Restless legs syndrome: diagnosis and review of management options

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Abstract: Restless legs syndrome (RLS) is one of the commonest movement disorders affecting sleep and also daytime functioning. The prevalence may be 8%–10% of the white Caucasian population. The diagnosis is simple and is based on a well-validated clinical questionnaire, yet misdiagnosis is common and the condition remains underdiagnosed and consequently inappropriately treated, often causing great distress to the sufferers. In spite of robust evidence for effective treatment of RLS, patients may often be told to "put up with the symptoms" and suffer the consequence of years of poor sleep which may lead to major lifestyle changes. This review addresses the diagnostic issues, the differential diagnosis, and the evidence base for treatment of the common condition.

Keywords: restless legs syndrome, Ekbom's syndrome, periodic limb movement, dopaminergic

Introduction

Restless legs syndrome (RLS), also known as Ekbom's syndrome, is a common movement disorder with sensorimotor symptoms occurring during sleep and quiet wakefulness (Ekbom 1945). Yoakum has described RLS as the "the most common disorder you've never heard of" and this may be an appropriate description of RLS (Yoakum 1994). The term restless legs syndrome was first introduced in 1945 by Karl-Axel Ekbom, a Swedish neurologist and surgeon, who described and systematically characterized the condition (Ekbom 1945). RLS can present in primary care and secondary care, across a range of specialities, and in the UK, the condition remains under-recognized and is often regarded as a neurosis in spite of evidence that RLS adversely affects quality of life (Chaudhuri et al 2001, 2004; Kirsch et al 2002; Chaudhuri 2003; Abetz et al 2004). Although RLS is effectively treatable, and there is a growing evidence base for drug treatment of RLS, the condition is generally poorly treated and investigated and often prescribed inappropriate drugs.

Patients' descriptions of RLS are wide and varied, including "Elvis legs" and an "electric current" running through their legs (Allen and Earley 2001; Allen et al 2003). With such a broad, unusual spectrum of reported sensations, RLS is frequently misunderstood and misdiagnosed, and even classified as a psychogenic disorder (Allen and Early 2001; Chaudhuri 2003).

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Historical aspects

Ekbom (1945) distinguished between the sensory form of RLS (asthenia crurum paraesthesia) and the painful variant of RLS (asthenia crurum dolorosa). However, the earliest description of restless legs associated with sleep disabilities came from Sir Thomas Willis, an English physician and Sedleian professor of natural philosophy

Table 1 The diagnostic criteria for RLS (Walters et al 1995)

Minimum diagnostic criteria	Additional features
1. Desire to move limbs, usually associated with para/dysesthesia	Supportive features: (a) Dopaminergic drug responsiveness (b) PLMS/PLMA (c) Positive family history
2. Motor restlessness	
3. Symptoms worse or exclusively present at rest – partial/temporary relief with activity	Associated features: (a) Chronic progressive course with periodic exacerbations (b) Normal neurological examination (except neuropathy) (c) Sleep disturbance
4. Symptoms worse in the evening or at night	

Abbreviations: PLMA, periodic limb movements with arousal; PLMS, periodic limb movements during sleep.

in Oxford in 1672 who alluded to RLS in a chapter titled "Instructions for curing the watching-evil" written in Latin (Willis 1672). More recently, abnormal involuntary movements during sleep such as nocturnal myoclonus (subsequently termed periodic limb movements during sleep [PLMS]) have been reported to have a strong association with RLS (Symonds 1953; Lugaresi et al 1965). The diagnosis of RLS had been difficult owing to lack of validated diagnostic criteria till 1995. The International Restless Legs Study Group defined and validated such criteria in 1995 (Walters 1995). Revised criteria for the diagnosis of RLS were formulated from a consensus conference held at the National Institutes of Health on May 1–3, 2002 in Bethesda, MA, USA (Allen et al 2003).

Diagnosis and differential diagnosis

Four essential criteria are all necessary for diagnosis (Table 1). The supportive and associated features help in uncertain cases.

RLS needs to be differentiated from nocturnal leg cramps and positional discomfort and akathisia (Table 2). Other differential diagnoses are noted in Table 3 (Mrowka et al 2004; Tse et al 2004). It is clear from the above criteria that any condition that causes legs to be restless or fidgety is not necessarily due to RLS.

Associations

Increasing age and female sex are risk factors for the development of RLS. The three common associations of RLS are iron deficiency anemia, renal failure–uremia, and pregnancy (Ondo 2002; Chaudhuri 2003; Jobges et al 2004). Association with Parkinson's disease (PD) remains controversial but possible (Appiah-Kubi et al 2002; Ondo et al 2002; Garcia-Borreguero et al 2003; Maniak et al 2004; Rye 2004). Figures suggest that up to 20% of sporadic PD cases may have additional RLS and a link with a genetically determined form of PD (Parkin gene mutation positive) has been suggested (Ondo et al 2002; Maniak et al 2004). Reports of RLS in patients with large fibre and small fibre neuropathy are variable and range from 5% to 8.8%, rates not higher than controls (Rutkove et al 1996; Ondo 2002;

Table 2 The most common differential diagnoses of RLS (Mrowka et al 2004; Tse et al 2004)

General disorders
- Nocturnal leg cramps
- Akathisia
- Burning feet syndrome – small fibre neuropathy
- Nocturnal dystonia in feet or toes
- The syndrome of painful legs and moving toes
- Vascular disease (varicose veins, intermittent claudication)
- Vesper's curse (a condition associated with congestive heart failure causing nocturnal pain in the lower limbs extending to the lumbosacral region)

Sleep-related disorders
- Insomnia
- REM sleep behavior disorder
- Sleep apnoea syndrome
- Sleep onset myoclonus

Abbreviations: REM, rapid eye movement; RLS, restless legs syndrome.

Table 3 The differences between akathisia, cramps, positional discomfort, and RLS (Mrowka et al 2004)

	Akathisia	RLS
MR	All the time	At rest/sleep
Aetiology	Neuroleptics Dopaminergic dysfunction	Dopaminergic drugs used to treat
Site	Face/tongue/upper limb/lower limb	Usually lower limb
Movements	Fast and choreic	Slow and repetitive
Leg cramps and positional discomfort		
	Cramps	**Positional discomfort**
MR	Not present	Aching sensation (no MR)
Relief with movement	Usually not	May be helped by massaging legs
Visible muscle contraction	Yes	No
Site:	Usually calf muscle	Symmetrical and lower limbs

Abbreviations: MR, motor restlessness; RLS, restless legs syndrome.

Chaudhuri 2003; Jobges et al 2004; Tse et al 2004). During pregnancy, RLS has been reported in 11%–27% of women usually during the third trimester (Goodman et al 1988; Ondo 2002; Chaudhuri 2003). Other secondary causes of RLS are listed in Figure 1. PLMS were first reported by Lugaresi et al (1965) and polysomnographic studies have recorded PLMS (more than five per hour) in up to 87.8% of RLS patients (Lugaresi et al 1965; Montplaisir et al 1997; Garcia-Borreguero et al 2003). Prevalence estimates of PLMS are variable and range from 6% in the general population to 58% in a subpopulation of subjects over 60 years old (Lugaresi et al 1965; Rothdach et al 2000; Garcia-Borreguero et al 2003). PLM can occur in lower and upper limbs during quiet wakefulness as well. PLM occurs commonly with RLS and is defined as repetitive flexing of lower limb joints (hip, knee, or ankle and occasionally the upper limb) and dorsiflexion or fanning of toes, for periods of 0.5–5 seconds at intervals of 5–90 seconds, and needs polysomnography for diagnosis (Atlas Task Force 1993; Chaudhuri 2003).

Management and treatment of RLS: do all patients with RLS need treatment? Who needs treatment and what to treat?

Not all patients with RLS need pharmacological treatment. Confirmation of diagnosis and reassurance is sufficient for most patients with RLS, and only approximately 20% of all RLS patients may have symptoms severe enough to merit pharmacological treatment (Henning et al 1999; Chaudhuri 2003).

Treatment should begin by examining the patient's lifestyle and looking for opportunities to initiate lifestyle changes, especially with regard to substances known to exacerbate symptoms (Table 4) (Henning et al 1999; Chaudhuri 2003; Chaudhuri et al 2004; DeKokker et al 2005).

In many cases not severe enough to merit pharmacological treatment, self-help measures may enable a patient to cope with symptoms of RLS. These so called "self-

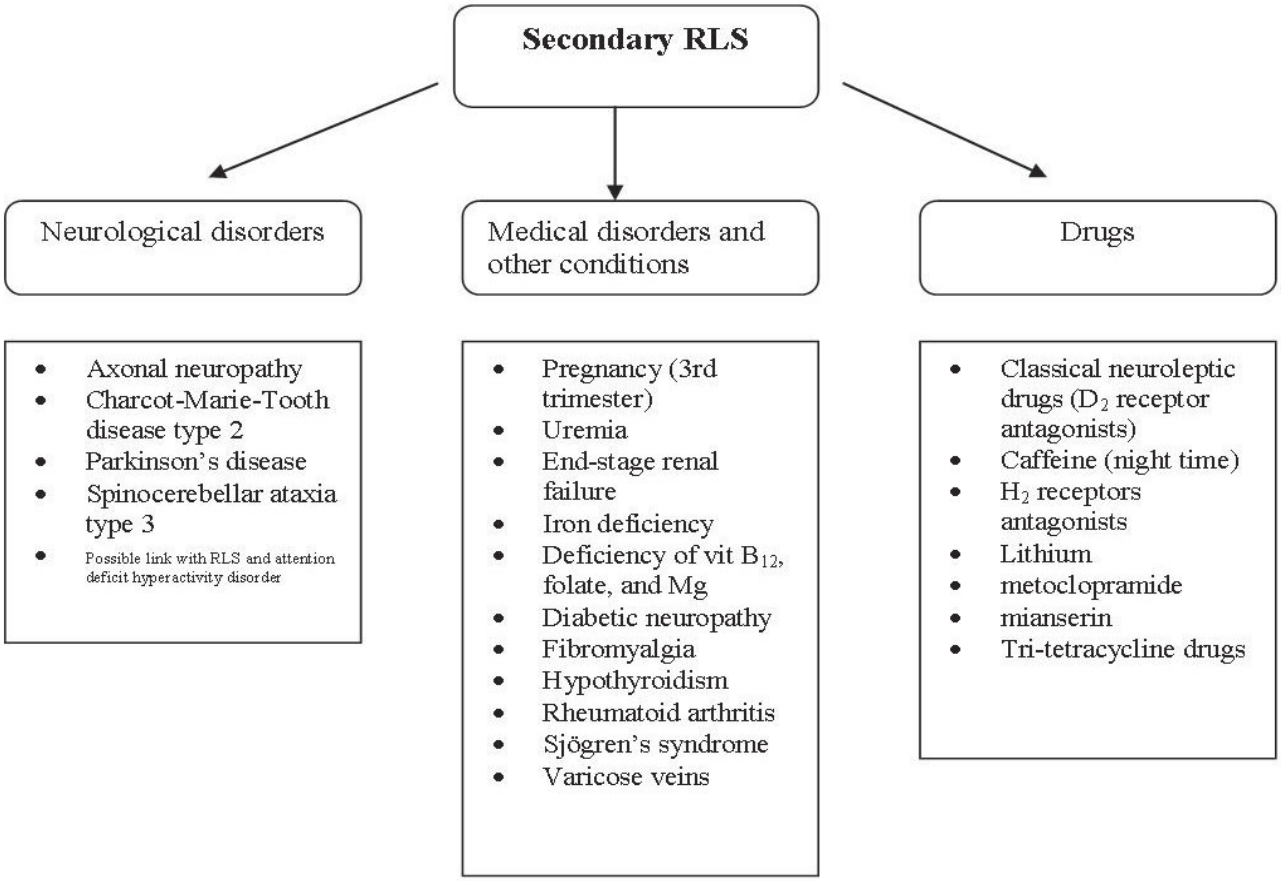

Figure 1 Some secondary causes of restless legs syndrome (RLS)

Table 4 Factors influencing treatment of RLS (DeKokker et al 2005)

- Age of the patient
  - side effects of benzodiazepines in the elderly
  - postural hypotension related to aging may be aggravated by dopamine agonists/levodopa
- Symptom severity
- Frequency and regularity of symptoms
  - many patients have paroxysmal RLS and may need "targeted/timed" or "on demand" treatment
- Presence of co-morbidity (such as cardiac disease) and pregnancy

Abbreviations: RLS, restless legs syndrome.

directed activities" are aimed to distract the mind from the symptoms of RLS and may include:

- Asking the patient to read an interesting book during the onset of symptoms
- Using a hot or cold massage
- Stretching
- Rubbing/massaging legs
- Brief spells of exercise

Sleep hygiene is often used for management of sleep disorders and can be adapted for RLS (Table 5). It is important to ensure that patients have not been given drugs that worsen RLS (Table 6).

Support groups such as the Ekbom Support Group, RLS: UK in the UK and websites are available to assist the patients with this distressing condition and to provide useful information and services (Chaudhuri 2003).

Those with chronic severe symptoms or regular recurrent symptoms (>2 attacks per week) should be treated symptomatically. Primary and secondary RLS need to be differentiated and treated accordingly. The commonest secondary causes of RLS include iron deficiency anemia, and all RLS patients must have serum ferritin levels checked (some believe transferrin receptor assays are better). Those with low normal or low ferritin levels (<45 µg/dL depending on local laboratory values) should receive oral iron supplementation for a trial period. However in many RLS patients, oral iron supplements may not be as efficacious as previously thought. As a result, various studies have been conducted to compare oral with intravenous iron supplementation, but sufficient data are still lacking (O'Keefe et al 1994; Henning et al 1999; Davis et al 2000; Chaudhuri 2003). Blood transfusions may also be considered an option for treatment in severely anemic patients with RLS.

Table 5 A suggested programme for sleep hygiene adapted for RLS

- Regular hour for going to bed at night
- Ambient room temperature
- Using the bed for sleep and sexual relations only, not for reading, watching television as excessive/restful time in bed precipitates sensory RLS
- Avoiding tea/coffee before bed
- Avoiding diuretics before bedtime
- Some people find sleeping late and rising late may be beneficial.

Abbreviations: RLS, restless legs syndrome.

Table 6 Some drugs that may worsen RLS

- Antidepressants (tricyclic including amitryptiline)
- Calcium channel blocking antihypertensives
- Antiemetics (except domperidone)
- Excessive consumption of caffeine in coffee, tea, chocolate, or soda
- Phenytoin
- Fluoxetine
- Excessive alcohol at bedtime

Abbreviations: RLS, restless legs syndrome.

Pharmacological treatment

Despite the fact that RLS is a treatable condition, which generally responds well to various medications, the treatment options are limited by the fact that at present none of the treatment options are licensed in the UK. It is envisaged that the situation will soon change and at least two or three products are likely to gain license for use in RLS soon. An established body of evidence is now gathered from double-blind, placebo-controlled trials providing level 1 evidence that dopamine agonists (DAs) are effective for treatment of RLS and currently should be considered the drug of first choice in most patients (Chaudhuri 2003; DeKokker et al 2005). Before DAs were available, levodopa was considered effective for RLS, although high rates of augmentation and rebound-related complications have limited the role of levodopa in the treatment of RLS (Allen and Earley 1996; Chaudhuri 2003; DeKokker et al 2005). Trials are being considered to look at the role of enhanced formulations of levodopa (combined with entacapone) in the treatment of variants of RLS. Tables 7 and 8 list dopaminergic and nondopaminergic (usually used as second-line treatment) treatment options available for RLS.

Dopaminergic drugs

Dopamine agonists (DAs)

These are generally considered the first-line pharmacological agents for both RLS and PLM, and have been proven to be very effective in relieving both (a) symptoms

Table 7 Dopaminergic drugs used for the treatment of RLS/PLM

Levodopa + decarboxylase inhibitors	Levodopa+ decarboxylase inhibitors+ COMT inhibitors	DAs: ergot	DAs: nonergot
Sinemet	Stalevo[a]	bromocriptine	ropinirole[b]
Madopar		pergolide[b]	pramipexole[b]
		cabergoline[b]	talipexole
		lisuride	apomorphine
		2-DHEC	rotigotine[b]
			piribedil

[a] Clinical trials possible.
[b] Double-blind, placebo-controlled trial data are available (DeKokker et al 2005).
Abbreviations: COMT, catechol-O-methyltransferase; DAs, dopamine agonists; DHEC, dihydroergocriptine; PLM, periodic limb movement; RLS, restless legs syndrome.

experienced in the awake state, including the subjective feelings of discomfort and other associated movement abnormalities, and (b) problems relating to sleep and nocturnal arousals (Earley et al 1998; Chaudhuri 2003; Tse et al 2004). Virtually all the DAs are effective to some degree. In cases where a definitive diagnosis of RLS has been made, a dramatic response with the use of night-time DAs is expected and some recommend use of this strategy as a challenge test for RLS (Earley et al 1998). As a general guideline most DAs should be started well below the recommended dosage used for PD and gradually titrated upwards, in line with the clinical response. Side-effects include nausea, nasal stuffiness, and hypotension and we routinely use domperidone prophylaxis for 2 weeks for preventing nausea. Nasal stuffiness or postural hypotension is rarely clinically serious. Newer DAs such as cabergoline (1–4 mg nocte), pramipexole (0.5–1.5 mg nocte or in divided doses), ropinirole (0.25–4 mg nocte), rotigotine transdermal patches (4.5 mg nocte), and apomorphine (nocturnal subcutaneous infusion 18–48 mg over 12 hours) have also all recently been shown to have beneficial effects on symptoms of RLS, PLM, and overall quality of nocturnal sleep (Reuter et al 1999; Montplaisir et al 2000; Stiasny et al 2002; Partinen et al 2004; Stiasny-Kolster, Benes, et al 2004; Stiasny-Kolster, Kohnen, et al 2004; Trenkwalder, Garcia-Borreguero, et al 2004; Walters et al 2004). Several of these trials (pergolide, cabergoline, ropinirole, rotigotine, pramipexole) have all used randomized, double-blind, placebo-controlled design. Some key DAs are discussed below.

Bromocriptine and pergolide Although bromocriptine (5–20 mg) was one of the first DAs described in the treatment of RLS, to date pergolide has been most frequently studied (Earley et al 1998; Stiasny et al 2001). Stiasny et al (2001) demonstrated lasting relief from symptoms throughout the night where pergolide (0.10–0.75 mg) was administered as a single evening dose or as two divided doses (0.05 mg twice daily) in two open-label trials. These findings were also confirmed in a similar trial comparing the efficacy of pergolide (0.125–0.25 mg) with that of levodopa (250–500 mg) and also in a recently published double-blind, placebo-controlled trial (Trenkwalder, Hundemer, et al 2004; DeKokker et al 2005). In comparison with levodopa, pergolide caused a statistically significant improvement in both PLMS and RLS, while bromocriptine, in a comparative analysis with levodopa, demonstrated similar therapeutic effects in terms of relieving RLS symptoms; however, levodopa did demonstrate better tolerability (DeKokker et al 2005).

Ropinirole The recently published TREAT-RLS study is the largest trial reported so far, including 284 patients from 10 European countries, investigating the efficacy of ropinirole

Table 8 Nondopaminergic drugs used for treatment of RLS/PLM

Anti-epileptic drugs	Opioids	Benzodiazepines	Adrenergic drugs	Other
gabapentin	oxycodone	clonazepam	propranolol	Iron (oral)
carbamazepine	propoxyphene	triazolam	clonidine	IV iron[b]
levetiracetam[a]	methadone	nitrazepam		
pregabalin[a]	tramadol	temazepam		
	SR morphine			

[a] clinical trials possible.
[b] Treatment with IV iron being investigated and not recommended currently.
Abbreviations: PLM, periodic limb movement; RLS, restless legs syndrome; SR, slow release.

in a 12-week, randomized, double-blind, placebo-controlled design followed by a 12-month open-label extension (Trenkwalder, Garcia-Borreguero, et al 2004). At 12 weeks, ropinirole at a mean dose of 1.9 mg/day significantly improved RLS severity scale scores compared with placebo ($p = 0.0036$). A high placebo response rate was a problem in this trial, but the improvement in clinical global impression, measures of health-related quality of life, and sleep were significantly in favor of ropinirole treatment at 12 weeks. The results of the TREAT-RLS 2 study involving a total of 267 patients receiving a 0.25–4 mg evening dose of ropinirole have been published recently and have confirmed the superiority of ropinirole over placebo in the treatment of RLS (Walters et al 2004).

Pramipexole In a recent placebo-controlled, crossover, polysomnographic study involving 109 patients, pramipexole given at dose range of 0.125–0.75 mg/day nocte (of the salt preparation) markedly reduced restlessness and PLM during the day and night; however, its effects on sleep architecture were similar to those recorded with patients using the placebo (Montplaisir et al 1999; Partinen et al 2004). A large multicenter European study has recently reported the efficacy of pramipexole in the treatment of RLS (Oertel and Stiasny-Kolster 2005). Few sufficiently long-term follow-up studies have reported on the continued efficacy of DA treatment. One study (Montplaisir et al 2000) reported continued efficacy of pramipexole (0.25–0.75 mg evening dose per day) during follow-up for about 8 months, while Stiasny-Kolster, Benes, et al (2004) have reported continuing efficacy of cabergoline at 1 year follow-up. Recent reports suggest that depression and low mood may be a problem in RLS and the proposed psychotropic action of pramipexole may be particularly useful in this regard (Corrigan et al 2000; Goldberg et al 2004).

Cabergoline Cabergoline, an ergot DA, has the longest half-life (65 hours) of all the DAs and therefore has the added advantage of being active for up to 24 hours. Work from our group and others has demonstrated the efficacy of cabergoline in PD patients with RLS, and it has recently been proven to be well tolerated in both young and elderly patients, with acceptable side-effect profiles (Appiah-Kubi et al 2002, 2003). Studies suggest that cabergoline is well tolerated in patients with severe RLS who have failed other therapies and also those experiencing augmentation (Appiah-Kubi et al 2002). More recently, a double-blind, placebo-controlled trial in 85 patients randomized to placebo and 0.5, 1, and 2 mg of cabergoline reported marked improvement of RLS severity at bedtime and during the day and satisfaction with sleep compared with placebo with all doses of cabergoline throughout a 1-year follow-up period (Stiasny-Kolster, Benes, et al 2004).

Rotigotine and apomorphine Rotigotine is a nonergot agonist used as a cutaneous patch. In a randomized, double-blind, placebo-controlled trial involving 63 patients with RLS, rotigotine significantly reduced RLS severity scores compared with placebo at 4.5 mg daily dose (Stiasny-Kolster et al 2002; Stiasny-Kolster, Kohnen, et al 2004). Further trials using rotigotine transdermal delivery system for RLS are underway. Apomorphine, a subcutaneously administered nonergot DA, has also been shown to be effective for symptoms of RLS used as an overnight infusion in severe cases (Reuter et al 1999). Sumanirole, a dual-acting DA, has been evaluated in a double-blind manner for the treatment of RLS but has been withdrawn from clinical development.

Other dopaminergic drugs reported to be of benefit in RLS include orphenadrine, piribedil, dihydroergocriptine, and amantadine (Henning et al 1999; Stiasny et al 2001; Chaudhuri 2003; DeKokker et al 2005). In future, decision of which DA to use will depend on licensing, cost of the DA, and the clinician's familiarity with the drug and side-effect profile, particularly the relative merits of using a nonergot versus an ergot agonist. Ergot agonists have been linked to a small risk of cardio-pleuro-pulmonary fibrosis, while nonergot agonists seem to have a slightly increased risk of inducing sudden sleep onset in susceptible patients. However, these observations were found only in PD patients and their relevance to RLS patients is unclear.

Levodopa Eight small-scale, double-blind and seven open-label studies have shown that levodopa in conjunction with a peripheral decarboxylase inhibitor (100 mg levodopa with 25 mg carbidopa or benserazide) is consistently effective for treatment of RLS symptoms (Ondo 2002; Allen et al 2003; Jobges et al 2004). However, the benefits of levodopa treatment are complicated by the emergence of treatment-related side effects such as rebound and augmentation.

a) *Rebound* (Atlas Task Force 1993; Chaudhuri 2004) represents re-emergence of RLS symptoms in the later part of the night or shortly after waking in the morning, and often necessitates the use of a second dose during the night, taken later at night, or alternatively the use of a slow-release formula. This phenomenon may occur due to the short half-life of levodopa.
b) *Augmentation* (Allen and Early 1996, 2001; Chaudhuri 2004) is a paradoxical effect associated with levodopa

(and DAs to a lesser extent), involving the loss of efficacy, the earlier onset of RLS symptoms before the scheduled dosage, a shorter latency to the onset of the RLS symptoms while at rest, involvement of other body parts (ie, arms), or an actual worsening in reported RLS symptoms. This phenomenon has been demonstrated in patients on long-term therapy as well as in some patients shortly after starting levodopa therapy, and the augmentation rate following chronic levodopa use has been reported to be as high as 85% (Chaudhuri 2004; DeKokker et al 2005).

DAs also appear to be superior to levodopa based on a handful of comparative studies. One study reported that pergolide was superior to levodopa in suppressing PLM (79% vs 45%), while another study reported a greater improvement in RLS severity scale following ropinirole (1.45 mg/day, 73.5%) compared with levodopa (190 mg/day, 33.5%) in hemodialysis patients with RLS (Allen et al 2003; Jobges et al 2004).

Controlled-release levodopa prolongs the therapeutic effect into the second half of the night and may, therefore, be suitable for reducing rebound. The role of standard levodopa used with an additional catechol-O-methyl-transferase (COMT) inhibitor such as entacapone, or Stalevo (a combined preparation of levodopa with entacapone), is being investigated and this strategy may prove particularly beneficial for patients who need to take treatment in an intermittent basis, such as during long flights.

Augmentation with DAs and management Augmentation, although uncommon, has been occasionally reported with the use of other DAs. Some claim that rates can be as high as 27% with pergolide but these symptoms are often mild and helped by an afternoon dose. Augmentation has been reported in up to 7% of patients on pramipexole and our observations suggest in about 2%–3% of cases on cabergoline (Atlas Task Force 1993; O'Keefe et al 1994; Kirsch et al 2002; DeKokker et al 2005). However, a recent trial by Stiasny-Kolster et al reports an augmentation rate of 9% at 1 year in those taking cabergoline (Stiasny-Kolster, Benes, et al 2004). Augmentation is also rarely seen with the use of ropinirole. An additional early afternoon dose is helpful, but in some patients the dose of the agonist needs to be increased to the full dose. If this fails, a switch to an alternative agonist or a nondopaminergic agent such as gabapentin needs to be considered.

Nondopaminergic drugs

Anti-epilepetic drugs

Gabapentin and carbamazepine have been most widely evaluated in open-label and double-blind studies. Recently, Garcia-Borreguero and colleagues reported the results of a double-blind, crossover, polysomnography-controlled study with gabapentin in 24 patients. Gabapentin at doses up to 1850 mg/day improved periodic limb movements, sleep architecture, and pain scores (Garcia-Borreguero et al 2003). At 6 weeks, no augmentation was observed. In a 4-week, open, randomized trial, gabapentin was also compared with the DA ropinirole and was as effective as ropinirole in symptom reduction. A double-blind, randomized, controlled trial of carbamazepine showed effective reduction in the number of episodes of restless legs per week, but PLMS was not consistently reduced (Jobges et al 2004). Levetiracetam and pregabaline have also been reported to be beneficial in RLS. We feel that gabapentin seems to be beneficial particularly in cases of RLS associated with painful sensations, and studies have reported that gabapentin may be beneficial for RLS associated with uremia and hemodialysis (Tse et al 2004; DeKokker et al 2005). One open trial has reported similar efficacy of gabapentin (800 mg daily) to ropinirole (0.8 mg daily) (Happe et al, 2003).

Opioids

In the 17th century, opiates were actually used in the treatment of conditions that closely resembled RLS. In double-blind, placebo-controlled trials, several workers have reported the beneficial effects of drugs such as oxycodone and propoxyphone in providing symptomatic relief of both RLS and PLMS (Allen et al 1992; Walters et al 1993; Henning et al 1999). Stronger opioids such as methadone, levorphanol, and sustained-release morphine should be reserved for the treatment of severe cases and for those not responding to dopaminergic treatment or in RLS associated with pain (asthenia crurum dolorosa) (Tse et al 2004). More recently, Ondo (2005) has reported the sustained efficacy and good tolerability of methadone (5–40 mg/day) in RLS patients who failed dopaminergic treatment, with a 75% reduction in symptoms and no augmentation between 4 and 44 months.

Benzodiazepines

A range of benzodiazepines has been used for RLS (clonazepam [0.5–4 mg], triazolam [0.125–0.5 mg], and

temazepam [15–30 mg]); clonazepam is the only benzodiazepine to be studied in controlled trials. Two double-blind, crossover studies involving only six patients reported contradictory results – either no or modest benefit in leg symptoms and sleep (Tse et al 2004). Overall, studies suggest that clonazepam can be helpful for treatment of RLS. An added benefit, relating specifically to clonazepam, is that it has also been successful in the treatment of related motor sleep disorders, such as rapid eye movement (REM) behavior disorders, which may coexist in patients suffering from RLS (Chaudhuri 2003). However, the confounding effect of benzodiazepines on sleep architecture, respiratory depression, and dependence are concerns, although in a single study conducted with patients with nocturnal respiratory disturbances, benzodiazepines were well tolerated (Stisany et al 2001; Tse et al 2004). Additional (to levodopa or DAs) dosing of a benzodiazepine may help when insomnia is associated with RLS. The role of modern sedatives such as zolpidem, zopiclone, and zaleplon in the treatment of RLS has not been established to date.

Adrenergic drugs

Clonidine, a centrally acting alpha adrenergic blocker, suppresses noradrenergic activity and at doses of 0.15–0.9 mg/day can be effective for idiopathic and uremic RLS cases (Tse et al 2004). One randomized, double-blind, placebo-controlled trial of clonidine at a mean dose of 0.5 mg/day showed greater subjective improvement of sensory symptoms and motor restlessness, and faster sleep onset, compared with placebo but no effect on PLM (Wagner et al 1996). For patients, whose symptoms are most prominent in the period just before sleep onset, clonidine might be especially useful. However, use of clonidine for RLS is complicated by its adverse effect profile, which aggravates depression and insomnia and may cause hypertensive crises with abrupt discontinuation (Tse et al 2004). Baclofen has also been studied but was shown to increase PLMS (Tse et al 2004).

Iron

Iron deficiency is implicated in the causation of RLS and an open-label trial showed that oral iron (200 mg thrice daily) was beneficial in those with low ferritin levels (< 18 ng/mL) (O'Keefe et al 1994; Tse et al 2004). However, a double-blind, placebo-controlled trial in RLS patients with normal or high ferritin levels reported no benefit with oral iron therapy (Davis et al 2000). In those with normal serum iron levels, intravenous iron improved symptoms in 21 out of 22 patients (Tse et al 2004). We feel that iron administration is likely to be helpful for iron-deficient patients with RLS, and we would use oral iron supplementation in patients with serum ferritin levels below 45–50 μg/dL. Oral treatment may take several months to be effective, but intravenous iron treatment may be poorly tolerated and is not recommended for general use (Tse et al 2004). A double-blind trial investigating the safety and efficacy of intravenous iron in the treatment of RLS is underway in the USA.

Other treatment issues

Therapy of RLS in children, pregnant women, and the elderly is less well understood and rather poorly documented and needs further large-scale trials. Many of the drugs are not safe to use in pregnancy.

Secondary RLS

The primary causes of secondary RLS such as iron deficiency, uremia, or neuropathy need to be investigated and treated. Most drugs listed above work in secondary RLS and evidence suggests that gabapentin or clonidine may have a good effect in RLS related to renal failure, while opioids are useful in pain-dominant secondary RLS. RLS and PLM occur in PD (Ondo et al 2002), and in such situations patients may need targeted night-time treatment for RLS with long-acting dopaminergic agents such as cabergoline or pramipexole (Appiah-Kubi et al 2002). Okun et al (2005) have reported resolution of RLS symptoms in a patient with dystonia treated by deep-brain stimulation of the internal globus pallidus.

Conclusions

RLS and PLM are common problems and in most patients may not require pharmacological treatment at diagnosis, but correct diagnosis, counselling, and reassurance are essential. Sadly, often these do not occur, causing patients and caregivers great distress due to regular sleepless nights and limb discomfort. The diagnosis of RLS can be made in the clinic in a matter of minutes without any sophisticated tests. The availability of effective treatment, which may have a dramatic effect on symptoms and quality of life, means physicians must be aware of the condition so that RLS no longer remains the "commonest condition you have never heard of".

References

Abetz L, Allen R, Follet A, et al. 2004. Evaluating the quality of life of patients with restless legs syndrome. *Clin Ther*, 26:925–35.

Allen RP, Earley CJ. 1996. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep*, 19:205–13.

Allen RP, Kaplan PW, Buchholz DW et al. 1992. Double blinded, placebo controlled comparison of high dose propoxyphene and moderate dose carbidopa/levodopa for the treatment of periodic limb movements of sleep. *Sleep Res*, 21:166.

Allen RP, Earley CJ. 2001. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol*, 18:128–47.

Allen RP, Picchietti D, Hening WA, et al. 2003. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*, 4:101–19.

Appiah-Kubi L, Pal S, Chaudhuri KR. 2002. Restless legs syndrome (RLS), Parkinson's disease and sustained dopaminergic therapy for RLS. *Sleep Med*, 3(Suppl):S51–55.

Appiah-Kubi L, Nisbet A, Burn DJ, et al. 2003. Use and tolerability of cabergoline in young and older people with Parkinson's disease: a multicentre observational study. *J Applied Research*, 3:356–62.

Atlas Task Force of the American Sleep Disorders Association. 1993. Recording and scoring of leg movements. *Sleep*, 16:748–59.

Chaudhuri KR. 2004. Augmentation and rebound. In Chaudhuri KR, Odin P, Olanow CW (eds). Restless legs syndrome. London and New York: Taylor & Francis and Thomson Publishing Services. p 109–12.

Chaudhuri KR. 2003. The restless legs syndrome. Time to recognize a very common movement disorder. *Prac Neurol*, 3:204–13.

Chaudhuri KR, Appiah-Kubi L, Trenkwalder C. 2001. Restless legs syndrome. *J Neurol Neurosurg Psychiatry*, 71:143–6.

Chaudhuri KR, Forbes A, Grosset AL, et al. 2004. Diagnosing restless legs syndrome (RLS) in primary care. *Curr Med Res Opin*, 20: 1785–95.

Corrigan MH, Denahan AQ, Wright CE, et al. 2000. Comparison of pramipexole, fluoxetine and placebo in patients with major depression. *Depress Anxiety*, 11:58–65.

Davis BJ, Rajput A, Rajput ML, et al. 2000. A randomized, double blind placebo controlled trial of iron in restless legs syndrome. *Eur Neurol*, 43:70–5.

DeKokker A, Whitehead H, Chaudhuri KR. 2005. Therapeutic strategies in restless legs syndrome. *Future Prescriber*, 6:5–10.

Earley CJ, Yaffee JB, Allen RP. 1998. Randomized, double blind placebo controlled trial of pergolide in restless legs syndrome. *Neurology*, 51:1599–602.

Ekbom KA. 1945. Restless legs syndrome. *Acta Med Scand*, 158:4–122.

Garcia-Borreguero D, Odin P, Serrano C. 2003. Restless legs syndrome and PD: a review of the evidence for a possible association. *Neurology*, 61(Suppl):S49–55.

Goldberg J, Burdick KE, Endick CJ. 2004.Preliminary randomized placebo-controlled trial of pramipexole added to mood stabilizers for treatment resistant bipolar depression. *Am J Psychiatry*, 161:564–6.

Goodman JDS, Brodie C, Ayida GA. 1988. Restless legs syndrome in pregnancy. *BMJ*, 297:1101–2.

Happe S, Sauter C, Klosch G et al. 2003. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology*, 48:82–6.

Henning W, Allen R, Earley C, et al. 1999. The treatment of restless legs syndrome and periodic limb movement disorder. *Sleep*, 22:970–99.

Jobges M, Odin P, Chaudhuri KR. 2004. Epidemiology. In Chaudhuri KR, Odin P, Olanow CW (eds). Restless legs syndrome. London and New York: Taylor & Francis and Thomson Publishing Services. p 21–36.

Kirsch J, Abetz L, Allen R, et al. 2002. The impact of restless legs syndrome (RLS) on quality of life (QoL) [abstract]. *Eur J Neurol*, 9(Suppl 2):198 [P3136].

Lugaresi E, Coccagna G, Tassinari CA, et al. 1965. Polygraphic data on motor phenomena in the restless legs syndrome. *Riv Neurol*, 35: 550–61.

Maniak S, Kabakei K, Pichler I, et al. 2004. Restless legs syndrome (RLS) in a large family (Family LA) with *Parkin*-associated Parkinson's disease (PD). *Mov Disord*, 19(Suppl):S354.

Montplaisir J, Boucher S, Poirier G, et al. 1997. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord*, 12:61–5.

Montplaisir J, Denesle R, Petit D. 2000. Pramipexole in the treatment of restless legs syndrome: a follow up study. *Eur J Neurol*, 7(Suppl 1): S27–31.

Montplaisir J, Nicolas A, Denesle R, et al. 1999. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology*, 52:938–43.

Mrowka M, Chaudhuri KR, Odin P. 2004. Pathophysiology of restless legs syndrome. In Chaudhuri KR, Odin P, Olanow CW (eds). Restless legs syndrome. London and New York: Taylor & Francis and Thomson Publishing Services. p 37–48.

Oertel W, Stiasny-Kolster K. 2005. Effective treatment of restless legs syndrome (RLS) with pramiexole: results of a 6 week, multi-centre, double blind and placebo controlled study [abstract]. *Eur J Neurology*, 12(Suppl 2):P2205.

O'Keefe ST, Gavin K, Lavan JN. 1994. Iron status and restless legs syndrome in the elderly. *Age Ageing*, 23:200–3.

Okun MS, Fernandez HH, Foote KD. 2005. Deep brain stimulation of the globus pallidus internus treats restless legs associated with dystonia. *Mov Disord*, 20:500–1.

Ondo WG. 2002. Epidemiology of restless legs syndrome. *Sleep Med*, 3(Suppl):S13–15.

Ondo WG. 2005. Methadone for refarctory restless legs syndrome. *Mov Disord*, 20:345–8.

Ondo WG, Vuong KD, Jankovic J. 2002. Exploring the relationship between Parkinson disease and restless legs syndrome. *Arch Neurol*, 59: 421–4.

Partinen M, Hirvonen K, Alakuijala A, et al. 2004. Rapid relief from RLS symptoms with pramipexole: results of a large polysomnographic study [abstract]. *Neurology*, 62(Suppl 5):LBS.002.

Reuter I, Ellis CM, Chaudhuri KR. 1999. Nocturnal subcutaneous apomorphine infusion in Parkinson's Disease and restless legs syndrome. *Acta Neurol Scand*, 100:163–7.

Rothdach A J, Trenkwalder C, Haberstock J, et al. 2000. Prevalence and risk factors of RLS in an elderly population. The MEMO study. *Neurology*, 54:1064–8.

Rutkove SB, Matheson JK, Logigian EL. 1996. Restless legs syndrome in patients with polyneuropathy. *Muscle Nerve*, 19:670–2.

Rye DB. 2004. Parkinson's disease and RLS: the dopaminergic bridge. *Sleep Med*, 5:317–28.

Stiasny K, Moller JC, Bodenschartz R, et al. 2002. Rotigotine CDS (Constant Delivery System) in the treatment of moderate to advanced stages of restless legs syndrome – a double blind placebo-controlled study [abstract]. *Mov Disord*, 17(Suppl 5):S241.

Stiasny K, Wetter TC, Trenkwalder C, et al. 2001. Restless legs syndrome and its treatment by dopamine agonists. *Parkinsonism and Relat Disord*, 7:21–5.

Stiasny-Kolster K, Benes H, Peglau I, et al. 2004. Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology*, 63: 2272–9.

Stiasny-Kolster K, Kohnen R, Schollmayer E, et al. 2004. The 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. *Mov Disord*, 19:1432–8.

Symonds CP. 1953. Nocturnal myoclonus. *J Neurol Neurosurg Psychiatry*, 16:166–71.

Trenkwalder C, Garcia-Borreguero D, Montagna P, et al. 2004. Therapy with ropinirole; efficacy and tolerability in RLS. TREAT RLS 1 Study Group. *J Neurol Neurosurg Psychiatry*, 75:92–7.

Trenkwalder C, Hundemer HP, Lledo A, et al. PEARLS Study Group. 2004. Efficacy of pergolide intreatment of restless legs syndrome: the PEARLS study. *Neurology*, 62:1391–7.

Tse W, Koller W, Olanow CW. 2004. Restless legs syndrome: differential diagnosis and treatment. In Chaudhuri KR, Odin P, Olanow CW (eds). Restless legs syndrome. London and New York: Taylor & Francis and Thomson Publishing Services. p 85–108.

Wagner M, Walters AS, Coleman RG et al. 1996. Randomized double blind study of clonidine in restless legs syndrome. *Sleep*, 19:52–8

Walters AS, Wagner MI, Henning WA et al. 1993. Successful treatment of the idiopathic RLS in a randomized double blind trial of oxycodone versus placebo. *Sleep*, 16:327–32.

Walters AS. 1995. Toward a better definition of restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord*, 10:634–42.

Walters AS, Ondo WG, Dreykluft T, et al. on behalf of the TREAT RLS 2 (Therapy with Ropinirole: Efficacy And Tolerability in RLS 2) Study Group. 2004. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: A 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord*, 19:1414–23.

Willis T. 1672. De anima brutorum. London: Wells and Scott.

Yoakum R. 1994. Night walkers: do your legs seem to have a life of their own? Your torment has a name. *Modern Maturity*, 55:82–4.