, Tripathi M, Srivastava AK, Jain S. Restless legs syndrome: diagnosis and treatment. *Journal of the Association of Physicians of India* 2003; **51:** 782–783.
196. Silber MH, Shepard J-WJ, Wisbey JA. Pergolide in the management of restless legs syndrome: an extended study. *Sleep* 1997; **20:** 878–882.
197. Noel S, Korri H, Vanderheyden JE. Low dosage of pergolide in the treatment of restless legs syndrome. *Acta Neurologica Belgica* 1998; **98:** 52–53.
198. Winkelmann J, Wetter TC, Stiasny K, Oertel WH, Trenkwalder C. Treatment of restless leg syndrome with pergolide – an open clinical trial. *Movement Disorders* 1998; **13:** 566–569.
199. Benes H. Idiopathisches Restless-legs-Syndrom: Behandlung mit Lisurid. *Nervenheilkunde* 2001; **20:** 119–122.
200. Danoff SK, Grasso ME, Terry PB, Flynn JA. Pleuropulmonary disease due to pergolide use for restless legs syndrome. *Chest* 2001; **120:** 313–316.
201. Bassetti C, Clavadetscher S, Gugger M, Hess CW. Pergolide-associated 'sleep attacks' in a patient with restless legs syndrome. *Sleep Medicine* 2002; **3:** 275–277.

202. Stiasny K, Moller JC, Oertel WH. Safety of pramipexole in patients with restless legs syndrome. *Neurology* 2000; **55:** 1589–1590.
203. Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. *Sleep Medicine* 2002; **3:** S23–S25.
204. Teive HA, de Quadros A, Barros FC, Werneck LC. Sindrome das pernas inquietas com heranca autossomica dominante piorada pelo uso de mirtazapina: relato de caso. *Arquivos de Neuro-Psiquiatria* 2002; **60:** 1025–1029.
205. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. *Sleep* 2003; **26:** 819–821.
206. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). *Sleep Medicine* 2004; **5:** 9–14.
207. Trzepacz PT, Violette EJ, Sateia MJ. Response to opioids in three patients with restless legs syndrome. *American Journal of Psychiatry* 1984; **141:** 993–995.
208. Hening WA, Walters A, Kavey N, Gidro-Frank S, Cote L, Fahn S. Dyskinesias while awake and periodic movements in sleep in restless legs syndrome: treatment with opioids. *Neurology* 1986; **36:** 1363–1366.
209. Walters A, Hening W, Cote L, Fahn S. Dominantly inherited restless legs with myoclonus and periodic movements of sleep: a syndrome related to the endogenous opiates? *Advances in Neurology* 1986; **43:** 309–319.
210. Sandyk R, Bernick C, Lee SM, Stern LZ, Iacono RP, Bamford CR. L-dopa in uremic patients with the restless legs syndrome. *International Journal of Neuroscience* 1987; **35:** 233–235.
211. Sandyk R, Bamford CR, Gillman MA. Opiates in the restless legs syndrome. *International Journal of Neuroscience* 1987; **36:** 99–104.
212. Montplaisir J, Lorrain D, Godbout R. Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanism. *European Neurology* 1991; **31:** 41–43.
213. Vahedi H, Kuchle M, Trenkwalder C, Krenz CJ. Peridurale Morphiumanwendung bei Restless-Legs-Status. *Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* 1994; **29:** 368–370.
214. Walters AS, Winkelmann J, Trenkwalder C, *et al*. Long-term follow-up on restless legs syndrome patients treated with opioids. *Movement Disorders* 2001; **16:** 1105–1109.
215. Jakobsson B, Ruuth K. Successful treatment of restless legs syndrome with an implanted pump for intrathecal drug delivery. *Acta Anaesthesiologica Scandinavica* 2002; **46:** 114–117.
216. Ayres SJ, Mihan R. Leg cramps (systremma) and 'restless legs' syndrome. Response to vitamin E (tocopherol). *California Medicine* 1969; **111:** 87–91.
217. Blattler W, Muhlemann M. Restless legs und nachtliche Beinkrampfe – Vergessenes zur Diagnose – Neues zur Therapie. *Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine* 1982; **112:** 115–117.
218. Mountifield JA. Restless leg syndrome relieved by cessation of smoking. *CMAJ* 1985; **133:** 426–427.
219. Ha HC. Regional intravenous analgesia for restless legs syndrome. *Pain Clinic* 1988; **2:** 121–123.
220. Sandyk R, Kwo-on-Yuen PF, Bamford CR. The effects of baclofen in the restless legs syndrome: evidence for endogenous opioid involvement. *Journal of Clinical Psychopharmacology* 1988; **8:** 440–441.
221. Dimmitt SB, Riley GJ. Selective serotonin receptor uptake inhibitors can reduce restless legs symptoms. *Archives of Internal Medicine* 2000; **160:** 712.
222. Hu J. Acupuncture treatment of restless leg syndrome. *Journal of Traditional Chinese Medicine* 2001; **21:** 312–316.
223. Kapur N, Friedman R. Oral ketamine: a promising treatment for restless legs syndrome. *Anesthesia and Analgesia* 2002; **94:** 1558–1559.
224. Lin Z. How to treat restless leg syndrome with traditional Chinese medicine? *Journal of Traditional Chinese Medicine* 2003; **23:** 306–307.
225. Strang RR. The symptom of restless legs. *Medical Journal of Australia* 1967; **1:** 1211–1213.
226. Lipinski JF, Zubenko GS, Barreira P, Cohen BM. Propranolol in the treatment of neuroleptic-induced akathisia. *Lancet* 1983; **2:** 685–686.
227. Derom E, Elinck W, Buylaert W, van der Straeten M. Which beta-blocker for the restless leg? *Lancet* 1984; **1:** 857.
228. Ginsberg HN. Propranolol in the treatment of restless legs syndrome induced by imipramine withdrawal. *American Journal of Psychiatry* 1986; **143:** 938.
229. Bastani B, Westervelt FB. Effectiveness of clonidine in alleviating the symptoms of 'restless legs'. *American Journal of Kidney Diseases* 1987; **10:** 326.
230. Cavatorta F, Vagge R, Solari P, Queirolo C. Risultati preliminari con clonidina nella sindrome delle gambe senza riposo in due pazienti uremici emodializzati. *Minerva Urologica e Nefrologica* 1987; **39:** 93.
231. Novelli G, Mediati RD, Casali R, Palermo P. Treatment of 'restless legs syndrome' with gabapentin. *Pain Clinic* 2000; **12:** 61–63.
232. Read DJ, Feest TG, Nassim MA. Clonazepam: effective treatment for restless legs syndrome in uraemia. *British Medical Journal (Clinical Research Edition)* 1981; **283:** 885–886.
233. Salvi F, Montagna P, Plasmati R, *et al*. Restless legs syndrome and nocturnal myoclonus: initial clinical manifestation of familial amyloid polyneuropathy. *Journal of Neurology, Neurosurgery and Psychiatry* 1990; **53:** 522–525.
234. Horiguchi J, Yamashita H, Mizuno S, *et al*. Nocturnal eating/drinking syndrome and neuroleptic-induced restless legs syndrome. *International Clinical Psychopharmacology* 1999; **14:** 33–36.
235. Bruno RL. Abnormal movements in sleep as a post-polio sequelae. *American Journal of Physical Medicine and Rehabilitation* 1998; **77:** 339–344.
236. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. *Pediatric Neurology* 2000; **22:** 182–186.
237. Sharif AA. Entacapone in restless legs syndrome. *Movement Disorders* 2002; **17:** 421.
238. Scherbaum N, Stuper B, Bonnet U, Gastpar M. Transient restless legs-like syndrome as a complication of opiate withdrawal. *Pharmacopsychiatry* 2003; **36:** 70–72.
239. Lipinski JF, Sallee FR, Jackson C, Sethuraman G. Dopamine agonist treatment of Tourette disorder in

children: results of an open-label trial of pergolide. *Movement Disorders* 1997; **12:** 402–407.
240. Brown LK, Heffner JE, Obbens EA. Transverse myelitis associated with restless legs syndrome and periodic movements of sleep responsive to an oral dopaminergic agent but not to intrathecal baclofen. *Sleep* 2000; **23:** 591–594.
241. Hanna PA, Kumar S, Walters AS. Restless legs symptoms in a patient with above knee amputations: a case of phantom restless legs. *Clinical Neuropharmacology* 2004; **27:** 87–89.
242. Estivill E, Fuente-Panell V, Segarra-Isern F, Albares-Tendero J. Sindrome de piernas inquietas en un paciente con amputacion de ambas piernas. *Revista de Neurologia* 2004; **39:** 536–538.
243. Lauerma H, Markkula J, Hyvonen H, Kyyronen K. Idiopathic restless legs syndrome and psychoses. *Nordic Journal of Psychiatry* 1997; **51:** 205.
244. Burns KE. Use of tramadol to control restless legs syndrome after orthopedic surgery. *Hospital Pharmacy* 2000; **35:** 673.
245. Freye E, Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): a case study. *European Journal of Pain* 2000; **4:** 307–311.
246. Nordlander NB. Therapy in restless legs. *Acta Medica Scandinavica* 1953; **145:** 453–457.
247. Popkin RJ. Orphenadrine citrate (Norflex) for the treatment of 'restless legs' and related syndromes. *Journal of the American Geriatrics Society* 1971; **19:** 76–79.
248. Morgan LK. Letter: Restless legs: precipitated by beta blockers, relieved by orphenadrine. *Medical Journal of Australia* 1975; **2:** 753.
249. Botez MI, Fontaine F, Botez T, Bachevalier J. Folate-responsive neurological and mental disorders: report of 16 cases. Neuropsychological correlates of computerized transaxial tomography and radionuclide cisternography in folic acid deficiencies. *European Neurology* 1977; **16:** 230–246.
250. Botez MI, Cadotte M, Beaulieu R, Pichette LP, Pison C. Neurologic disorders responsive to folic acid therapy. *Canadian Medical Association Journal* 1976; **115:** 217–223.
251. Yatzidis H, Koutsicos D, Agroyannis B, Papastephanidis C, Plemenos M, Delatola Z. Biotin in the management of uremic neurologic disorders. *Nephron* 1984; **36:** 183–186.
252. Sandyk R. L-Tryptophan in the treatment of restless legs syndrome. *American Journal of Psychiatry* 1986; **143:** 554–555.
253. Yasuda T, Nishimura A, Katsuki Y, Tsuji Y. Restless legs syndrome treated successfully by kidney transplantation – a case report. *Clinical Transplants* 1986; **12:** 138.
254. Sandyk R, Iacono RP, Bamford CR. Spinal cord mechanisms in amitriptyline responsive restless legs syndrome in Parkinson's disease. *International Journal of Neuroscience* 1988; **38:** 121–124.
255. Kerr PG, van Bakel C, Dawborn JK. Assessment of the symptomatic benefit of cool dialysate. *Nephron* 1989; **52:** 166–169.
256. O'Keeffe ST, Noel J, Lavan JN. Restless legs syndrome in the elderly. *Postgraduate Medical Journal* 1993; **69:** 701–703.
257. Kanter AH. The effect of sclerotherapy on restless legs syndrome. *Dermatologic Surgery* 1995; **21:** 328–332.
258. Reuter I, Ellis CM, Ray-Chaudhuri K. Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome. *Acta Neurologica Scandinavica* 1999; **100:** 163–167.
259. Rye DB, DeLong MR. Amelioration of sensory limb discomfort of restless legs syndrome by pallidotomy. *Annals of Neurology* 1999; **46:** 800–801.
260. Ishizu T, Ohyagi Y, Furuya H, *et al*. A patient with restless legs syndrome/periodic limb movement successfully treated by wearing a lumbar corset. *Rinsho Shinkeigaku. Clinical Neurology* 2001; **41:** 438–441.
261. Kryger MH, Otake K, Foerster J. Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers. *Sleep Medicine* 2002; **3:** 127–132.
262. Silber MH, Richardson JW. Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. *Mayo Clinic Proceedings* 2003; **78:** 52–54.
263. McLean AJ. The use of the dopamine-receptor partial agonist aripiprazole in the treatment of restless legs syndrome. *Sleep* 2004; **27:** 1022.
264. Ware JC, Blumoff R, Pittard JT. Peripheral vasoconstriction in patients with sleep related periodic leg movements. *Sleep* 1988; **11:** 182–186.
265. Laschewski F, Sanner B, Konermann M, Kreuzer I, Horstensmeyer D, Sturm A. Ausgepragte Hypersomnie einer 13jahrigen bei periodic leg movement. *Pneumologie* 1997; **3**(Suppl. 51)**:** 725–728.
266. Staedt J, Stoppe G, Riemann H, Hajak G, Ruther E, Riederer P. Lamotrigine in the treatment of nocturnal myoclonus syndrome (NMS): two case reports. *Journal of Neural Transmission* 1996; **103:** 355–361.
267. Oshtory MA, Vijayan N. Clonazepam treatment of insomnia due to sleep myoclonus. *Archives of Neurology* 1980; **37:** 119–120.
268. Rousseau JJ, Debatisse DF. Etude clinique et polygraphique de deux observations de 'nocturnal myoclonus' sensibles au clonazepam. *Acta Neurologica Belgica* 1985; **85:** 318–326.
269. Guilleminault C, Crowe C, Quera-Salva MA, Miles L, Partinen M. Periodic leg movement, sleep fragmentation and central sleep apnoea in two cases: reduction with clonazepam. *European Respiratory Journal* 1988; **1:** 762–765.
270. Romano TJ. Pharmacotherapy. Presence of nocturnal myoclonus in patients with fibromyalgia syndrome. *American Journal of Pain Management* 1999; **9:** 85.
271. Malek-Ahmadi P. Bupropion, periodic limb movement disorder, and ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 1999; **38:** 637–638.
272. Leonhardt M, Abele M, Klockgether T, Dichgans J, Weller M. Pathological yawning (chasm) associated with periodic leg movements in sleep: cure by levodopa. *Journal of Neurology* 1999; **246:** 621–622.
273. Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. *Sleep* 1999; **22:** 297–300.
274. Rodrigues RN, Silva AA. Sonolencia diurna excessiva pos-traumatismo de cranio: associacao com movimentos periodicos de pernas e disturbio de comportamento do sono REM: relato de caso. *Arquivos de Neuro-Psiquiatria* 2002; **60:** 656–660.

275. Santamaria J, Iranzo A, Tolosa E. Development of restless legs syndrome after dopaminergic treatment in a patient with periodic leg movements in sleep. *Sleep Medicine* 2003; **4:** 153–155.
276. Kavey N, Walters AS, Hening W, Gidro-Frank S. Opioid treatment of periodic movements in sleep in patients without restless legs. *Neuropeptides* 1988; **11:** 181–184.
277. Ancoli-Israel S, Seifert AR, Lemon M. Thermal biofeedback and periodic movements in sleep: patients' subjective reports and a case study. *Biofeedback and Self Regulation* 1986; **11:** 177–188.
278. Hanly P, Zuberi N. Periodic leg movements during sleep before and after heart transplantation. *Sleep* 1992; **15:** 489–492.
279. Lee MS, Choi YC, Lee SH, Lee SB. Sleep-related periodic leg involvements associated with spinal cord lesions. *Movement Disorders* 1996; **11:** 719–722.
280. Paradiso G, Khan F, Chen R. Effects of apomorphine on flexor reflex and periodic limb movement. *Movement Disorders* 2002; **17:** 594–597.
281. Gulden J. Levodopa in the treatment of restless legs syndrome. *Fortschritte der Medizin* 1994; **112:** 61–62.
282. Hain C. Development of opioid dependence in a not diagnosed restless legs syndrome. *Psychiatrische Praxis* 2002; **29:** 321–323.
283. Horiguchi J, Inami Y, Miyoshi N, Kakimoto Y. Restless legs syndrome in four parkinsonian patients treated with amantadine. *Rinsho Shinkeigaku. Clinical Neurology* 1985; **25:** 153–156.
284. Kastin AJ, Kullander S, Borglin NE, *et al*. Extrapigmentary effects of melanocyte-stimulating hormone in amenorrhoeic women. *Lancet* 1968; **1:** 1007–1010.
285. Nassr DG. Paradoxical response to nitrazepam in a patient with hypersomnia secondary to nocturnal myoclonus. *Journal of Clinical Psychopharmacology* 1986; **6:** 121–122.
286. Petiau C, Zamagni M, Trautmann D, Sforza E, Krieger J. Periodic movements during sleep syndrome. *Journal de medecine de Strasbourg* 1995; **26:** 166–169.
287. Satzger-Harsch U. Current studies: therapy with L-dopa/benserazide relieves excruciating symptoms in restless leg syndrome. *Ärztliche Praxis Neurologie Psychiatrie* 1998; **11:** 40.
288. Schwarz J, Trenkwalder C. Restless legs syndrome: treatment with L-dopa or L-dopa slow release preparations. *Aktuelle Neurologie* 1996; **23:** 26–29.
289. Staedt J, Stoppe G, Kogler A, *et al*. Nachtliches Myoklonie-Syndrom (NMS) und Restless-Legs-Syndrom (RLS) – Ubersicht und Fallbeschreibung. *Fortschritte der Neurologie-Psychiatrie* 1994; **62:** 88–93.
290. Stiasny K. Restless legs syndrome: sometimes are hot and cold showers sufficient. *Ärztliche Praxis Neurologie Psychiatrie* 1999; **3:** 38–40.
291. Trenkwalder C. Dyskinesia on dopaminergic therapy for restless legs syndrome? *Internistische Praxis* 2003; **43:** 99–100.
292. Vaskivskyj M. Vliv hyperemizujici vodolecby na syndrom neklidnych nohou. *Fysiatricky a Reumatologicky Vestnik* 1973; **51:** 308–309.