Scientific Review

Restless Legs Syndrome

FE Glasauer*¹

¹*Department of Neurosurgery, State University of NY at Buffalo, School of Medicine & Biomedical Sciences, Buffalo, New York, USA*

Restless Legs Syndrome (RLS) is a well-defined symptom complex and is frequently associated with sleep disturbance and a recognized family history. It occurs either as idiopathic RLS or in association with many medical, neurological or vascular disorders. The neurological examination and routine investigations in idiopathic RLS are normal. Polysomnography supports the diagnosis of RLS by documenting the associated sleep disturbances and periodic limb movements in sleep (PLMS). Although MRI studies disclose no intracerebral lesions, recent Positron Emission Tomography (PET) and single photon emission computed tomography (SPECT) studies point to some involvement of the basal and red nuclei and the cerebellum. No definitive etiology is known for this condition, but several pathophysiological mechanisms have been proposed. There is supportive evidence that RLS is a Central Nervous System (CNS) dysfunction, suggesting widespread involvement of the descending dopaminergic (DA) pathways, possibly originating in the diencephalon or upper brainstem. This is corroborated by the successful treatment of RLS with DA agents, sedatives, and neurotransmitters. However, RLS can also occur with spinal disorders and spinal cord lesions implying the existence of a spinal generator. The incidence of RLS in pregnancy is well known and its association with vascular disorders supports another mechanism in some patients. The primary treatment of RLS is largely symptomatic and quite effective with DA agents, DA agonists, opioids and other neurotransmitters. The treatment of RLS associated with various diseases is aimed at the correction of the underlying pathological or deficiency states. Antidepressant medications frequently precipitate or worsen the condition of RLS.

Spinal Cord (2001) **39**, 125–133

Keywords: RLS; PLMS; sleep disorders; DA agents; neurotransmitters

Frequency and onset

The syndrome of restless legs (RLS) was probably first described by Thomas Willis in 1672.¹ Ekbom, however, described the condition extensively and named it 'restless legs syndrome'.² Therefore, it is sometimes referred to as 'Ekbom syndrome'.³

RLS occurs either as idiopathic or in association with many medical conditions. It is not uncommon, afflicting 1% to 15% of the population and is equally distributed between men and women.^{4,5} It is, however, more prevalent in older people and in them affects women about twice as often as men and also manifests more severe symptoms.^{6,7} RLS is the fourth leading cause of insomnia and is diagnosed in 10% to 20% of patients suffering from that condition.⁸ RLS may be static, but typically has a chronic and progressive course. Occasionally, remis-

sions may occur in which the symptoms decrease significantly or cease for a period of time but more often symptoms remain and worsen.^{4,9,10} The incidence of RLS in pregnancy, usually in the second half of gestation, can be as high as 11% to 27%.^{5,11,12} The symptoms often appear initially during pregnancy and after delivery may disappear for many years.^{1,4}

The onset of idiopathic RLS begins at any age, even in infancy and early childhood.^{13,14} In a study by Walters *et al*,⁹ a third of the patients experienced their first symptoms before the age of 20. Frequent misdiagnoses in children and young adults are 'growing pains', attention deficit and hyperactivity disorders.^{13,15} Although RLS affects millions of people, it is rarely diagnosed by clinicians and most healthcare providers do not know of its existence.^{16,17} Some suggest that Caucasians and Asians are at higher risk, although little data about racial prevalence are available.¹⁸

*Correspondence: FE Glasauer, c/o State University of New York at Buffalo, Neurosurgery Editorial Office, 3 Gates Circle, Buffalo, New York, 14209-1194, USA

Diagnostic features

The diagnosis of RLS remains a clinical one based on subjective complaints. Therefore, the international RLS Study Group¹⁴ developed and defined as minimal criteria for diagnosis of RLS the following four features.

1. Paresthesias

These abnormal sensations are variably described as tingling, burning, crawling, aching, grabbing or painful and are commonly associated with an urge to move. Some patients report an urge or inner feeling of restlessness without any clear precipitating sensations, while others report an indescribable uncomfortable feeling in their extremities or merely a need to move the limbs.^{11,14,19} The paresthesias affect primarily the legs, especially the calves, and may be bilateral or unilateral. About 20% to 30% of patients experience similar sensations in the arms but rarely in the trunk or elsewhere in the body.⁴

2. Motor restlessness

This is defined as any activity that can relieve the urge to move. Patients typically walk around or pace the floor. A wide variety of movements may be tried for relief such as rocking, stretching and flexing the legs, jiggling while seated, deep knee bends, riding an exercise bicycle or tossing and turning in bed. Some patients describe benefits simply by standing. These varied movements are under voluntary control and although they can be suppressed by the patients, this may then greatly increase their discomfort. As an alternative, some patients resort to rubbing the leg or foot or taking hot or cold baths as a counter-stimulus to the leg sensations.^{4,14,20,21}

3. Worsening of symptoms with relaxation

A distinctive and unusual characteristic of RLS is that the sensory and motor symptoms are evoked by rest, either during quiet wakefulness or on attempts to sleep. Symptoms are worse when lying down or sitting with at least partial and temporary relief by activity.^{4,14,18}

4. Variability of symptoms

Over the course of the day/night cycle, symptoms are worse in the evening and early in the night. Patients are less bothered during the daytime and often obtain some relief near dawn.

Associated features

1. Sleep disturbance

Patients primarily have difficulty getting to sleep and staying asleep. Their periodic limb movements in sleep

(PLMS) can arouse and awaken them.³ In severe cases patients obtain only a few hours of sleep at night followed by excessive daytime sleepiness. PLMS and sensory symptoms in RLS are influenced by a circadian rhythm that may be contributing to nighttime worsening.²²

2. PLMS

These are repetitive, often stereotyped movements that typically recur at intervals of 15 to 40 s during non-REM sleep. They usually involve the legs, but may sometimes involve the arms. Involuntary limb movements may also occur while awake and at rest. Synonyms for these include resting 'dyskinesias while awake' (DWA). Between 70% to 90% of patients with RLS will have PLMS on polysomnographic studies and approximately 1/3 of those with PLMS will have RLS as well.¹ PLMS are sometimes absent in patients with idiopathic RLS and similarly PLMS may occur independently of RLS.^{4,14}

3. Dyskinesia

This occurs while awake and almost exclusively at rest. These are typically brisk movements commonly occurring in the legs; they may occur at random, periodically, or in clusters. They may take variable forms but most characteristically they are flexion jerks.¹⁴ According to Kuny,²³ RLS patients display a 'depressive-anxiety, hypochondric expression'.

4. Family history

Although idiopathic RLS can occur sporadically, a family history suggestive of autosomal dominant inheritance is found in 25% to 60% of patients.^{9,14,17} In contrast, only 13% of the secondary RLS patients have a positive family history.^{18,24} Genetic studies are currently underway. Using DNA mapping techniques, preliminary linkage studies reported a possible candidate gene locus for RLS.¹

Trenkwalder *et al*¹⁰ described a studied kindred of familial RLS with 20 affected members investigated in four generations. All patients showed sensory symptoms of their legs and worsening of symptoms with increasing age. The mean age of onset fell from 51.5 years in the second generation to 19.8 years in the fourth generation. Winkelmann *et al*²⁵ analysed 300 patients from 16 families and found 42.3% of patients with idiopathic and 11.7% with uremic RLS as definite hereditary RLS. They also found that patients with familial RLS had their onset of symptoms at a younger age and significant worsening of symptoms during pregnancy. Walters *et al*²⁶ studied a mother and her three children, as well as a 26-year-old patient from a second family, with typical signs of RLS and emphasized the occurrence in childhood and adolescence. One of the largest studies affected 81 family members and showed a preponderance of females

(1.4:1) and variations in penetrance and anticipation, which suggested possible genetic heterogeneity.²⁷ Other studies of affected family members with RLS, some of them spanning three to five generations, have been reported.^{28,29}

Potential underlying causes

RLS is found to be associated with a wide variety of conditions which include medical, neurological, vascular disorders and also exogenous substances. The high incidence of RLS in the second half of pregnancy has already been pointed out. Although the majority of suggested causes are from anecdotal reports, several medical conditions have been well studied.

Among the medical disorders and the metabolic abnormalities are Mg, Fe, Folate, Vitamin A and Vitamin B deficiencies, blood dyscrasias and all anemias. Machtey³⁰ raised the question of regarding RLS as a metabolic abnormality of primary or secondary type, mostly affecting the elderly.

Twenty-five per cent of patients with iron deficiency anemia have symptoms of RLS.³¹ Abnormally low serum iron (62.5%) and iron saturation (77%) levels were demonstrated in a relatively large population of patients with RLS. These measurements may reflect an as yet unidentified defect of iron transport or metabolism.³² Whether the iron deficiency is primarily responsible for causing RLS or whether it simply aggravates the symptoms has not been determined.¹⁷ RLS patients are also found to have fewer symptoms if their ferritin levels are greater than 50 mcg/l.³⁵ Iron deficiency may impair the normal production of dopamine by interfering with the function of an iron containing protein in D2 receptors.

The high frequency (15% to 40%) of RLS in patients with uremia and renal failure on dialysis is well known.^{8,14} The prevalence in patients with endstage renal disease is equally high (20% to 40%).³⁴ After successful kidney transplantation, RLS can resolve.¹ Collado-Seidel *et al*,³⁵ in a study of uremic patients with RLS found significantly lower intact parathyroid hormone level secretions.

Symptoms of RLS were significantly prevalent in patients with fibromyalgia (31%) and in rheumatoid arthritis (15%).^{36,37} Other medical conditions in which symptoms of RLS are observed are diabetes, chronic respiratory insufficiency, post-gastrectomy states, Sjogren's syndrome, hypothyroidism, porphyria and carcinoma among many others.^{1,11,38} Familial amyloidosis resulting in peripheral neuropathy has also been thought to be associated.³⁹

Neurological disorders in which RLS is frequently observed include chronic myelopathy; diabetic, alcoholic, and chronic idiopathic polyneuropathy; Parkinson's disease and REM behavior disorders.^{5,11} In a group of patients evaluated for polyneuropathy, 5% had symptoms of RLS. These patients had mild predominantly sensory polyneuropathy.⁴⁰ RLS seems not uncommon in cryoglobulinemic neuropathy where it is

significantly associated with symmetrical sensory polyneuropathy.⁴¹ A patient with polyneuropathy secondary to Lyme disease developed RLS; the latter symptoms improved after treatment with antibiotics alone.⁴⁰ A more unusual case of RLS triggered by lumbosacral radiculopathy was reported by Walters *et al*.⁴²

Lee *et al*⁴³ discussed sleep-related PLM associated with spinal cord lesions. Glasauer and Egnatchik⁴⁴ reported a patient presenting with symptoms of RLS and considered the presence of a foramen magnum meningioma as its etiology. Hemmer *et al*⁴⁵ reported the onset of RLS following thoracic myelitis due to neuro-borreliosis. In this case the symptoms of RLS developed during the period of recovery. Another reported possible etiology for RLS is saphenous nerve compression.⁴⁶ Gemignani *et al*⁴⁷ found an unexpectedly high incidence of RLS (37%) in patients with Charcot-Marie-Tooth disease, type 2. RLS was also found in 45% of patients with spinocerebellar ataxia, type 3 (CSC 3), but rarely in patients with genetically different types of autosomal dominant cerebellar ataxia.⁴⁸

In a recent study by Oboler *et al*,⁴⁹ peripheral vascular disease, hypocalcemia and coronary artery disease were all found to have significantly increased odds ratios in patients with RLS. Other vascular disorders included venous insufficiency and peripheral micro-embolism.⁵⁰ A higher incidence of RLS was also found in patients with both saphenous and non-truncal varicose vein disease.⁵¹ In a study of cardiac patients, 6% reported moderate to severe RLS symptomatology.⁵²

Although the adverse effect of caffeine and alcohol on RLS is well known, medications such as lithium, neuroleptics and others have a similar effect. An extensive list of conditions associated with RLS-PLMS is reported by O'Keeffe¹¹ and others.^{19,53}

Neurological and laboratory findings

The neurological examination in patients with idiopathic RLS is usually normal.^{4,19} Electromyogram (EMG) and nerve conduction studies may document any accompanying peripheral neuropathy or radiculopathy.^{10,14} Electrophysiological testing in primary RLS patients suggests that polyneuropathy is of an axonal nature.⁴⁰ Based on morphometric analysis of sural nerves which showed a significant reduction in myelinated fiber density, Iannaccone *et al*⁵⁴ suggested that axonal neuropathy is often present in patients with primary RLS. Trenkwalder *et al*⁵⁵ observed that electromyographically measured muscle contractions were preceded by sensory discomfort in all patients with RLS. No difference in the recorded patterns was observed between patients with idiopathic and uremic RLS. EMG and recruitment pattern and the probable persistence during sleep as PLMS supported their hypothesis of a propriospinal origin of these involuntary jerks. Doppler sonography of the legs should be performed to identify possible underlying disorders.³

Polysomnography, especially all night studies, supports the diagnosis of RLS by documenting the sleep disturbances and PLMS by the K complex. The K complex is the characteristic wave of stage II sleep and occurs with the leg jerk in PLMS, roughly assuming the time course of cyclical, alternating pattern.^{11,53,56} The relationship of RLS and the occurrences of K complexes and alpha activity have been described.⁵⁷ There is also an important positive correlation between PLM and K complexes in spinal cord injured and non-paraplegic subjects.⁵⁸ All night polysomnographic findings showed that increasing sleep latency, number of awakenings and decreasing sleep efficiency all were associated with worsening of symptoms.^{17,59} Sleep quality was estimated to be worse in uremic RLS, suggesting that uremia itself worsens the motor symptoms of RLS, probably as a result of increased excitability.⁶⁰

Trenkwalder *et al.*²² found the circadian rhythm of the RLS of particular interest because DA drugs play a major role in its treatment. Because human studies also show evidence for circadian variation in DA and related noradrenergic neurotransmission, it is possible that the circadian factor in RLS is related to changes in catecholamine activity. It is further intriguing that circadian variations in the activity of these neurotransmitters influence melatonin synthesis, which may be important for sleep regulation. Based on the striking response of RLS patients to DA agents and the suggestion that DA plays a key role in the pathogenesis of this condition, these authors⁶¹ concluded that this response suggests that any DA deficit is likely to be presynaptic, but possibly 'upstream' from dopa-decarboxylase. They have not investigated postsynaptic receptors in RLS.

Latency of the soleus H reflex and the duration and onset latency of the direct and indirect blink reflex responses studied in idiopathic RLS patients were all normal. MRI studies showed no structural lesions in patients with idiopathic RLS.⁶² However, in patients with Multiple Sclerosis (MS) who also suffered from RLS, higher MRI lesion loads were found in infratentorial regions compared to patients without RLS.⁶³

Similarly, electron microscopy showed no structural abnormalities in peripheral nerve endings.⁶⁴ Adler *et al.*⁶⁵ found olfactory function to be normal in patients with idiopathic RLS but significantly reduced in patients with Parkinson's disease. Prolactin and cortisol plasma levels were normal in RLS patients that were never medicated suggesting a normal circadian rhythm.⁶⁶ Somatosensory and brainstem auditory evoked responses were normal. Tergau *et al.*⁶⁷ demonstrated significantly reduced intracortical inhibition for both foot and hand muscles by paired transcranial magnetic stimulation, suggesting that the entire motor cortex is disinhibited in RLS.

SPECT studies support the association between pain and decreased regional cerebral blood flow (rCBF) to the caudate nucleus as reported in fibromyalgia syndrome. The increase in anterior

cingulate rCBF with increasing pain also corroborates the findings of increased thalamic rCBF during pain stimulation.⁶⁸ Recent functional MRI and PET scanning have drawn attention to the possible role of upper brainstem, diencephalon, red nucleus and cerebellum in the pathogenesis of RLS. Patients with RLS show normal ¹⁸F-dopa striatal (putamen) uptake, but D2 binding is mildly (10%) reduced in the putamen and caudate nucleus.^{1,3,17,61,67,69} A SPECT study with I-123 IBZM, a specific D2-receptor ligand, showed a decrease in D2-receptor binding sites in the striatum of patients with RLS.^{70,71} Bucher *et al.*,⁷² using high-resolution functional MRI, localized cerebral generators associated with sensory leg discomfort (SLD) in RLS. Patients with SLD showed significant activation in the cerebellum bilaterally and in the contralateral thalamus. The combined SLD/PLMS condition was associated with bilateral cerebellar and red nucleus activation.

Possible etiologies

The exact cause of RLS is not known but the condition is characterized by no known abnormality of either muscle or peripheral nerves.⁵ However, there is supportive evidence that RLS is a CNS dysfunction and probably more than one mechanism is implicated.

RLS is considered a disorder of the central sensory-motor integration and the pathophysiological mechanism suggests an imbalance between the serotonergic and dopaminergic pathways involving the descending dopaminergic system.^{24,53,73} However, the occurrence of RLS and PLMS in numerous conditions indicates that more than one neurotransmitter and pathway may be involved. The popular hypothesis has been that the dopaminergic system is the primary site of dysfunction and the opioid system is secondarily affected.^{53,74} Studies also have implicated a possible underactivity of the serotonin and γ -aminobutyric acid neurotransmitter systems.¹⁹

Results of SPECT studies have suggested a deficiency of DA D₂ receptors.¹⁹ However, the involvement of the DA system, like postsynaptic striatal D2 receptors, in RLS and SCA3 is a matter of debate.⁴⁸ DA receptors have a diurnal variation paralleling that of the RLS/PLMS syndrome.⁵³ Exacerbation of RLS in the evening when DA activity is at its lowest level, and exacerbation with iron deficiency, are further evidence in support of impaired DA transmission in RLS.^{17,57} An increase in the symptoms and the more frequent occurrence of RLS in older people also may reflect a decrease of DA activity in old age.²¹ Although normal somatosensory and brainstem auditory evoked responses in patients suffering from RLS provide no evidence of an afferent sensory disturbance, they support the hypothesis that RLS and PLMS are a reflection of the suppression of descending inhibitory influences on pyramidal tract function. Others suggest a disturbance of the inhibitory reticulospinal pathways.¹¹

The locus of involuntary motor activity in RLS is likely to be subcortical.² A good location for this modulating center would be in the peri-aqueductal gray matter of the midbrain/diencephalon region. It provides the necessary connection to the reticular activating system, it is near the extrapyramidal system, the hypothalamus, and the peduncles for motor transmission and near the sensory relay pathways to account for dysesthesias.⁵³

Electrophysiologic studies and findings of reduced intracortical inhibition, however, suggest that the underlying abnormality may be at, or rostral to, the pons.^{11,67} MRI and PET scanning have drawn attention to the possible role of the upper brainstem and diencephalon.¹⁷ Localization of the RLS induced involuntary movements and their distribution patterns favor a brainstem or spinal cord origin of movements. The findings by Bucher *et al*⁷² indicated that the red nucleus and brainstem are involved in the generation of PLM in patients with RLS. The brainstem activation may reflect the disinhibition effects of the reticular formation on spinal pathways. They therefore concluded that reticular structures in the brainstem appear to be the primary generators of RL symptomatology. Based on electrophysiological studies, Trenkwalder *et al*⁵⁵ suggested a brainstem disinhibition phenomenon as the pathophysiological mechanism that activates a spinal generator. Other investigators evoke a diencephalic-spinal DA system.¹⁷ As the face is not involved in RLS, the generator is likely below the level of the facial nucleus in the brainstem.¹

Another hypothesis is that RLS is a spinal or propriospinal rather than a basal ganglia disease. This hypothesis is supported by several observations. DA containing neurons have been demonstrated in the spinal cord.^{40,75,76} DA receptors have a diurnal variation paralleling that of RLS-PMLS syndrome. Levels of free DA and homovanillic acid (HVA) were found elevated in the spinal fluid of a patient with RLS-PMLS, indicating a decreased turnover of DA metabolites.⁵³ DA may help blunt the effect of nociceptive impulses generated by partial deafferentation onto the motor neuron pool. This could occur because: (1) DA itself is deficient in the spinal cord and is being replaced; or (2) DA has some antinociceptive properties.⁴⁰

RLS occurring after myelitis also supports the hypothesis that a lesion of the spinal cord could generate RLS. Hemmer *et al*⁴⁵ speculated that the spinal cord lesion led to an uncovering of a spinal generator triggering the irresistible leg movements. This process may be modulated by abnormal periphery sensory input from, for instance, a peripheral neuropathy.²⁰ The effect of treatment with DA drugs may be due to a DA influence on the spinal generator rather than on basal ganglion circuits.⁶¹ Recent studies provide evidence of enhanced excitability of the spinal cord mechanisms, facilitated by the loss of supraspinal inhibition, together with the

pattern of muscle activation in patients with RLS-PLMS, suggests a propriospinal mechanism.¹⁷ It has been indicated that in patients with PLMS and associated spinal cord lesions the DA system suppresses the activity of the disinhibited lumbosacral generator.⁴³ Additionally, the occurrence of PLMS in subjects with spinal cord injury, including complete thoracic transection, casts doubt on its central origin.¹⁷ In a study of polio survivors by Bruno,⁷⁷ nearly two-thirds of the patients reported abnormal movements in sleep, presenting poliovirus-induced damage to the spinal cord and brain as the possible cause. The manifestation of abnormal movements following a spinal cord injury, multiple sclerosis or spondylosis suggests that the spinal cord can contribute to the genesis of PLMS due to inhibition or release of segments below the lesion.⁶³ The DA inhibitory role on abnormal motor activity is impaired by the spinal cord lesion and thus might be restored by treatment with DA agents.⁵⁸ The decrease in PLM after physical activity can be due to release of β -endorphins suggesting participation of the opioid system.⁷⁸ Physical activity by spinal cord injured patients can help minimize sleep complaints, in particular those related to leg movements.⁷⁹

The association of RLS with the later stages of pregnancy, with venous insufficiency, peripheral embolism, and relief of the symptoms by vasodilators provide support for yet another mechanism in some patients.¹¹ The vascular theory postulates an impairment in the local circulation, causing ischemia or a build-up of toxic metabolites. Another suggestion considers microcirculatory changes in the small superficial veins as cause of the restless sensations by stimulation of afferent nerve fibers.⁶ RLS in patients with both saphenous and non-truncal varicose vein disease, responds frequently and rapidly to scleral therapy.⁵¹

The various suggested etiologies reviewed above do not solve the problem of RLS but rather emphasize the need for more clinical and basic research to provide new insights into the pathophysiology of RLS.

Treatment

Treatment of RLS can be broken down into several categories: (a) primary treatment to reduce subjective symptoms; (b) specific treatment directed to an underlying cause; (c) efficacy and usefulness of secondary treatment; and (d) ancillary treatments that are non pharmacological modes and may assist therapy.

Primary treatment

Drug therapy for idiopathic RLS is largely symptomatic and must be adapted to the individual patient.^{1,20} In severe cases a combination of medications may be beneficial. However, the placebo effect in RLS should not be ignored.⁸⁰

Dopaminergic agents These improve all features of RLS including subjective discomfort, dyskinesias while awake, and sleep quality in PLMS. DA precursors are most often used, either as regular L-dopa/carbidopa (Sinemet) or sustained release (SR) compounds, (Sinemet-CR). A combination therapy of standard and SR-L-Dopa was found more efficient in maintaining sleep and improve symptoms.^{81,82} This has also been found a safe and effective therapy for patients in endstage renal disease with RLS.^{18,34,83} Various approaches to the treatment of idiopathic and uremic RLS are reviewed by Trenkwalder *et al*⁸⁴ and the practical management of therapy outlined. Janzen *et al*³⁴ stated that peak plasma levodopa concentrations are achieved in 15–60 min from the time of administration.

Allen and Earley⁸⁵ emphasized the side effects of levo-dopa: the problem with morning end-of-dose rebound that increases leg movements and the markedly augmented RL symptoms occurring in the afternoon and evening prior to taking the next nightly dose. They considered augmentation to be the major adverse effect of treatment and can be even greater for patients with severe RLS. Others also reported on the rebound phenomenon of levo-dopa.^{4,34,53,86,87}

Two DA agonists, bromocriptine (Parlodel), and pergolide (Permax), taken in divided doses before bedtime, have been successfully tried.^{4,5,11,40,53,88} Pergolide is a potent, long-acting ergoline compound with D1 and D2 receptor agonist properties. It has been found superior to L-Dopa in the treatment of RLS and PLMS including its use in uremic patients.^{89–92} A side effect of pergolide, however, is a significant symptomatic hypotension; therefore the drug must be increased carefully.¹⁸ A combination of pergolide with domperidone (Motilium) provides a well-tolerated and effective treatment of sensorimotor symptoms and sleep disorder in patients with primary RLS.^{93–96} Their mean and maximal daily maintenance doses are comparatively low and the augmentation effects mild.^{97,98}

Pramipexole (Mirapex), a full D3-receptor agonist, dramatically reduces PLMS, alleviates leg discomfort at bedtime and during the night and is the most potent therapeutic agent tested for RLS.^{71,99,100} A preliminary report on the use of ropinirole (Requip), a non-ergoline DA agonist with relative greater D3 and D4 affinity than pergolide, also appears promising.¹⁰¹

Benzodiazepines These sedative medications are useful for treatment of both RLS and PLMS. Their major effect is in improving the quality of sleep. Clonazepam (Klonopin) is the more favored medication, but temazepam (Restoril) and triazolam (Halcion) are also being used.^{4,11,53,56,102}

Opioids Narcotic medications are clearly useful for treating RLS including codeine, propoxyphene (Darvon), oxycodone HCL, acetaminophen (Percocet) and pentazocine (Talwin). Tolerance and addictive beha-

vior, however, are the main problems.^{4,5,11} The effective treatment with oxycodone (Percodan) resulting in significant improvement of RLS has been reported.¹⁰³ Tramadol (Melanate), a central analgesic seems to be superior in the treatment of RLS. It has fewer side effects and a lower abuse potential than classical opioids.¹⁰⁴ Vahedi *et al*¹⁰⁵ reported on dramatic relief of severe RLS obtained with epidural morphine after long-standing abuse of various analgesics.

Other medications Recently the use of gabapentin has been recommended as a successful treatment of RLS. γ -aminobutyric acid (GABA) is an inhibitory neurotransmitter found mainly in the brain with only traces in peripheral nerves and other tissues. Gabapentin (Neurontin) has been successfully marketed as an anti-convulsive drug.^{54,106,107} Side effects include dizziness, nausea, and drowsiness.¹⁰⁸ Trazodone (Desyrel) and nefazodone (Serzone) afford complete relief in some mild to moderate cases.⁵³ In some patients, however, methadone may be the only drug providing relief.⁵³

Baclofen (Lioresal) has been tried in PLMS, but its effect on RLS is not clear. Clonidine (Catapres), a centrally active α -adrenergic blocker, has been shown to be effective. It has a significant benefit upon waking symptoms and sleep latency and is particularly useful in treatment of children with RLS.⁴ High dose clonidine appears to be valuable in treating RLS when other therapy has failed.^{109,110} Carbamazepine (Tegretol) as well as propranolol hydrochloride (Inderal) are reported to be beneficial in the treatment of RLS.¹¹ According to Neustadt,¹¹¹ orphenadrine citrate (Norflex) is an extremely effective and safe medication for controlling symptoms of RLS and PLMS. Magnesium treatment may be an acceptable alternative in patients with mild or moderate RLS or PLMS-related insomnia.¹¹² Other agents mentioned to be useful include red wine, β -blockers, serotonin precursors, tricyclic anti-depressants and acetaminophen.¹¹³

Symptomatic treatment

When RLS is due to underlying systemic disorders, treatment of the underlying condition may alleviate the symptoms. Deficiency states may be corrected, such as iron supplementation in iron deficiency, folate supplements, especially in pregnant women, erythropoietin and transfusions in anemia and dialysis or kidney transplantation for uremia. The rutoside paroven (Venoruton) has a therapeutic effect in RLS patients associated with varicose veins.⁶ Other treatments include a number of different vitamins such as vitamin C, vitamin E or B-12 and magnesium supplements.^{11,53}

Adverse responses

Contrary to previous belief, smoking reportedly does not influence the symptoms of RLS.¹¹⁴ Reduction of

alcohol intake, however, may be helpful. Medications can precipitate or exacerbate the condition of RLS. Among dietary substances and medications that have been suggested to increase the symptoms are caffeine, lithium, neuroleptics and tricyclic antidepressants.¹ Paradoxically, some patients do respond favorably to tricyclics.^{4,18} Recurrence and/or increase in symptoms of RLS was observed after the use of the antidepressants fluoxetine (Prozac) and sertraline (Zoloft); both being selective serotonin re-uptake inhibitors.^{115,116} Similarly, the occurrence of RLS was observed in association with mianserin, a serotonin-inhibiting antihistamine.¹¹⁷ Worsening of symptoms has been described with paroxetine (Paxil), a phenylpiperidine derivative. This drug has a low affinity for α -adrenergic histamine H-1, serotonin 5-HT₂ and dopamine D₂ receptors.^{80,118}

Ancillary treatment

Modulation with activity As a rule physical measures are not very helpful. Non-pharmacologic therapies such as the use of vibration, thermal feedback or transcutaneous electrical nerve stimulation have been suggested.^{4,5,21} All patients are encouraged to exercise to a reasonable extent. Many RLS patients report that their symptoms appear associated with the degree of physical activity. A moderate degree of exercise tends to suppress symptoms, whereas either sustained activity or bursts of heightened exercise may worsen their symptoms.^{4,18}

Coping strategies, learning to live with RLS, and involving the family are essential. With these in mind a support group with newsletters for patients with RLS was established in the United States and Canada and lately in 1995 in Germany.^{4,80}

Conclusion

RLS is a fairly common condition with a well-defined symptom complex and occurs either as idiopathic RLS or in association with many underlying disorders. There is a high incidence of family history and a frequent association with sleep disorders. In idiopathic RLS there are no pathological findings or recognizable intracranial lesions. However, recent PET and SPECT studies revealed some involvement of basal ganglia and upper brainstem.

Although no precise etiology for this condition is known, there is evidence supporting a CNS dysfunction suggestive of involvement of the DA pathways. The disturbance may originate in the midbrain, diencephalon or upper brainstem. In addition there is documentation that RLS occurs with spinal disorders and yet another mechanism for vascular disease may be responsible in some patients.

The treatment of idiopathic RLS is primarily symptomatic and DA agents or agonists and other neurotransmitters are quite effective. The associated

underlying diseases of RLS should be treated and deficiency states corrected.

More basic and clinical research is necessary to obtain a better understanding of the pathophysiology of RLS.

Acknowledgements

I thank Drs Glen E Gresham and James J Czyrny for their critical review of the manuscript.

References

- 1 Trenkwalder C, Walters AS, Hening W. Periodic limb movement and restless legs syndrome. *Neurol Clinics* 1996; **14**: 629–650.
- 2 Ekblom KA. Restless legs. *Acta Med Scand* 1945; **158** (Suppl): 1–123.
- 3 Wetter TC, Pollmacher T. Restless legs and periodic leg movements in sleep syndromes. *Neurol* 1997; **244** (Suppl 1): 37–45.
- 4 Hening WA. *An introduction to restless legs syndrome and its treatment*. RLS Med Bulletin, RLS Foundation, Inc. 1992.
- 5 Jeddy TA, Berridge DC. Restless leg syndrome. *Br J Surg* 1994; **81**: 49–50.
- 6 Jones HJS, Derodra JK. Restless legs syndrome—a review. *Eur J Vasc Endovasc Surg* 1997; **14**: 430–432.
- 7 Rothdach A, Winkelmann J, Trenkwalder C, Berger K. Prevalence of restless legs syndrome in an elderly general population: The MEMO-study. *Neurol* 1999; **52** (Suppl 2): 287–288.
- 8 Feigen A. Restless legs syndrome. *JAMA* 1995; **274**: 1191–1192.
- 9 Walters AS *et al*. A questionnaire study of 138 patients with restless legs syndrome: the 'night-walkers' survey. *Neurol* 1996; **46**: 92–95.
- 10 Trenkwalder C, Seidel VC, Gasser T, Oertel WH. Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. *Movement Disorders* 1996; **11**: 389–394.
- 11 O'Keefe ST. Restless legs syndrome. A review. *Arch Intern Med* 1996; **156**: 243–248.
- 12 Goodman DS, Brodie C, Ayrida EA. Restless legs syndrome in pregnancy. *BMJ* 1988; **297**: 1101–1102.
- 13 Walters AS, Picchietti DL, Ehrenberg BL, Wagner ML. Restless legs syndrome in childhood and adolescence. *Ped Neurol* 1994; **11**: 241–245.
- 14 Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Movement Disorders* 1995; **10**: 634–642.
- 15 Picchietti DL *et al*. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *J Child Neurol* 1998; **13**: 588–594.
- 16 Boucher MA. Restless legs syndrome in home healthcare (review). *Home Healthcare Nurse* 1997; **15**: 551–556.
- 17 Chokroverty S, Jankovic J. Restless legs syndrome. A disease in search of identity. *Neurol* 1999; **52**: 907–910.
- 18 Dinwiddie LC. Restless legs syndrome: not just a problem for dialysis patients. *Anna J* 1997; **24**: 655–662.
- 19 Evidente VGH, Adler CH. How to help patients with restless legs syndrome. Discerning the indescribable and relaxing the restless. *Postgrad Med* 1999; **105**: 59–74.
- 20 Silber MH. Restless legs syndrome. Concise review for primary-care physicians. *Mayo Clin Proc* 1997; **72**: 261–264.
- 21 Winkelmann J, Collado-Seidel V, Trenkwalder C. Das Restless-Legs-Syndrom. *MMP* 1999; **22**: 67–71.
- 22 Trenkwalder C *et al*. Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. *Movement Disorders* 1999; **14**: 102–110.

- 23 Kuny St. Psychiatrische Katamnese bei Patienten mit 'restless legs'. *Schweiz med Wschr* 1991; **121**: 72–76.
- 24 Ondo W, Jankovic J. Restless legs syndrome-clinico-etiological correlates. *Neurol* 1996; **47**: 1435–1441.
- 25 Winkelmann J *et al*. Characteristics of the hereditary restless legs syndrome in a population of 300 patients. *Neurol* 1998; **50** (Suppl 4): 261–262.
- 26 Walters AS, Picchietti DL, Ehrenberg BL, Wagner ML. Restless legs syndrome in childhood and adolescence. *Ped Neurol* 1994; **11**: 241–245.
- 27 Lazzarini A *et al*. Studies of penetrance and anticipation in five autosomal-dominant restless legs syndrome pedigrees. *Movement Disorders* 1999; **14**: 111–116.
- 28 Boghen D, Peyronnard JM. Myoclonus in familial restless legs syndrome. *Arch Neurol* 1976; **33**: 368–370.
- 29 Walters AS, Picchietti D, Hening WA, Lazzarini A. Variable expressivity in familial restless legs syndrome. *Arch Neurol* 1990; **47**: 1219–1220.
- 30 Machtley I. Restless legs syndrome: a metabolic disorder? *Arch Int Med* 1996; **156**: 2389.
- 31 Ekbom KA. Restless legs syndrome. *Neurol* 1960; **10**: 868–873.
- 32 Aul EA, Davis BJ, Rodnitzky RL. The importance of formal serum iron studies in the assessment of restless legs syndrome. *Neurol* 1998; **51**: 912–913.
- 33 Sun ER *et al*. Iron and the restless legs syndrome. *Sleep* 1998; **21**: 371–377.
- 34 Janzen L, Rich JA, Vercaigne LM. An overview of levodopa in the management of restless legs syndrome in a dialysis population: pharmacokinetics, clinical trials, and complications of therapy. *Ann Pharmacother* 1999; **33**: 86–92.
- 35 Collado-Seidel V *et al*. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. *Am J Kidney Dis* 1998; **31**: 324–328.
- 36 Yunus MB, Aldag JC. Restless legs syndrome and leg cramps in fibromyalgia syndrome: a controlled study. *BMJ* 1996; **312**: 1339.
- 37 Reynolds G, Blake DR, Hall HS, Williams A. Restless legs syndrome and rheumatoid arthritis. *BMJ* 1986; **292**: 659–660.
- 38 Kurlan R. Postprandial (reactive) hypoglycemia and restless legs syndrome: related neurologic disorders? *Movement Disorders* 1998; **13**: 619–620.
- 39 Salvi F *et al*. Restless legs syndrome and nocturnal myoclonus: initial clinical manifestations of familial amyloid polyneuropathy. *J Neurol Neurosurg Psych* 1990; **53**: 522–525.
- 40 Rutkove SB, Matheson JK, Logigian EL. Restless legs syndrome in patients with polyneuropathy. *Muscle Nerve* 1996; **19**: 670–672.
- 41 Gemignani F *et al*. Cryoglobulinaemic neuropathy manifesting with restless legs syndrome. *J Neurol Sci* 1997; **152**: 218–223.
- 42 Walters AS, Wagner M, Hening WA. Periodic limb movements as the initial manifestation of restless legs syndrome triggered by lumbosacral radiculopathy. *Sleep* 1996; **19**: 825–826.
- 43 Lee MS, Choi YC, Lee SH, Lee SB. Sleep-related periodic leg movements associated with spinal cord lesions. *Movement Disorders* 1996; **11**: 719–722.
- 44 Glasauer FE, Egnatchik JE. Restless legs syndrome: an unusual cause for a perplexing syndrome. Case report. *Spinal Cord* 1999; **37**: 862–865.
- 45 Hemmer B *et al*. Restless legs syndrome after a borrelia-induced myelitis. *Movement Disorders* 1995; **10**: 521–522.
- 46 Lewis F. The role of the saphenous nerve in insomnia: a proposed aetiology of restless legs syndrome. *Med Hypotheses* 1991; **34**: 331–333.
- 47 Gemignani F *et al*. Charcot-Marie-Tooth disease type 2 with restless legs syndrome. *Neurol* 1999; **52**: 1064–1066.
- 48 Schoels L *et al*. Sleep disturbance in spinocerebellar ataxias: is the SCA3 mutation a cause of restless legs syndrome? *Neurol* 1998; **51**: 1603–1607.
- 49 Oboler SK, Prochazka AV, Meyer TJ. Leg symptoms in outpatient veterans. *West J Med* 1991; **155**: 256–259.
- 50 Harvey JC. Cholesterol crystal microembolism: a cause of the restless legs syndrome. *South Med J* 1976; **69**: 269–272.
- 51 Kanter AH. The effect of sclerotherapy on restless legs syndrome. *Dermat Surg* 1995; **21**: 328–332.
- 52 Winkelmann JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* 1996; **28**: 372–378.
- 53 Williams DC. Periodic limb movements of sleep and the restless legs syndrome. *Virg Med Quarterly* 1996; **123**: 260–265.
- 54 Iannaccone S *et al*. Evidence of peripheral axonal neuropathy in primary restless legs syndrome. *Movement Disorders* 1995; **10**: 2–9.
- 55 Trenkwalder C, Bucher SF, Oertel WH. Electrophysiological pattern of involuntary limb movements in the restless legs syndrome. *Muscle Nerve* 1996; **19**: 155–162.
- 56 Inami Y *et al*. A polysomnographic study on periodic limb movements in patients with restless legs syndrome and neuroleptic-induced akathisia. *Hiroshima J Med Sci* 1997; **46**: 133–141.
- 57 Montplaisir J *et al*. Persistence of repetitive EEG arousals (K- α complexes) in RLS patients treated with L-DOPA. *Sleep* 1996; **19**: 196–199.
- 58 Tulio de Mello M, 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.
- 59 Montplaisir J *et al*. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome—a study of 133 patients diagnosed with new standard criteria. *Movement Disorders* 1997; **12**: 61–65.
- 60 Wetter TC *et al*. Polysomnographic sleep measures in patients with uremic and idiopathic restless legs syndrome. *Movement Disorders* 1998; **13**: 820–824.
- 61 Trenkwalder C *et al*. Positron emission tomographic studies in restless legs syndrome. *Movement Disorders* 1999; **14**: 141–145.
- 62 Bucher SF, Trenkwalder C, Oertel WH. Reflex studies and MRI in the restless legs syndrome. *Acta Neurol Scand* 1996; **94**: 145–150.
- 63 Hartmann M, Pfister RLS, Pfadenhauer K. Restless legs syndrome associated with spinal cord lesions. *J Neurol Neurosurg Psychiatry* 1999; **66**: 688–689.
- 64 Harriman DGF, Taverner D, Woolf AL. Ekbom's syndrome and burning paraesthesiae: a biopsy study by vital staining and electron microscopy of the intramuscular innervation with a note on age changes in motor nerve endings in distal muscles. *Brain* 1970; **93**: 393–406.
- 65 Adler CH, Gwinn KA, Newman S. Olfactory function in restless legs syndrome. *Movement Disorders* 1998; **13**: 563–565.
- 66 Collado-Seidel V *et al*. Circadian endocrine rhythms in restless legs syndrome. *Neurol* 1999; **52** (Suppl 2): 412–414.
- 67 Tergau F, Wischer S, Paulus W. Motor system excitability in patients with restless legs syndrome. *Neurol* 1999; **52**: 1060–1063.
- 68 San Pedro EC *et al*. Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus and anterior cingulate gyrus. *J Rheumat* 1998; **25**: 2270–2275.
- 69 Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome. 18F-dopa and 11C-raclopride PET studies. *Neurol* 1999; **52**: 932–937.
- 70 Staedt J *et al*. Single photon emission tomography (SPET) imaging of dopamine D2 receptors in the course of dopamine replacement therapy in patients with nocturnal myoclonus syndrome. *J Neural Transm* 1995; **99**: 187–193.
- 71 Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole. A double-blind randomized trial. *Neurol* 1999; **52**: 938–943.
- 72 Bucher SF *et al*. Cerebral generators involved in the pathogenesis of the restless legs syndrome. *Ann Neurol* 1997; **41**: 639–645.
- 73 Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. *Arch Neurol* 1982; **39**: 739.
- 74 Winkelmann J *et al*. Opioidergic and dopaminergic mechanisms in restless legs syndrome (RLS). *Neurol* 1999; **52** (Suppl 2): 411–413.

- 75 Albanese A, Altavista MC, Rossi P. Organization of central nervous system dopaminergic pathways. *J Neural Transm* 1986; **229** (Suppl): 3–17.
- 76 Lindvall O, Bjorklund A, Skagerberg G. Dopamine containing neurons in the spinal cord: anatomy and some function aspects. *Ann Neurol* 1983; **14**: 255–260.
- 77 Bruno RL. Abnormal movements in sleep as a post-polio sequelae. *Am J Phys Med Rehabil* 1998; **77**: 339–343.
- 78 De Mello MT *et al.* 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.
- 79 De Mello MT *et al.* 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.
- 80 Grandjean P. Das Restless-Legs-Syndrom – Neurere Aspekte. Review. *Schweiz Rundschau Med Praxis* 1997; **86**: 732–736.
- 81 Collado-Seidel V *et al.* A combination of standard and sustained-release L-dopa/benserazide improves periodic limb movements and subjective sleep quality in the restless legs syndrome. *Neurol* 1998; **50** (Suppl 4): 277–278.
- 82 Collado-Seidel V *et al.* A controlled study of additional sr-L-dopa in L-dopa responsive restless legs syndrome with late-night symptoms. *Neurol* 1999; **52**: 285–290.
- 83 Wetter TC *et al.* Treatment of idiopathic and uremic restless legs syndrome with L-dopa – a double-blind cross-over study (German). *Wiener Mediz Wochenschrift* 1995; **145**: 525–527.
- 84 Trenkwalder C, Stiasny K, Oertel WH. Therapie des idiopathischen und uraemischen Restless-Legs-Syndroms. *Nervenarzt* 1996; **67**: 265–276.
- 85 Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep* 1996; **19**: 205–213.
- 86 Guilleminault C, Cetel M, Philip P. Dopaminergic treatment of restless legs and rebound phenomenon. *Neurol* 1993; **43**: 445.
- 87 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.
- 88 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.
- 89 Staedt J *et al.* 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. *J Neural Transm* 1997; **104**: 461–468.
- 90 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. *J Neural Transm* 1998; **105**: 265–268.
- 91 Pieta J *et al.* Effect of pergolide on restless legs and leg movements in sleep in uremic patients. *Sleep* 1998; **21**: 617–622.
- 92 Gunning K, Gay C. Treatment of restless legs syndrome with pergolide. *J Family Practice* 1999; **48**: 250–251.
- 93 Wetter T *et al.* A polysomnographic, controlled study of pergolide in the treatment of restless legs syndrome. *Neurol* 1998; **50** (Suppl 4): 69–70.
- 94 Winkelmann J *et al.* Treatment of restless legs syndrome with pergolide – an open clinical trial. *Movement Disorders* 1998; **13**: 566–569.
- 95 Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurol* 1998; **51**: 1599–1602.
- 96 Wetter TC *et al.* A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurol* 1999; **52**: 944–950.
- 97 Silber MH, Shepard JW, Wisbey JA. Pergolide in the management of restless legs syndrome: an extended study. *Sleep* 1997; **20**: 878–882.
- 98 Noel S, Korri H, Vanderheyden JE. Low dosage of pergolide in the treatment of restless legs syndrome (letter). *Acta Neurol Belgica* 1998; **98**: 52–53.
- 99 Lin SC, Kaplan J, Burger CD, Fredrickson PA. Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clin Proc* 1998; **73**: 497–500.
- 100 Becker PM, Ondo W, Sharon D. Encouraging initial response of restless legs syndrome to pramipexole. *Neurol* 1998; **51**: 1221–1223.
- 101 Ondo W. Ropinirole for restless legs syndrome. *Movement Disorders* 1999; **14**: 138–140.
- 102 Joy MS. Clonazepam: benzodiazepine therapy for the restless legs syndrome (review). *Anna J* 1997; **24**: 686–689.
- 103 Walters AS *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.
- 104 Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. *J Clin Psychiatry* 1999; **60**: 241–244.
- 105 Vahedi H, Kuchle M, Trenkwalder C, Krenz CJ. Peridurale morphiumanwendung bei Restless-Legs-Status. *Anesthesiol Intensivmed Notfallmed Schmerzther* 1994; **29**: 368–370.
- 106 Cochran JW, Williams LB. Restless legs syndrome. *JAMA* 1996; **275**: 187.
- 107 Mellick GA, Mellick LB. Management of restless legs syndrome with gabapentin (Neurontin) (letter). *Sleep* 1996; **19**: 224–226.
- 108 Adler CH. Treatment of restless legs syndrome with gabapentin. *Clin Neuropharmacol* 1997; **20**: 148–151.
- 109 Zoe A, Wagner ML, Walters AS. High-dose clonidine in a case of restless legs syndrome (review). *Ann Pharmacother* 1994; **28**: 878–881.
- 110 Wagner ML *et al.* Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996; **19**: 52–58.
- 111 Neustadt DH. Therapy for restless legs syndrome. *Arch Int Med* 1996; **156**: 2389.
- 112 Hornyak M *et al.* Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. *Sleep* 1998; **21**: 501–505.
- 113 Hindmarsh JT. Restless legs syndrome. *Arch Int Med* 1996; **156**: 2390.
- 114 Lavigne GL *et al.* Cigarette smoking as a risk factor or an exacerbation factor for restless legs syndrome and sleep bruxism. *Sleep* 1997; **20**: 290–293.
- 115 Bakshi R. Fluoxetine and restless legs syndrome. Case report. *J Neurol Sci* 1996; **142**: 151–152.
- 116 Hargrave R, Beckley DJ. Restless legs syndrome exacerbated by sertraline (letter). *Psychosomatics* 1998; **39**: 177–178.
- 117 Markkula J, Lauerma H. Mianserin and restless legs. *Internat Clin Psychopharmacol* 1997; **12**: 53–58.
- 118 Sanz-Fuentenebro FJ, Huidobro A, Tejasdas-Rivas A. Restless legs syndrome and paroxetine. *Acta Psychiatr Scand* 1996; **94**: 482–484.