Drugs 2006; 66 (5): 607-624
0012-6667/06/0005-0607/$44.95/0

Management of Restless Legs Syndrome in Patients on Dialysis

Miklos Z. Molnar,[1,2,3] *Marta Novak*[1,4] and *Istvan Mucsi*[1,2,5]

1 Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary
2 1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary
3 Semmelweis University - Fresenius Medical Care Dialysis Center, Budapest, Hungary
4 Sleep Research Laboratory and Department of Psychiatry, University of Toronto, Toronto, Canada
5 Hungarian Academy of Sciences and Semmelweis University Nephrology Research Group, Semmelweis University, Budapest, Hungary

Contents

Abstract

Restless legs syndrome (RLS) is characterised by an urge to move the legs, uncomfortable sensations in the legs and worsening of these symptoms during rest with at least temporary relief brought on by activity. RLS occurs in 3–15% of the general population and in 10–30% of patients on maintenance dialysis. RLS may lead to severe sleep onset or maintenance insomnia, and greatly impaired quality of life.

Current recommendations suggest dopaminergic therapy (levodopa or dopamine receptor agonists: pramipexol, ropinirole, pergolide or cabergoline) as the first-line treatment for RLS. This group of medications is effective in reducing RLS symptoms in the general population; limited information is available on the effect of these drugs in patients with renal failure. However, it must be noted that most published studies in uraemic patients had short treatment periods and insufficient statistical power because of small sample size. Frequent adverse effects of levodopa, seen mainly with continuous use, may limit its use significantly. Rebound and augmentation, problems relatively frequently seen with levodopa, seem to be less prevalent with the use of dopamine receptor agonists, although properly designed comparative trials are still needed to address this question. Alternative treatment options for RLS are gabapentin, benzodiazepines and opioids. For all of these medications, there are only very limited data available on their effectiveness and safety profile in patients on maintenance dialysis. Referral to a specialist for RLS management should be considered for patients with refractory RLS.

1. Restless Legs Syndrome (RLS)

Restless legs syndrome (RLS) is a senso-motor disorder characterised by the following features: (i) an urge to move the legs causing restlessness; (ii) uncomfortable sensations in the legs at the same time; (iii) symptoms become worse during rest; and (iv) motor (and often mental) activity leads to a temporary partial or complete relief of symptoms. The age of onset of the disorder varies widely, from early childhood through to old age.[1,2] The symptoms are usually present deeply inside one or both lower limbs, but the arms may also become involved in a substantial number of patients with progressive disease.[3] RLS is frequently associated with periodic limb movements in sleep (PLMS).

RLS was first described in 1672 by Thomas Willis, who reported the case of a woman who experienced the sensory and motor features of RLS.[4] These symptoms worsened during rest and at night. It was not until 1945 that the Swedish neurologist, Ekbom, first fully characterised the clinical picture.[5,6]

RLS often leads to severe sleep onset insomnia[7] and seriously impaired quality of life.[7,8] In one prospective study, RLS was associated with premature discontinuation of dialysis sessions and significantly increased the risk of mortality during a 2.5-year follow-up in dialysed patients.[8] A similar association was shown with PLMS and mortality in patients with end-stage renal failure.[9]

Not everybody who has RLS needs treatment. Pharmacological therapy for RLS is indicated only in patients in whom RLS leads to significant insomnia or impaired quality of life as a result of RLS symptoms. RLS is usually more troublesome in patients on dialysis than in other patients as they have to spend several hours 3–4 days a week immobilised in a dialysis chair, which presents regular periods of physical inactivity, largely precipitating RLS symptoms.

1.1 Diagnosis of RLS

RLS is classified into primary or idiopathic and secondary forms. Secondary RLS is usually associated with a variety of underlying medical disorders, such as iron deficiency, pregnancy, end-stage renal

failure, rheumatoid arthritis and diabetes mellitus. The diagnosis of primary RLS is based on the presence of typical symptoms in the absence of any of these disorders. An autosomal dominant mode of inheritance has been proposed with variable expressivity,[10-12] and studies suggest that up to 92% of individuals with primary RLS report a positive family history.[2,13]

RLS is best diagnosed by an experienced clinician. Clinical diagnostic criteria for RLS were established by the International RLS Study Group (IRLSSG)[14] and these have been recently modified.[15] This modification described four essential diagnostic criteria of RLS: (i) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (ii) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (iii) the symptoms are partially or totally relieved by physical (and sometimes even mental) activity, at least as long as activity continues; and (iv) the symptoms are worse in the evening or night than during the day, or only occur in the evening or night. Polysomnography (PSG) may be helpful to diagnose refractory RLS. In many patients, PSG may also be helpful to recognise coexisting PLMS.

On the basis of scientific evidence and expert opinion, the Medical Advisory Board of the Restless Legs Syndrome Foundation suggested a pragmatic classification that includes intermittent, daily and refractory types of RLS.[16] 'Intermittent RLS' is troublesome enough when present to require treatment but it is not sufficiently frequent to require regular daily medication use. 'Daily RLS' requires daily treatment, and RLS is considered 'refractory' when daily RLS does not respond to a dopaminergic agent or if intolerable adverse effects are experienced.[16]

Validated questionnaires may be useful in screening large populations. Recently, the RLS Questionnaire (RLSQ), based on the diagnostic criteria of the IRLSSG, has been developed and validated.[17] This instrument was used in a recent epidemiological survey,[18] and also in patients with end-stage renal failure.[7,19]

1.2 Epidemiology of RLS in Patients with Chronic Kidney Disease

Symptoms of RLS occur in 3–15% of the general population.[20,21] In recent publications, the diagnostic criteria for RLS established by the IRLSSG[14] were used. Reported prevalence is still quite variable, even in the general population (between 0.6% and 10.6%).[22-26] The prevalence is often higher in women than in men,[23,24,27-30] and it increases with age.[18]

Very limited information is available on the epidemiology of RLS in patients with chronic kidney disease not yet requiring dialysis, i.e. the predialysis population. In a single-centre survey, using the RLSQ, our group found a 6% prevalence in 94 patients with chronic kidney disease.[31] In patients on dialysis, the reported RLS prevalence is between 5% and 83%[7,19,32-38] (table I). This large variability could be, in part, attributed to heterogeneity of the study populations, but also to differences in case definition and instruments used to diagnose RLS. Recent studies, using the IRLSSG criteria, reported a more narrow range of prevalence between 7% and 33%, and the prevalence was similar throughout different countries in Asia, Europe and North America (table I).[7,19,32,36,37,39-41] In all these studies enrolling dialysis patients, no clinical parameters or socio-demographic characteristics were consistently associated with RLS.

Only a few studies have reported on RLS in kidney transplant patients. In one study of 11 patients, the symptoms of RLS disappeared after transplantation in all patients within 1 month, but reappeared in those patients whose kidney graft had failed.[51] Our group, using the RLSQ, assessed

Table I. Studies reporting on the prevalence of restless legs syndrome in patients with end-stage renal disease

Study (year)	No. of patients	No. of centres	Reported prevalence (%)	Use of IRLSSG 1995 criteria[14] +/− modification
Roger et al.[28] (1991)	55		40	No
Holley et al.[34] (1992)	70	1	83	No
Walker et al.[42] (1995)	54	1	57	No
Winkelman et al.[33] (1996)	204	1	20	No
Collado-Siedel et al.[35] (1998)	136	2	23	Yes
Hui et al.[43] (2000)	201	1	62	Yes
Huiqi et al.[44] (2000)	38	1	34	Yes
Miranda et al.[45] (2001)	166	2	26	Yes
Hui et al.[46] (2002)	43	1	70	Yes
Cirignotta et al.[36] (2002)	114	1	33	Yes
Kutner and Bliwise[47] (2002)	308		56	No
Sabbatini et al.[38] (2002)	694	21	37	No
Takaki et al.[37] (2003)	490	4	12	Yes
Goffredo et al.[40] (2003)	176	1	15	Yes
Bhowmik et al.[39] (2003)	121	1	7	Yes
Gigli et al.[41] (2004)	601		22	Yes
Mucsi et al.[32] (2004)	78	2	15	Yes
Unruh et al.[8] (2004)	894	80	15	No
Micozkadioglu et al.[48] (2004)	322	1	5	Yes
Rijsman et al.[49] (2004)	48	1	58	Yes
Molnar et al.[19] (2005)				
dialysis	176	9	11	Yes
kidney transplant	816	1	4.8	Yes
Mucsi et al.[7] (2005)	333	9	14	Yes
Siddiqui et al.[50] (2005)	277	5	46	Yes

IRLSSG = International Restless Legs Syndrome Study Group.

about 1000 patients with kidney transplants and found that the prevalence of RLS was 5%, significantly lower than the value obtained in patients on dialysis.[19]

1.3 Pathogenesis of RLS

The exact pathophysiology of RLS is as yet unknown but it is widely accepted that it involves disruption of the dopaminergic function in the CNS. Several studies provide suggestive evidence pointing to dysfunction of subcortical brain areas in the condition, and there is increasing evidence supporting a proposed relationship between brain iron metabolism and RLS (for reviews see[52-54]).

It is suggested that uraemic factors play a role in the pathogenesis of RLS associated with renal failure. This hypothesis is supported by the findings that symptoms of the disorder improved promptly after successful kidney transplantation and returned in patients whose grafts had failed.[51] In a cross-sectional study, involving >1000 transplanted and >200 waitlisted dialysis patients, we found that the prevalence of the disorder was 11% in the waitlisted group versus 5% in the transplanted group.[19] Furthermore, dialysis dose was a weak but significant predictor of RLS in a multivariate model[7] in our recent analysis. On the other hand, no treatment-related factors (dialysis dose, length of dialysis, surface or type of dialysis membrane) seemed to be consistently associated with RLS in surveys in dialysis patients.[7,35,37]

More data are needed to substantiate the possible role of uraemic factors in the pathogenesis of end-stage renal disease (ESRD)-associated RLS. Additional factors (neuropathy, anaemia, iron deficiency, comorbidity, immobilisation during therapy) are clearly involved in the pathogenesis of RLS in patients with renal disease.

2. Treatment of RLS

The focus of this review is to provide a practical guide to the management of RLS in patients on maintenance dialysis. Unfortunately, there are very limited treatment data available in uraemic patients; consequently, treatment recommendations for this population are largely derived from extrapolation of data obtained in the general population. Specifically, most of the recommendations suggested in this review for uraemic patients coincide with the recommendations of the Medical Advisory Board of the RLS Foundation.[16] Although that paper, just as ours, builds heavily on available trial data, it cannot be considered strictly 'evidence based'.

Because of the scarcity of information in uraemic patients, comment is made in this review on data obtained in the general population when discussing different treatment options. In fact, most studies in the general population are relatively small (except some of the more recent trials with dopamine receptor agonists), and most trials also have problems with their design. Large, prospective randomised studies comparing the efficiency and adverse-effect profile of different drugs are still missing. Augmentation, a significant concern with the use of dopaminergic treatment, has not been assessed and compared systematically. Many trials, especially in uraemic patients, had a crossover design. The severity of RLS fluctuates; therefore, comparing different treatments at different timepoints raises some significant concern. Furthermore, most studies are relatively short. As RLS is a chronic condition (although symptoms may wax and wane), data from long-term follow-up studies are also needed. Finally, outcome measures reported in the different studies also vary substantially. Periodic leg movement index (PLMI), sleep parameters obtained with PSG, subjective symptom-severity scales and quality-of-life measures are used. It is not always possible to determine in the different studies if an outcome is clinically relevant or if an improvement is clinically significant.

In spite of all the problems listed above, one can still conclude from the available data that after other potentially modifiable factors (anaemia, iron deficiency) were ruled out or corrected, the first-line drug treatment for RLS in dialysis patients should be dopaminergic therapy (levodopa or dopamine receptor agonists). Gabapentin, benzodiazepines and opioids may provide viable treatment alternatives (table II).

2.1 Nonpharmacological Treatment

Several substances can precipitate or aggravate symptoms of RLS, such as caffeine, alcohol and nicotine. Tricyclic antidepressants,[55] selective serotonin re-uptake inhibitors,[56] lithium,[57] dopamine antagonists,[58] dopamine-blocking antiemetics (such as metoclopramide) and sedative antihistamines may also worsen RLS symptoms. Metoclopramide (for frequent nausea and vomiting) and antihistamines (for distressing itch) are frequently used in dialysis patients. It is the first step in the treatment plan for RLS to stop these medications if possible.

Activities leading to mental alertness, such as video games and crossword puzzles may also reduce RLS symptoms.[16]

2.2 Correction of Anaemia and Iron Therapy

Earlier studies frequently identified anaemia as a risk factor for RLS in the ESRD population.[28,59] Correction of anaemia with erythropoietin decreased the PLMS index (number of PLMS per hour

Table II. Drugs that may be considered for the treatment of restless legs syndrome (RLS) in dialysis patients

Agent	Initial dose (mg)	Maximal daily dose in patients on dialysis (mg)	Dose adjustment in renal failure	Removal by haemodialysis
Levodopa	50	200	Only small amounts of levodopa are excreted unchanged in the urine; it is unlikely that dose adjustments are necessary in renal failure	Because of the large volume of distribution and rapid metabolism, it is doubtful that significant amounts would be removed by dialysis
Pramipexole	0.125	1.5	Clearance of pramipexole is reduced in patients with renal impairment and dose reduction is suggested	Pramipexole is not recommended in haemodialysis patients according to the product information
Pergolide	0.05	0.5–1	Clearance of pergolide is reduced in patients with renal impairment and dose reduction is suggested	No data available
Cabergoline	0.5	2	Only small amounts of cabergoline are excreted in the urine; it is unlikely that dose adjustments are necessary in renal failure	No data available
Ropinirole	0.25	3–4	No difference in the pharmacokinetics of ropinirole in patients with moderate renal impairment (CrCl between 30 and 50 mL/min); and thus no dosage adjustment is necessary. Use of the drug in patients with severe renal impairment has not yet been investigated	Removal by haemodialysis is unlikely because of the relatively high volume of distribution
Gabapentin	100 after each dialysis	300 after each dialysis	Renal impairment: CrCl 30–59 mL/min, 200–600 mg/day; CrCl 15–29 mL/min, 100–300 mg/day; CrCl 15 mL/min, 100–200 mg/day. For patients with CrCL <15 mL/min, reduce daily dose in proportion to creatinine clearance	Patients receiving haemodialysis should receive gabapentin for RLS post-haemodialysis
Oxycodone	5	15–20	Dose conservatively	Insignificant
Tramadol	50	200	Dose administration interval needs to be increased for patients with CrCl <30 mL/min	During a 4-hour haemodialysis session, tramadol was significantly removed
Methadone	2.5–5	10–20	Dose administration interval needs to be increased for patients with renal impairment	No
Clonazepam	0.25	2	Adjustments do not appear necessary in renal failure	No

CrCl = creatinine clearance.

of sleep) and improved quality of sleep in ten haemodialysis patients in the SLEEPO study.[60] Iron supplementation might also be an effective treatment option for RLS symptoms.[61,62] In a double-blind, placebo-controlled trial enrolling 25 dialysis patients, parenteral iron-dextran therapy significantly improved RLS symptom severity. The treatment effect was seen during the first and second week of treatment, but diminished later.[63] No significant adverse effect was associated with the iron therapy. The results of another pilot study suggested that supplemental injections of ferrous gluconate 450mg (given as a course of three separate 150mg infusions over a 5- to 10-day period if symptoms of RLS returned after the initial dose, and provided the serum ferritin level was <200 μg/L) can sustain improvements achieved with an initial dose of ferrous gluconate 1000mg.[62] Definitive controlled studies are clearly needed to substantiate these preliminary results.

In recent years, parenteral iron has been used more aggressively in dialysis units, and there are no data to substantiate whether a further increase in the dose of parenteral iron in dialysis patients with RLS would bring additional benefit. Further studies to specifically address this question are needed.

2.3 Dopaminergic Agents

2.3.1 Levodopa

Levodopa is a short-acting drug with a rapid onset and offset of action.[64] It is rapidly absorbed from the gastrointestinal tract and metabolised readily by the gut, liver and kidney to dopamine. The plasma half-life of levodopa is about 0.8–1.6 hours. To prevent peripheral decarboxylation, levodopa is usually administered together with a peripheral dopa-decarboxylase inhibitor (benserazide or carbidopa). About 80% of the ingested levodopa is excreted by the kidneys as metabolites (table II).

Several studies, although most were relatively small, have established the efficacy of levodopa with a peripheral decarboxylase inhibitor for the treatment of RLS in the general population (for review, see[10] and[65]).[66] In the first double-blind, crossover, placebo-controlled trial lasting for 4 weeks, levodopa 200mg with benserazide significantly reduced the frequency of awakenings and the duration of awake periods in 13 non-uraemic patients with RLS symptoms.[67] Levodopa did not seem to improve objective measures of sleep efficiency either after short-[66] or long-term administration. This may be because of its short half-life, as levodopa/benserazide seems to be more effective in the first hours after drug intake than at the end of the night.[68,69] Adding slow-release levodopa to the traditional levodopa may improve effectiveness and/or tolerability.[66,70,71] Still, further studies are needed to establish if sustained release formulation of the drug will have a more substantial effect on sleep efficiency.

To date, four studies have been published that report on the effect of levodopa on RLS in uraemic patients (table III).[69,72-74] In an early study of eight consecutive dialysis patients levodopa/carbidopa improved RLS symptoms in six of eight patients.[72] Levodopa was also effective in a randomised, double-blind crossover study enrolling 17 patients with idiopathic and 11 patients with uraemic RLS. The drug significantly reduced the number of periodic leg movements, and improved sleep quality and quality of life.[69] More recently, it was reported that low-dose levodopa/carbidopa improved some of the polysomnographic sleep parameters in dialysis patients with nocturnal movement disorders.[74] In a recent randomised, prospective crossover study enrolling 11 patients on haemodialysis, slow-release levodopa was less effective than ropinirole, a dopamine receptor agonist, in reducing RLS symptoms and increasing sleep time.[75]

Levodopa is effective in reducing RLS symptoms both in idiopathic and in uraemic RLS, and it has been approved for the treatment of idiopathic and uraemic RLS in several European countries. In long-term studies, up to 80% of the patients receiving levodopa developed augmentation (see section 2.3.3); therefore, current recommendations suggest its use only for intermittent RLS.[16,81] The usual dose of levodopa to treat RLS is 100–200mg with either carbidopa or benserazide taken at bedtime. There is no need to reduce dose in dialysis patients.[69]

2.3.2 Dopamine Agonists

Both ergot-dopamine agonists (bromocriptine, pergolide and cabergoline) and non-ergot dopamine agonists (pramipexole, ropinirole and rotigotine) have been shown to be effective in treating RLS in the general population. The effect of dopamine agonists develops 90–120 minutes after intake; thus, it is recommended to take these medicines 2 hours before sleep.[16]

Table III. Studies reporting on the pharmacological therapy of restless legs syndrome (RLS) in uraemic patients (pts)

Study (year)	Study design	No. of pts	Comparator	Outcome	Adverse effects	Effect size
Levodopa						
Sandyk et al.[72] (1987)	Open-label	8		Relief of symptoms		
Wetter et al.[73] (1995)	Randomised, controlled, double-blind, crossover	17 with PLMD and 11 uraemic pts with RLS	Placebo	Decreased PLMI, improvement in sleep quality		
Trenkwalder et al.[69] (1995)	Randomised, controlled, double-blind, crossover	11 HD, 17 idiopathic	Placebo	Decreased PLMI, improvement in sleep quality, improvement in quality of life	No severe	PLMI (uraemic pts): levodopa: 69 ± 59; placebo: 97 ± 53
Walker et al. (1996)[74]	Randomised, controlled, double-blind, crossover	5 HD	Placebo	Decreased PLMI, increase in the amount of slow-wave sleep		PLMI: levodopa 61 ± 28; placebo 101 ± 29
Pramipexole						
Miranda et al.[76] (2004)	Open-label	10 HD	Uncontrolled	Improvement in IRLSSG severity scale and PLMI		Baseline: PLMI 109 ± 42; IRLSSG scale 26 ± 6; End: PLMI 38 ± 27; IRLSSG scale 8 ± 8
Ropinirole						
Pellecchia et al.[75] (2004)	Open-label, prospective, randomised, controlled, crossover	11 HD	Levodopa SR	Ropinirole was superior to levodopa SR in reducing 6-item IRLS scores and in increasing sleep time and CGI scale	Vomiting in one pt taking levodopa	6-Item IRLS score: levodopa 17 ± 3 to 11 ± 4; ropinirole 17 ± 3 to 4 ± 4
Pergolide						
Pieta et al.[77] (1998)	Double blind, controlled, crossover	8 HD and CAPD	Placebo	5 pts noted subjective improvement in RLS, PLMI did not change	Nausea, nightmares	Baseline: PLMI 54 ± 22; End: PLMI 36 ± 12 (p = NS)
Gabapentin						
Thorp et al.[78] (2001)	Randomised, double blind, controlled crossover	16 HD	Placebo	Gabapentin was more effective than placebo based on questionnaire	Lethargy	Baseline: 6.9 ± 0.7; placebo 5.8 ± 2.3; gabapentin 3.0 ± 2.2
Micozkadioglu et al.[48] (2004)	Open-label, controlled	15 HD	Levodopa	Gabapentin was more effective based on IRLSSG rating scale		IRLSSG scale; median (min./max.): Baseline: 17 (14/20) Levodopa: 10 (8/20) Gabapentin: 3 (2/8)
Clonazepam						
Read et al.[79] (1981)	Open-label	15 with ESRD		Improved		
Braude and Barnes[80] (1982)	Case report					

CAPD = continuous ambulatory peritoneal dialysis; **CGI** = Clinical Global Impression scale; **ESRD** = end-stage renal disease; **HD** = haemodialysis; **IRLS** = International Restless Legs Scale; **IRLSSG** = International RLS Study Group; **PLMD** = periodic limb movement disorder; **PLMI** = Periodic Limb Movement Index; **SR** = sustained release.

Currently, pergolide, cabergoline and ropinirole are the most studied dopamine agonists in the non-uraemic population, and they are suggested to be the drug of choice in most patients with idiopathic and secondary RLS requiring either daily or intermittent therapy.[16] These drugs may be less likely to cause adverse effects than levodopa, but augmentation may still occur. Furthermore, there is no large, well designed study available that has compared dopamine receptor agonists with levodopa or with each other. In one small study that compared ropinirole with levodopa in dialysis patients, ropinirole seemed to be superior in reducing RLS symptoms and increasing sleep time.[75]

The most frequent adverse effects of dopamine receptor agonists are mild and transient, including nausea, lightheadedness and fatigue. Less frequent adverse effects are nasal stuffiness, insomnia, constipation and leg oedema. These adverse effects are reversible if the medication is stopped. Ergot-dopamine receptor agonists were reported to be associated with restrictive cardiac valve disease[82,83] and also with an increased risk of pleuropulmonary fibrosis.[84] In the opinion of the authors of this review, this serious adverse effect may preclude the use of these drugs in the long-term treatment of RLS. Finally, pramipexole, ropinirole and pergolide have been reported to be associated with falling asleep during activities of daily living without warning (sleep attacks) both in patients with Parkinson's disease and in patients with RLS.[85] These sleep attacks may be related to excessive daytime sleepiness related to the underlying disease or the dopaminergic drugs used. On the other hand, a recent survey suggested that the use of dopaminergic agents was associated with a reduced risk for sleep attacks.[86] According to the results of that survey (in which male sex and older age were significant predictors of sleep attacks, with 70.8% of male RLS patients >63 years of age reporting sudden onset of sleep), elderly male patients with RLS, and also patients using these medications, should receive appropriate counselling about this potentially serious condition, and removing driving privileges may need to be considered in patients at high risk for these sleep attacks.

Further studies are needed to establish the role of dose escalation in the case of augmentation with different dopamine agonists. Similarly, additional data are needed on the use of these drugs in patients with different degrees of renal failure and also in patients treated with different dialysis modalities.

Pramipexole

Pramipexole is a dopamine agonist with a half-life of 8–10 hours and is mainly eliminated through the kidneys (table II). Most studies have enrolled patients with no significant renal impairment. In three open-label studies, the administration of pramipexole 0.125–1.6 mg/day resulted in improvement of RLS symptoms in 75–80% of patients.[87-89] In a randomised, controlled trial involving ten patients, pramipexole (up to 1.5 mg/day) significantly relieved RLS symptoms and also reduced the frequency of PLMS.[90] In a single-blind, placebo-controlled, cross-over trial, pramipexole significantly improved the total score of the IRLSSG questionnaire, sleep quality and daytime sleepiness, depression and quality of life in 11 patients with RLS.[91] The treatment effect seemed to be stable in longer term follow-up studies.[92,93] With prolonged use, augmentation did occur but it was usually mild and manageable with increased doses early in the day.[93] Another study did not confirm these results, and found that augmentation and tolerance were common with extended use of pramipexole.[94]

Only one study has examined pramipexole in uraemic patients (table III).[76] In this study, 172 patients on haemodialysis were screened using the IRLSSG criteria; ten patients were enrolled in that uncontrolled study. Patients were evaluated with the IRLSSG severity scale and PSG. Pramipexole 0.125–0.75 mg/day was well tolerated. The mean

score on the severity scale and the PLMS index decreased significantly during the study period. However, sleep latency, total hours of sleep, number of awakenings and sleep efficiency showed no significant change.[76]

Pramipexole should be started at a dose of 0.125mg once daily. The dose may be increased by 0.125mg every 2–3 days until relief is obtained. Most patients require ≤0.5mg but higher doses may be needed in some. The daily dose should probably not exceed 0.75mg in dialysis patients, although this has not been systematically studied.[76]

Ropinirole

Ropinirole is a synthetic dopamine agonist with relatively greater D_3 and D_4 affinity than dopamine, bromocriptine and pergolide.[95] The half-life of ropinirole is 6–8 hours and it is mainly excreted by the liver (table II).

Although the trials with ropinirole to date have been relatively short, their results suggest that the drug alleviates RLS symptoms. Results from two randomised, placebo-controlled, double-blind, 12-week trials (TREAT RLS [Therapy with Ropinirole; Efficacy And Tolerability in RLS] 1 and 2) showed that ropinirole is effective in the treatment of RLS.[96,97] These results were confirmed in two subsequent trials.[98,99] In a small randomised, controlled trial, ropinirole significantly decreased PLMS and RLS symptoms. Adverse effects were dose related.[100] Ropinirole was associated with improved severity scores on the IRLSSG severity scale, and also with complete resolution of the symptoms in about 35% of the patients receiving the drug.

Only one study involving dialysis patients has been reported to date (table III). In this open, randomised, crossover trial enrolling eleven patients on maintenance haemodialysis, the efficacy and adverse effects of ropinirole versus sustained-release levodopa were compared.[75] Ropinirole was superior to sustained-release levodopa in reducing scores on the 6-item International Restless Legs Scale (IRLS) and significantly increased sleep time.[75] Four patients reported complete disappearance of RLS symptoms while taking ropinirole. No adverse event was detected during ropinirole administration in this study.

The initial dose is 0.25mg once daily 1–2 hours before bedtime. The dose may be increased by 0.25mg every 2–3 days. The majority of the patients require ≤2mg but doses up to 8 mg/day may be necessary. The drug is probably not removed by haemodialysis and no dose reduction seems to be necessary when administered to patients with renal impairment.

Pergolide

Pergolide is a long acting D_1 and D_2 receptor agonist with a half-life of approximately 12–16 hours; the major route of excretion is the kidney (table II).

Pergolide significantly reduces RLS symptoms and PLMS, and improves sleep quality and sleep time. Several small randomised, double-blind studies demonstrated a beneficial effect of pergolide on PLMI, RLS symptom severity and sleep in the general population.[101-103] Pergolide was superior to levodopa treatment in a small randomised, double-blind, crossover trial.[101] Pergolide with domperidone was also effective in patients with severe RLS who had previously experienced augmentation while receiving long-term treatment with levodopa.[104] A recent large randomised, double-blind study confirmed that pergolide is more effective than placebo in treating RLS.[105]

In a small study enrolling eight patients on long-term haemodialysis or continuous peritoneal dialysis in a double-blind, placebo-controlled and crossover design, five of eight patients noted subjective improvement of the symptoms of RLS and sleep quality (table III).[77] However, the patients continued to have very disrupted sleep and an objective

improvement in sleep architecture could not be documented.[77]

Pergolide is associated with restrictive cardiac valve disease in patients with Parkinson's disease[83] and it is also associated with an increased risk of pleuropulmonary fibrosis.[84] These risks, in our opinion, would be likely to preclude its use in RLS.

Cabergoline

In a randomised clinical trial of 85 patients with severe RLS, cabergoline 0.5–1.2 mg/day was more effective than placebo in treating RLS symptoms;[106] 6 of 66 patients treated with the drug reported mild augmentation. Other studies also confirmed the effectiveness of cabergoline in the treatment of RLS.[107-110] Cabergoline has a long half-life (65 hours) and it is metabolised mainly in the liver. Dose adjustment in patients with renal impairment does not seem to be necessary; however, no data are available with cabergoline in the ESRD population.

2.3.3 Augmentation and Rebound

The use of levodopa, especially for prolonged periods, is significantly hampered by problems such as tachyphylaxis, rebound, recurrence and augmentation. A decreasing response with continuous use (tachyphylaxis) of levodopa has been reported in some but not all studies. In about 25% of the patients treated with levodopa, RLS symptoms may recur in the second half of the night (recurrence) or early in the morning when the effect of the drug is wearing off (rebound).[69,111]

Augmentation is defined as earlier onset of symptoms, increased intensity of symptoms, or spread of the symptoms to other body parts, early during the day after an evening dose of medication. Augmentation has frequently (35–85%) been seen in patients treated with levodopa,[71,111] but it has also been reported in patients taking pergolide,[112,113] and pramipexole.[94] Studies with ropinirole were usually too short to detect augmentation. Mild forms of augmentation may be managed by increasing the dose administration frequency of the drug, but more commonly the drug has to be stopped and substituted with an alternative medication. At the present time, it is not possible to compare the prevalence of augmentation with the different dopaminergic treatments, as several studies have not reported such prevalences or they were too short to detect the phenomenon. Furthermore, in studies reporting prevalence data, augmentation was not assessed in a standardised way.

2.4 Nondopaminergic Agents

2.4.1 Gabapentin

Gabapentin is an anticonvulsant, with a half-life of 5–7 hours which is increased to approximately 132 hours in dialysis patients (table II). Gabapentin is primarily excreted through the kidneys.

The first suggestion of the effectiveness of gabapentin in RLS in the general population was published in 1997.[114] Similar results were reported in several small studies.[115,116] The first randomised, placebo-controlled trial with gabapentin was published in 2002.[117] Twenty-four patients were evaluated using the RLS Rating Scale and the Pittsburgh Sleep Scale. Gabapentin was associated with reduced symptoms, PLMS index and improved sleep architecture compared with placebo.

Two trials enrolling dialysis patients have recently been reported (table III).[48,78] In a randomised, double-blind, placebo-controlled, crossover study involving 16 patients on maintenance haemodialysis, gabapentin 200–300mg given after each haemodialysis session was associated with significant clinical improvement of RLS symptoms.[78] Eleven patients responded to gabapentin, one patient responded to both drugs and one patient responded only to placebo. Two patients dropped out because of lethargy caused by gabapentin. A recent study, involving 15 patients on maintenance dialysis, compared gabapentin with levodopa. Gabapentin seemed to be more effective than levodopa[48] in

improving some domains of quality of life, sleep quality, sleep disturbances and sleep latency.[48]

Gabapentin may be alternative therapy for daily RLS[16] in patients who perceive their RLS as painful. The drug may also be useful when RLS occurs in the setting of a painful peripheral neuropathy or an unrelated chronic pain syndrome.

As gabapentin is mainly excreted through the kidneys and its half-life is greatly prolonged in patients with renal impairment, the dose of the drug needs to be reduced substantially in dialysis patients. For the treatment of RLS in dialysis patients, the suggested dose is 100–300mg given after each dialysis session (assuming three 4-hour dialysis sessions per week). In a case study reporting on two patients on haemodialysis, gabapentin seemed to be associated with symptomatic myopathy.[118]

2.4.2 Benzodiazepines

Benzodiazepines are also used to treat RLS. Clonazepam is employed most frequently but sporadic data with other benzodiazepines (diazepam, temazepam) have also been reported.[119] Benzodiazepine receptor agonists (zolpidem, zapelon, triazolam) may also effectively improve sleep-onset insomnia, frequently associated with RLS. Because of the lack of clinical trials, RLS experts recommend the use of benzodiazepines or benzodiazepine agonists only in intermittent RLS.[16,120,121] The main mode of action of benzodiazepines is improving sleep quality, rather than movement disorder;[122] therefore, this group of medications may be considered for patients in whom the leading complaint is clinically significant insomnia.

Benzodiazepines are associated with a number of adverse effects, including drowsiness, ataxia, somnolence, diplopia, dysarthria, respiratory depression, confusion (primarily in the elderly) and paradox reaction. Benzodiazepines may also facilitate obstructive sleep apnoea. Finally, there are concerns regarding the potential for dependency. Consequently, risks and benefits should be weighed carefully, and proper counselling and follow-up should be provided when considering benzodiazepines (or, for similar reasons, opioids).

Clonazepam

Clonazepam is a benzodiazepine with a half-life of 18–50 hours (table II). It is mainly eliminated through the liver; therefore, dose adjustment does not seem to be necessary in patients with renal failure.

The first randomised, placebo-controlled, double-blind trials examining the effectiveness of clonazepam in RLS reported conflicting results.[123,124] In a subsequent paper, reporting on 20 patients with PLMS, clonazepam 0.5–2mg each night effectively reduced the number of leg movements. PSG demonstrated a significant decrease in the number of leg movements and significant improvement in sleep parameters in the clonazepam group compared with placebo.[125] These results were confirmed in a similar study.[126]

The first report using clonazepam in a renal patient was published in 1981.[80] In an open trial, 14 of 15 patients with ESRD and RLS responded to clonazepam 1–2 mg/day (table III).[79]

Clonazepam may be a potential alternative, especially in those whose leading complaint is significant insomnia, to treat RLS in dialysis patients at a dose of 0.5–2 mg/day.

2.4.3 Opioids

Opiates were first suggested for RLS by Willis in 1684.[127] The finding that the endogenous opioid system may play a role in the pathogenesis of RLS provided theoretical foundations to the suggestion that opioids might, indeed, have a therapeutic effect in RLS.[128] A variety of opioids including codeine, oxycodone,[129] methadone,[130] tramadol[131] and propoxyphene[68,132] have been reported to be potentially useful in treating RLS in uncontrolled trials.[133] Opioids seem to have long-term efficacy in the treatment of RLS and PLMS, but clinical and

PSG parameters should be periodically monitored to detect the potential development of sleep apnoea.[132]

The Medical Advisory Board of the RLS Foundation recommends low-potency opioids (such as propoxyphene or codeine) or opioid agonists (tramadol) for treating intermittent RLS, and this medication can also be an alternative for treating daily RLS.[16] For patients with refractory RLS, high-potency opioids (such as oxycodone, hydrocodone or methadone) or tramadol may be useful.[16] No data are available on the effectiveness of opioids in treating RLS in patients on maintenance dialysis. Because of potential accumulation of metabolites leading to significant adverse effects, propoxyphene should not be regularly administered to patients on dialysis.

2.4.4 Other Medications

Some other drugs may also be effective in the therapy of RLS in selected patients; data regarding these drugs are from a small number of mainly open studies.

The first randomised, double-blind, crossover study of a dopamine agonist used bromocriptine, an ergot-dopamine agonist (7.5mg at bedtime).[129] Both carbamazepine[130,131] and valproic acid[134] have been tested in patients with RLS, and both drugs showed efficacy in relieving RLS symptoms and arousals associated with PLMS. The short-acting benzodiazepine agonist zolpidem may be used for intermittent RLS, especially if the patient has significant sleep-onset insomnia.[135] Clonidine could also be used as an alternative treatment for mild, intermittent RLS.[136]

No data have been published about the use of these drugs to treat RLS in uraemic patients.

3. Overall Treatment Recommendation for Dialysis Patients

RLS is very probably underdiagnosed and undertreated in both the general population and in patients with ESRD. This is particularly unacceptable as RLS may be the cause of severe sleep-onset or maintenance insomnia, and it significantly impairs quality of life. Furthermore, effective treatment options are available. On the basis of the proposed pathophysiological mechanisms and experimental data, we suggest that the recommendations of the Medical Advisory Board of the RLS Foundation,[16,81] which are designed for use in the general population, should also be followed in patients with significant kidney disease. These recommendations, although they build heavily on existing clinical research data, are openly based on expert opinion. It should also be noted that only a few studies have been reported on the treatment effect of the medications used to treat RLS in patients on dialysis. Furthermore, many of these published studies were short and had insufficient statistical power because of their small sample size.

RLS should only be treated in patients with severe and troublesome symptoms, which impair quality of life and/or sleep. Renal anaemia and iron deficiency should be corrected with appropriate administration of erythropoietin and intravenous iron. Medications should be employed alongside non-pharmacological treatment options (such as abstinence from caffeine, nicotine and alcohol, discontinuation of drugs potentially precipitating or aggravating RLS symptoms, and mental alerting activities).

Dopaminergic therapy is the mainstay of pharmacological therapy in patients on dialysis. At the present time, there are not sufficient data to establish whether any one of these drugs is more effective or has fewer adverse effects than the others, since well designed, comparative studies have not been published. In intermittent RLS, such as symptoms oc-

curring only or mainly during dialysis or while attending events such as theatre or concerts, levodopa with a decarboxylase inhibitor taken before the event should be tried. Alternatively, low-dose dopamine agonists can be used. In patients in whom intermittent RLS is associated with severe insomnia, benzodiazepines, low-potency opioids or benzodiazepine receptor agonists, taken at bedtime, could be tried.

For daily treatment of RLS in dialysis patients, ropinirole is probably the treatment of choice, although it should be pointed out that only one study enrolling 11 patients compared ropinirole with levodopa in dialysis patients.[75] Ropinirole has to be taken approximately 1 hour before usual symptom onset.[137] The use of pramipexole has not been adequately studied in dialysis patients, according to the product information;[138] however, it was used in a small trial with no apparent adverse effects.[76] Should augmentation occur, increasing the dosage, changing the time of administration (in mild cases), or switching to a different dopamine agonist or an alternative therapy may reduce the symptoms. Gabapentin, benzodiazepines and opioids may be considered as alternative treatments for daily RLS in patients who can not tolerate dopaminergic therapy.

Referral to a specialist with interest in RLS should be considered in daily and refractory RLS.

Acknowledgements

This work of Dr Novak and Dr Mucsi is supported by grants from the National Scientific Research Funds (OTKA TS 040889, OTKA T038409, NKFP 1/002/2001), the Ministry of Health (218/2003) and TeT Foundation (2005/06, MN). Dr Mucsi is a Bekesy Postdoctoral Fellow of the Hungarian Ministry of Education; Dr Novak is recipient of the Hungarian Eotvos Scholarship. The authors have no potential conflicts of interest directly related to the contents of this article.

References

1. Walters AS, Hickey K, Maltzman J, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology 1996; 46 (1): 92-5
2. Winkelmann J, Wetter TC, Collado-Seidel V, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 2000; 23: 597-602
3. Michaud M, Chabli A, Lavigne G, et al. Arm restlessness in patients with restless legs syndrome. Mov Disord 2000 Mar; 15 (2): 289-93
4. Willis T. *De Anima Brutorum*. London: Wells and Scott, 1672
5. Ekbom K. Restless legs syndrome. Neurology 1960; 10: 868-73
6. Ekbom K. Restless legs: a clinical study. Acta Med Scand Suppl 1945; 158 Suppl. 1: 1-122
7. Mucsi I, Molnar MZ, Ambrus C, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. Nephrol Dial Transplant 2005 Mar; 20 (3): 571-7
8. Unruh ML, Levey AS, D'Ambrosio C, et al. Restless legs symptoms among incident dialysis patients: association with lower quality of life and shorter survival. Am J Kidney Dis 2004 May; 43 (5): 900-9
9. Benz RL, Pressman MR, Hovick ET, et al. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis 2000 Jun; 35 (6): 1052-60
10. Hening W, Allen R, Earley C, et al. The treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine Review. Sleep 1999 Nov 1; 22 (7): 970-99
11. Winkelmann J, Muller-Myhsok B, Wittchen HU, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol 2002 Sep; 52 (3): 297-302
12. Montplaisir J, Boucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997 Jan; 12 (1): 61-5
13. Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996 Dec; 47 (6): 1435-41
14. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995 Sep; 10 (5): 634-42
15. Allen RP, Picchietti D, Hening WA, et al. 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 2003 Mar; 4 (2): 101-19
16. Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004 Jul; 79 (7): 916-22
17. Allen R, Earley C. Validation of a diagnostic questionnaire for the restless legs syndrome (RLS) [abstract]. Neurology 2001; 56 (4A Suppl. 3): A19
18. Nichols DA, Allen RP, Grauke JH, et al. Restless legs syndrome symptoms in primary care: a prevalence study. Arch Intern Med 2003 Oct 27; 163 (19): 2323-9
19. Molnar MZ, Novak M, Ambrus C, et al. Restless legs syndrome in patients after renal transplantation. Am J Kidney Dis 2005 Feb; 45 (2): 388-96
20. Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000 Jul 24; 160 (14): 2137-41

21. Schmitt BE, Gugger M, Augustiny K, et al. Prevalence of sleep disorders in an employed Swiss population: results of a questionnaire survey [in German]. Schweiz Med Wochenschr 2000 May 27; 130 (21): 772-8
22. Tan EK, Seah A, See SJ, et al. Restless legs syndrome in an Asian population: a study in Singapore. Mov Disord 2001 May; 16 (3): 577-9
23. Ulfberg J, Nystrom B, Carter N, et al. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord 2001 Nov; 16 (6): 1159-63
24. Berger K, Luedemann J, Trenkwalder C, et al. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004 Jan 26; 164 (2): 196-202
25. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005 Jun 13; 165 (11): 1286-92
26. Hogl B, Kiechl S, Willeit J, et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. Neurology 2005 Jun 14; 64 (11): 1920-4
27. Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 2000 Mar 14; 54 (5): 1064-8
28. Roger SD, Harris DC, Stewart JH. Possible relation between restless legs and anaemia in renal dialysis patients. Lancet 1991 Jun 22; 337 (8756): 1551
29. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res 2002 Jul; 53 (1): 547-54
30. Rijsman R, Neven AK, Graffelman W, et al. Epidemiology of restless legs in The Netherlands. Eur J Neurol 2004 Sep; 11 (9): 607-11
31. Mendelssohn DM, Novak M, Dunai A, et al. Sleep disorders and quality of life in chronic kidney disease patients in the predialysis stage. J Am Soc Nephrol 2004; 15: 132 A
32. Mucsi I, Molnar MZ, Rethelyi J, et al. Sleep disorders and illness intrusiveness in patients on chronic dialysis. Nephrol Dial Transplant 2004 Jul; 19 (7): 1815-22
33. Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis 1996 Sep; 28 (3): 372-8
34. Holley JL, Nespor S, Rault R. A comparison of reported sleep disorders in patients on chronic hemodialysis and continuous peritoneal dialysis. Am J Kidney Dis 1992 Feb; 19 (2): 156-61
35. Collado-Seidel V, Kohnen R, Samtleben W, et al. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. Am J Kidney Dis 1998 Feb; 31 (2): 324-8
36. Cirignotta F, Mondini S, Santoro A, et al. Reliability of a questionnaire screening restless legs syndrome in patients on chronic dialysis. Am J Kidney Dis 2002 Aug; 40 (2): 302-6
37. Takaki J, Nishi T, Nangaku M, et al. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. Am J Kidney Dis 2003 Apr; 41 (4): 833-9
38. Sabbatini M, Minale B, Crispo A, et al. Insomnia in maintenance haemodialysis patients. Nephrol Dial Transplant 2002 May; 17 (5): 852-6
39. Bhowmik D, Bhatia M, Gupta S, et al. Restless legs syndrome in hemodialysis patients in India: a case controlled study. Sleep Med 2003 Mar; 4 (2): 143-6
40. Goffredo Filho GS, Gorini CC, Purysko AS, et al. Restless legs syndrome in patients on chronic hemodialysis in a Brazilian city: frequency, biochemical findings and comorbidities. Arq Neuropsiquiatr 2003 Sep; 61 (3B): 723-7
41. Gigli GL, Adorati M, Dolso P, et al. Restless legs syndrome in end-stage renal disease. Sleep Med 2004 May; 5 (3): 309-15
42. Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. Am J Kidney Dis 1995 Nov; 26 (5): 751-6
43. Hui DS, Wong TY, Ko FW, et al. Prevalence of sleep disturbances in Chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 2000 Oct; 36 (4): 783-8
44. Huiqi Q, Shan L, Mingcai Q. Restless legs syndrome (RLS) in uremic patients is related to the frequency of hemodialysis sessions. Nephron 2000 Dec; 86 (4): 540
45. Miranda M, Araya F, Castillo JL, et al. Restless legs syndrome: a clinical study in adult general population and in uremic patients [in Spanish]. Rev Med Chil 2001 Feb; 129 (2): 179-86
46. Hui DS, Wong TY, Li TS, et al. Prevalence of sleep disturbances in Chinese patients with end stage renal failure on maintenance hemodialysis. Med Sci Monit 2002 May; 8 (5): CR331-6
47. Kutner NG, Bliwise DL. Restless legs complaint in African-American and Caucasian hemodialysis patients. Sleep Med 2002 Nov; 3 (6): 497-500
48. Micozkadioglu H, Ozdemir FN, Kut A, et al. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. Ren Fail 2004 Jul; 26 (4): 393-7
49. Rijsman RM, de Weerd AW, Stam CJ, et al. Periodic limb movement disorder and restless legs syndrome in dialysis patients. Nephrology (Carlton) 2004 Dec; 9 (6): 353-61
50. Siddiqui S, Kavanagh D, Traynor J, et al. Risk factors for restless legs syndrome in dialysis patients. Nephron Clin Pract 2005; 101 (3): c155-60
51. Winkelmann J, Stautner A, Samtleben W, et al. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. Mov Disord 2002 Sep; 17 (5): 1072-6
52. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol 2001 Mar; 18 (2): 128-47
53. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med 2004 Jul; 5 (4): 385-91
54. Winkelmann J, Prager M, Lieb R, et al. "Anxietas tibiarum": depression and anxiety disorders in patients with restless legs syndrome. J Neurol 2005 Jan; 252 (1): 67-71
55. Garvey MJ, Tollefson GD. Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatry 1987 Mar; 44 (3): 269-72
56. Bakshi R. Fluoxetine and restless legs syndrome. J Neurol Sci 1996 Oct; 142 (1-2): 151-2
57. Terao T, Terao M, Yoshimura R, et al. Restless legs syndrome induced by lithium. Biol Psychiatry 1991 Dec 1; 30 (11): 1167-70

58. Winkelmann J, Schadrack J, Wetter TC, et al. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. Sleep Med 2001 Jan; 2 (1): 57-61
59. Silber MH, Richardson JW. Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. Mayo Clin Proc 2003 Jan; 78 (1): 52-4
60. Benz RL, Pressman MR, Hovick ET, et al. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (the SLEEPO study). Am J Kidney Dis 1999 Dec; 34 (6): 1089-95
61. Earley CJ, Heckler D, Allen RP. The treatment of restless legs syndrome with intravenous iron dextran. Sleep Med 2004 May; 5 (3): 231-5
62. Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. Sleep Med 2005 Jul; 6 (4): 301-5
63. Sloand JA, Shelly MA, Feigin A, et al. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. Am J Kidney Dis 2004 Apr; 43 (4): 663-70
64. Benes H, Kurella B, Kummer J, et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep 1999 Dec 15; 22 (8): 1073-81
65. Hening WA, Allen RP, Earley CJ, et al. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004 May 1; 27 (3): 560-83
66. Saletu M, Anderer P, Hogl B, et al. Acute double-blind, placebo-controlled sleep laboratory and clinical follow-up studies with a combination treatment of rr-L-dopa and sr-L-dopa in restless legs syndrome. J Neural Transm 2003 Jun; 110 (6): 611-26
67. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide [letter]. Arch Neurol 1982; 39: 739
68. Kaplan PW, Allen RP, Buchholz DW, et al. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep 1993 Dec; 16 (8): 717-23
69. Trenkwalder C, Stiasny K, Pollmacher T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. Sleep 1995 Oct; 18 (8): 681-8
70. Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. Neurology 1999 Jan 15; 52 (2): 285-90
71. Trenkwalder C, Collado Seidel V, Kazenwadel J, et al. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? Mov Disord 2003 Oct; 18 (10): 1184-9
72. Sandyk R, Bernick C, Lee SM, et al. L-dopa in uremic patients with the restless legs syndrome. Int J Neurosci 1987 Aug; 35 (3-4): 233-5
73. Wetter TC, Trenkwalder C, Stiasny K, et al. Treatment of idiopathic and uremic restless legs syndrome with L-dopa: a double-blind cross-over study [in German]. Wien Med Wochenschr 1995; 145 (17-18): 525-7
74. Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. Sleep 1996 Apr; 19 (3): 214-8
75. Pellecchia MT, Vitale C, Sabatini M, et al. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. Clin Neuropharmacol 2004 Jul-Aug; 27 (4): 178-81
76. Miranda M, Kagi M, Fabres L, et al. Pramipexole for the treatment of uremic restless legs in patients undergoing hemodialysis. Neurology 2004 Mar 9; 62 (5): 831-2
77. Pieta J, Millar T, Zacharias J, et al. Effect of pergolide on restless legs and leg movements in sleep in uremic patients. Sleep 1998 Sep 15; 21 (6): 617-22
78. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. Am J Kidney Dis 2001 Jul; 38 (1): 104-8
79. Read DJ, Feest TG, Nassim MA. Clonazepam: effective treatment for restless legs syndrome in uraemia. BMJ (Clin Res Ed) 1981 Oct 3; 283 (6296): 885-6
80. Braude W, Barnes T. Clonazepam: effective treatment for restless legs syndrome in uraemia. BMJ (Clin Res Ed) 1982 Feb 13; 284 (6314): 510
81. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003 Aug 12; 61 (3): 304-9
82. Horvath J, Fross RD, Kleiner-Fisman G, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord 2004 Jun; 19 (6): 656-62
83. Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004 Apr 10; 363 (9416): 1179-83
84. Danoff SK, Grasso ME, Terry PB, et al. Pleuropulmonary disease due to pergolide use for restless legs syndrome. Chest 2001 Jul; 120 (1): 313-6
85. Plowman BK, Boggie DT, Morreale AP, et al. Sleep attacks in patients receiving dopamine-receptor agonists. Am J Health Syst Pharm 2005 Mar 1; 62 (5): 537-40
86. Möller J, Körner Y, Cassel W, et al. Sudden onset of sleep and dopaminergic therapy in patients with restless legs syndrome. Sleep Med 2006. In press
87. Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome: an open label trial. Neuropsychobiology 2004; 50 (1): 65-70
88. Lin SC, Kaplan J, Burger CD, et al. Effect of pramipexole in treatment of resistant restless legs syndrome. Mayo Clin Proc 1998 Jun; 73 (6): 497-500
89. Becker PM, Ondo W, Sharon D. Encouraging initial response of restless legs syndrome to pramipexole. Neurology 1998 Oct; 51 (4): 1221-3
90. Montplaisir J, Nicolas A, Denesle R, et al. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology 1999 Mar 23; 52 (5): 938-43
91. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. Eur Arch Psychiatry Clin Neurosci 2002 Aug; 252 (4): 185-94

92. Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol 2000 May; 7 Suppl. 1: 27-31
93. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep 2003 Nov 1; 26 (7): 819-21
94. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med 2004 Jan; 5 (1): 9-14
95. Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. Neurology 1997 Jul; 49 (1 Suppl. 1): S58-62
96. Walters AS, Ondo WG, Dreykluft T, et al. 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 2004 Dec; 19 (12): 1414-23
97. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004 Jan; 75 (1): 92-7
98. Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep 2004 Aug 1; 27 (5): 907-14
99. Adler CH, Hauser RA, Sethi K, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology 2004 Apr 27; 62 (8): 1405-7
100. Bliwise DL, Freeman A, Ingram CD, et al. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. Sleep Med 2005 Mar; 6 (2): 141-7
101. Staedt J, Wassmuth F, Ziemann U, 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 (4-5): 461-8
102. Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. Neurology 1998 Dec; 51 (6): 1599-602
103. Wetter TC, Stiasny K, Winkelmann J, et al. A randomized controlled study of pergolide in patients with restless legs syndrome. Neurology 1999 Mar 23; 52 (5): 944-50
104. Winkelmann J, Wetter TC, Stiasny K, et al. Treatment of restless leg syndrome with pergolide--an open clinical trial. Mov Disord 1998 May; 13 (3): 566-9
105. Trenkwalder C, Hundemer HP, Lledo A, et al. Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS Study. Neurology 2004 Apr 27; 62 (8): 1391-7
106. Stiasny-Kolster K, Benes H, Peglau I, et al. Effective cabergoline treatment in idiopathic restless legs syndrome. Neurology 2004 Dec 28; 63 (12): 2272-9
107. Stiasny K. Clinical data on restless legs syndrome: a dose-finding study with cabergoline. Eur Neurol 2001; 46 Suppl. 1: 24-6
108. Zucconi M, Oldani A, Castronovo C, et al. Cabergoline is an effective single-drug treatment for restless legs syndrome: clinical and actigraphic evaluation. Sleep 2003 Nov 1; 26 (7): 815-8
109. Stiasny K, Robbecke J, Schuler P, et al. Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline: an open clinical trial. Sleep 2000 May 1; 23 (3): 349-54
110. Benes H, Heinrich CR, Ueberall MA, et al. Long-term safety and efficacy of cabergoline for the treatment of idiopathic restless legs syndrome: results from an open-label 6-month clinical trial. Sleep 2004 Jun 15; 27 (4): 674-82
111. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996 Apr; 19 (3): 205-13
112. Silber MH, Shepard JW, Wisbey JA. Pergolide in the management of restless legs syndrome: an extended study. Sleep 1997 Oct; 20 (10): 878-82
113. Stiasny K, Wetter TC, Winkelmann J, et al. Long-term effects of pergolide in the treatment of restless legs syndrome. Neurology 2001 May 22; 56 (10): 1399-402
114. Adler CH. Treatment of restless legs syndrome with gabapentin. Clin Neuropharmacol 1997 Apr; 20 (2): 148-51
115. Happe S, Klosch G, Saletu B, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology 2001 Nov 13; 57 (9): 1717-9
116. Happe S, Sauter C, Klosch G, et al. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology 2003; 48 (2): 82-6
117. Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002 Nov 26; 59 (10): 1573-9
118. Lipson J, Lavoie S, Zimmerman D. Gabapentin-induced myopathy in 2 patients on short daily hemodialysis. Am J Kidney Dis 2005 Jun; 45 (6): e100-4
119. Mitler MM, Browman CP, Menn SJ, et al. Nocturnal myoclonus: treatment efficacy of clonazepam and temazepam. Sleep 1986; 9 (3): 385-92
120. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. Am J Med 1996 Mar; 100 (3): 333-7
121. Montplaisir J, Godbout R, Boghen D, et al. Familial restless legs with periodic movements in sleep: electrophysiologic, biochemical, and pharmacologic study. Neurology 1985 Jan; 35 (1): 130-4
122. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. Eur Neuropsychopharmacol 2001 Apr; 11 (2): 153-61
123. Montagna P, Sassoli de Bianchi L, Zucconi M, et al. Clonazepam and vibration in restless legs syndrome. Acta Neurol Scand 1984 Jun; 69 (6): 428-30
124. Boghen D, Lamothe L, Elie R, et al. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. Can J Neurol Sci 1986 Aug; 13 (3): 245-7
125. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. J Neurol Neurosurg Psychiatry 1987 Dec; 50 (12): 1679-81
126. Horiguchi J, Inami Y, Sasaki A, et al. Periodic leg movements in sleep with restless legs syndrome: effect of clonazepam treatment. Jpn J Psychiatry Neurol 1992 Sep; 46 (3): 727-32

127. Willis T. The London practice of physick. London: Bassett and Crooke, 1685

128. Walters A, Hening W, Cote L, et al. Dominantly inherited restless legs with myoclonus and periodic movements of sleep: a syndrome related to the endogenous opiates? Adv Neurol 1986; 43: 309-19

129. Walters AS, Hening WA, Kavey N, et al. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. Ann Neurol 1988 Sep; 24 (3): 455-8

130. Telstad W, Sorensen O, Larsen S, et al. Treatment of the restless legs syndrome with carbamazepine: a double blind study. BMJ (Clin Res Ed) 1984 Feb 11; 288 (6415): 444-6

131. Lundvall O, Abom PE, Holm R. Carbamazepine in restless legs: a controlled pilot study. Eur J Clin Pharmacol 1983; 25 (3): 323-4

132. Walters AS, Winkelmann J, Trenkwalder C, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord 2001 Nov; 16 (6): 1105-9

133. Hening WA, Walters A, Kavey N, et al. Dyskinesias while awake and periodic movements in sleep in restless legs syndrome: treatment with opioids. Neurology 1986 Oct; 36 (10): 1363-6

134. Eisensehr I, Ehrenberg BL, Rogge Solti S, et al. Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid. J Neurol 2004 May; 251 (5): 579-83

135. Bezerra ML, Martinez JV. Zolpidem in restless legs syndrome. Eur Neurol 2002; 48 (3): 180-1

136. Wagner ML, Walters AS, Coleman RG, et al. Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. Sleep 1996 Jan; 19 (1): 52-8

137. GlaxoSmithKline. Requip® (ropinirole hydrochloride) tablets [online]. Available from URL: http://us.gsk.com/products/assets/us_requip.pdf [Accessed 2006 21 Mar]

138. Boehringer Ingelheim. Mirapex® pramipexole dihydrochloride prescribing information [online]. Available from URL: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt=/Prescribing+Information/PIs/Mirapex/Mirapex.pdf [Accessed 2006 Mar 21]

Correspondence and offprints: Dr *Istvan Mucsi*, Division of Nephrology, Humber River Regional Hospital, 200 Church Street, Toronto, M9N 1N8, Canada.
E-mail: mucsist@net.sote.hu