



Ropinirole in the treatment of restless legs syndrome

Rajdeep S Kakar and Clete A Kushida[†]

Ropinirole is an original nonergoline dopamine agonist indicated for the treatment of Parkinson's disease. However, recent developments in the study of restless legs syndrome have demonstrated another role for this drug. The symptoms of restless legs syndrome are responsive to dopaminergic agents such as ropinirole. The dosage of ropinirole needed to treat the symptoms of restless legs syndrome appears to be much smaller than what is necessary for Parkinson's disease therapy. The liver is primarily responsible for the metabolism of ropinirole, which has an elimination half-life of approximately 6 h. Ropinirole is generally well tolerated, with no serious adverse effects. Clinical studies have indicated that ropinirole can effectively reduce the motor symptoms of restless legs syndrome and improve overall sleep quality.

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Restless legs syndrome (RLS) is a common neurologic disorder characterized primarily by uncomfortable and unpleasant sensations in the legs, which are relieved by movement. According to the recently revised diagnostic criteria, RLS is a clinical diagnosis that depends on establishing the key features of the disorder [1]. The four essential diagnostic features of RLS include:

- A strong urge to move the legs, usually associated with uncomfortable sensations in the legs
- Symptoms that start or become worse with rest
- A temporary or partial relief of symptoms with movement, such as stretching or walking
- A worsening of symptoms in the evening or at night

RLS is characterized as a sleep disorder by the American Academy of Sleep Medicine due to the impact of RLS on sleep onset latency and sleep disruption during the night. Often patients describe their experiences of difficulty in initiating or maintaining sleep due to the severe discomfort in their legs at night. The pain or unpleasant sensations may present during the early morning hours, resulting in the patients pacing their bedroom

in frustration in the middle of the night. Feelings of aggravation and anxiety would be expected in anyone who has a disturbed major sleep period, with secondary daytime fatigue or sleepiness. Consistent sleep deprivation and emotional suffering as a consequence of RLS is likely to contribute to other significant health risks, including mood disorders, diminished immune function and increased risk of accidents.

Frequently, patients with RLS experience periodic leg movements (PLMs) that can occur during resting periods while awake or during sleep. PLMs are defined as repetitive movements of the lower extremities for periods of 0.5–5 sec at intervals of 5–90 sec, with at least four in a series [2]. When these PLMs occur during sleep, they have the ability to awake the patient from sleep, thus causing sleep disturbance. When multiple PLMs with arousal occur during the sleep period, there may be sleep fragmentation and a reduction in sleep efficiency, with consequent excessive daytime sleepiness or fatigue. In general, PLMs in sleep occur in approximately 80–90% of patients with RLS [3]. Thus, the presence of PLMs in sleep bolsters the diagnosis of RLS. However, the absence of such movements during sleep does not exclude a diagnosis of RLS.

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Affiliations

[†] Author for correspondence
Stanford University Center of
Excellence for Sleep Disorders
Research, Stanford Sleep Disorders
Center, Department of Psychiatry
and Behavioral Sciences,
401 Quarry Road, Suite 3301,
Palo Alto, CA 94305, USA
Tel: +1 650 723 6601
Fax: 1 650 725 8910
clete@stanford.edu

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Most RLS cases appear to be idiopathic in nature; however, with the increasing number of RLS patients with iron deficiency and low ferritin, this may be an incorrect assumption as it is unclear if these patients are being correctly classified as having nonidiopathic RLS. Clinical surveys of idiopathic RLS patients have shown that up to 60% report a positive family history [4]. Despite these reports, genetic analyses published to date have found different contributing chromosomes. Various other mechanisms for the development of RLS have been suggested. The role of spinal structures in the pathophysiology of RLS continues to evolve. One theory involves the presence of the central spinal pattern generator for gait, which is modulated by central dopaminergic neurons [5]. The current literature favors the dopaminergic A11 neurons as an RLS-generator over the nigrostriatal dopaminergic system (A9 neurons) responsible for the major symptoms of Parkinson's disease [6]. Another area of focus is the opiate system, indicated by the excellent treatment responses in RLS. It is known that the efficacy of opiates in pain relief is related to the dopaminergic system. Additionally, noradrenergic neurotransmission may also have a role in inducing RLS since dopamine is a precursor in the synthesis of norepinephrine. Finally, a fresh theme receiving attention is the circadian rhythm of RLS symptoms. It has been shown that physiologic concentrations of melatonin exert an inhibitory effect on dopaminergic secretion in several areas of the mammalian CNS, and the results of a recent study suggest that melatonin may be implicated in the worsening of RLS symptoms in the evening and during the night [7].

Although the pathophysiology of RLS is still not completely understood, the aforementioned recent developments all point to the involvement of the dopaminergic system in RLS. Additionally, there is growing evidence that an abnormality of the body's use and storage of iron may be the cause of the dopamine defect. For example, imaging studies using ligands targeted to pre- and postsynaptic dopamine sites have found a mild reduction of dopamine function in the striatum region of the brain [8,9]. It is still unclear whether this modest difference is suggestive of RLS involvement or simply a part of a more general dopamine dysfunction. Furthermore, not every study has found an abnormality of dopaminergic system imaging [10]. Studies of the cerebrospinal fluid in RLS patients obtained during periods with and without symptoms found no difference from controls in the dopamine metabolite, homovanillic acid [11,12]. However, this was also the case in Parkinson's disease, despite the fact that the dopaminergic system is much more impaired than in RLS, suggesting that this is not a sensitive method of measuring central dopamine deficiency. Therefore, dopamine involvement in RLS may be primarily pharmacologic, rather than physiologic.

Below are the three most important, reversible, secondary forms of RLS:

- End stage renal disease
- Pregnancy
- Iron deficiency anemia

are all associated with altered iron metabolism. In particular, iron deficiency has been found to be common in cases of secondary RLS. Low iron stores, as determined by a serum ferritin level of less than 50 mcg, have been shown to be associated with RLS symptoms [13]. Iron supplementation in such cases, even when there is no associated anemia, has been shown to be effective in reducing the symptoms of RLS. Recent data have documented the relative depletion of brain iron stores in RLS patients. Ferritin in cerebrospinal fluid has been found to be low in idiopathic RLS patients [14]. Also, magnetic resonance imaging studies of the brain have shown depletion of iron in the substantia nigra of such patients, which is related to RLS severity [15]. Autopsy reports have confirmed depletion of iron and alteration in levels of iron proteins [16]. Iron is required as a cofactor for hydroxylation of tyrosine hydroxylase, which is the rate-limiting enzyme for dopamine synthesis. These findings on iron deficiency have been included in a comprehensive model that explains how iron deficiency could lead to the dopamine abnormalities underlying RLS [17].

Recent prevalence studies confirm the notion that RLS is common in populations derived from northern and western Europe. One study of a population sample in Kentucky (USA), using a questionnaire that was based on the International RLS Study Group criteria (IRLSSG), found that 10% of respondents reported experiencing RLS symptoms on 5 or more nights per month [18,19]. Another study of working age women in Sweden (aged 18–64 years) found that 11.4% of these adults reported symptoms of RLS consistent with the IRLSSG diagnostic criteria [20]. A similar study of men found that 5.8% were affected [21]. There were significantly increased complaints of sleep problems and effects on daytime performance due to inadequate sleep in these women compared with those without RLS symptoms. In a population study of the elderly in Germany, 10.2% of the elderly were diagnosed with RLS, women at a higher prevalence (13.9%) than men (6.2%) [22]. Recently, a number of epidemiologic studies have examined RLS prevalence in other population groups. The large, multinational RLS Epidemiology, Symptoms and Treatment Primary Care Study found that 9.6% of patients reported experiencing symptoms at least weekly, and 88.4% of RLS sufferers reported at least one sleep-related symptom [23]. Although 64.8% reported consulting a physician about their symptoms, only 12.9% reported receiving a diagnosis of RLS by their physician. Two studies from Asia found lower prevalence in Japanese (3%) and Singapore (0.1%) populations than those typically seen in northern and western European populations [24,25]. Recent studies have suggested that PLMs during sleep may be more common in children than previously suspected. There is evidence that PLMs are especially common in children with attention deficit hyperactivity disorder (ADHD) [26,27].

As previously noted, the diagnosis of RLS is based on a clinical history of symptoms meeting the four cardinal features of this disorder. An objective diagnostic test for RLS has yet to be established. However, diagnostic tests such as the suggested immobilization test (SIT) and the polysomnogram (PSG) are

being used to fully evaluate patients with symptoms of RLS. A combination of the SIT, a provocation test conducted in the evening, with measurement of sensory discomfort and the presence of frequent PLMs during the awake epochs of the standard PSG can produce a high degree of diagnostic accuracy (reported sensitivity of 82%, specificity of 100% on sample tested) [28,29]. This may therefore be helpful as a confirmatory test if it is positive, but it does not rule out RLS if negative.

Since RLS is primarily a subjective disorder, the average office evaluation is limited to subjective rating scales to determine severity. The International RLS rating scale has been validated in an international multicenter study (IRLSSG) [19]. This rating scale is now being used as a measure of therapeutic efficacy in clinical trials. Its utility lies in its ability to measure both primary disease symptoms and disease impact on sleep and quality of life. Additional subjective measures include sleep logs and quality of life scales.

In general, pharmacologic treatment of RLS should be limited to patients who meet specific diagnostic criteria and experience clinically relevant RLS symptoms. Therapy should be tailored to the severity of the disease, the subjective complaints of a patient and a patient's desire for treatment. All medications that are helpful for RLS also appear to be effective in PLM disorder. In recent reviews of the literature, it has become clear that dopaminergic agents have been the focus of intense evaluation in RLS therapy [30–32]. RLS has primarily been treated by four types of medications: dopaminergic agents, opioids, benzodiazepines and anticonvulsants. However, dopaminergic agents, particularly dopamine agonists, have been the best-studied and most successful class of medications in the treatment of RLS.

Overview of the market

Levodopa with decarboxylase inhibitor is effective in the treatment of RLS and periodic leg movement disorder (PLMD) [31]. To date, levodopa has been the most studied dopaminergic agent as a treatment for RLS. The main side effects complicating its use in clinical practice are the high frequencies of RLS daytime augmentation (i.e., occurrence or worsening of daytime RLS symptoms with long-term medication usage) and early morning rebound of RLS symptoms, especially at higher doses.

Another agent effective in the treatment of RLS and PLMD is pergolide, an ergot-derived dopamine agonist. In one large clinical study, 78.6% remained on pergolide long-term, despite adverse effects of nausea, nasal congestion and mild augmentation [33]. In most cases, these adverse effects were either minor or could be adequately controlled. Other recent studies also confirm the objective and subjective benefits of pergolide in the treatment of RLS [34,35]. However, the development of serious complications that are typical of ergot-derived medications, such as pleuropulmonary fibrosis or cardiac valvulopathy, have been documented in isolated case reports [36,37].

Given the adverse effects associated with levodopa and pergolide, many researchers are putting more efforts in evaluating newer, nonergoline forms of dopamine agonists for RLS therapy. Pramipexole is one of these agents that have shown

promise. In a small, double-blinded, randomized and controlled study, pramipexole was significantly effective in relieving RLS sensorimotor symptoms by questionnaire assessment and reducing PLMs by polysomnogram [38]. Similarly, a more recent open label trial with pramipexole in 17 patients with RLS demonstrated improvements in both subjective findings and objective data using polysomnogram [39]. Other small studies have also shown subjective improvement in RLS symptoms [40–43]. The most commonly reported side effects in these studies were fluid retention/edema, daytime fatigue/sleepiness, gastrointestinal distress, insomnia/alertness, dizziness and occasional augmentation of RLS. These studies consistently report a benefit in using pramipexole in the treatment of RLS in adults. However, the actual degree of effectiveness remains unclear due to the inadequate number of large studies.

Finally, it should be mentioned that gabapentin has also been shown to improve the symptoms associated with RLS. Gabapentin is a structural analogue of γ -aminobutyric acid. A recent 4-week open clinical trial comparing gabapentin and ropinirole in the treatment of idiopathic RLS showed that these two agents were similar in their effects and tolerability [44]. The mean dosage of gabapentin in this study was 800 ± 397 mg, while the mean dosage of ropinirole was 0.78 ± 0.47 mg. In most patients, RLS symptoms were still improved after 6–10 months of follow-up. Further double-blinded, placebo-controlled trials are necessary to determine the definitive role of gabapentin in the treatment of RLS.

Another nonergot dopamine agonist that is being actively studied in the treatment of RLS is ropinirole. Ropinirole is approved for treatment of the signs and symptoms of idiopathic Parkinson's disease (PD). The effectiveness of ropinirole was demonstrated in randomized, controlled trials in patients with early PD who were not receiving concomitant levodopa therapy as well as in patients with advanced PD on concomitant levodopa [45–48].

Pharmacology

Ropinirole is a selective dopamine agonist at the D₂, D₃ and D₄ dopamine receptor subtypes, binding with higher affinity to D₃ receptors than the other receptor subtypes [49]. Ropinirole binds to both central and peripheral dopamine receptors.

Pharmacokinetics, pharmacodynamics & metabolism

Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1–2 h. In clinical studies, over 88% of a radiolabeled dose was recovered in the urine and absolute bioavailability was 55%, indicating a first-pass effect [49]. Food does not affect the extent of absorption of ropinirole. Its elimination half-life is approximately 6 h [50]. Steady-state concentrations can be expected within 2 days of dosing. Ropinirole is widely distributed throughout the body, and it has low protein binding that is independent of its plasma concentration. Ropinirole is extensively metabolized to inactive metabolites by the liver. The major metabolic pathways are *N*-despropylation and hydroxylation to form the inactive metabolites. The major

cytochrome P450 isozyme involved in the metabolism of ropinirole is CYP1A2 [49]. Less than 10% of the administered dose is excreted as unchanged drug in the urine.

Since clinical studies showed that CYP1A2 is the major enzyme responsible for the metabolism of ropinirole, there is the potential for inhibitors or substrates of this enzyme to alter its clearance. Therefore, if therapy with a drug known to be a potent inhibitor of CYP1A2 is started or stopped during treatment with ropinirole, adjustment of the ropinirole dose may be required.

Since therapy with ropinirole is initiated at a subtherapeutic dosage and gradually titrated upward according to symptomatic effects, adjustment of the initial dose based on gender, weight or age is not necessary [49]. Also, no dosage adjustment is necessary in patients with moderate renal impairment (i.e., creatinine clearance between 30 and 50 ml/min) [51]. A recent open-label crossover trial demonstrated that ropinirole was superior to levodopa sustained release in relieving symptoms consistent with RLS in a population of patients on chronic hemodialysis [52]. As ropinirole is mainly metabolized in the liver, the use of this drug is not recommended in patients with significant hepatic dysfunction. In general, with any of the dopamine agonists, treatment of RLS should involve using the lowest effective dose to avoid adverse effects.

Clinical efficacy

There have been a number of studies that have evaluated the efficacy of ropinirole as monotherapy in the treatment of PD; however, clinical efficacy studies evaluating its role in the treatment of RLS have been limited. Until recently, there were only five small clinical studies supporting the use of ropinirole in RLS therapy. One study was a single-blinded, nonrandomized crossover trial investigating the acute effects of ropinirole 0.5 mg in untreated RLS patients [53,54]. According to evaluations performed with psychomotor tasks and standard nocturnal polysomnography, there were significant improvements in objective and subjective sleep quality measures. Ropinirole treatment resulted in increases in both total sleep time and sleep efficiency, as compared with placebo. The other four studies were open-label clinical series that varied in duration of treatment, from 1 to 10 months, and the sample sizes were small (five to 16 subjects) [55–58]. The treatment dosage ranged from 0.25 to 4.0 mg. PLMs were measured (using PSG) in one study, and the others used subjective tools. The study using objective data found improvements in sleep efficiency and PLMs, both immediately after beginning treatment with ropinirole and 1 month later [55]. All studies reported significant reductions of symptom severity through subjective ratings while on treatment.

Given the promising results of these initial clinical studies, the thrust to fully evaluate the potential role of ropinirole in RLS treatment has recently produced larger, double-blinded, placebo-controlled trials. The first of these trials was a 12-week randomized comparison involving 284 patients from ten European countries [59]. The mean daily dose of ropinirole at 12 weeks was 1.9 mg. The daily dose was administered near

bedtime. There was a significant improvement in subjective rating scales in the ropinirole group as compared with placebo at week 12. Furthermore, based on these subjective ratings scales, the benefits of ropinirole were apparent by week 1. Ropinirole also resulted in major enhancements in sleep and quality of life end points. The most common adverse effects were nausea (37.7%) and headache (19.9%).

Another double-blinded, placebo-controlled study of ropinirole was performed as a crossover trial of 22 RLS patients [60]. Patients were treated with up to 6.0 mg/day over a 4-week study period. The average daily dose of ropinirole during treatment was 4.6 mg, divided in twice-daily doses between 18:00 and 19:00, and at bedtime. The degree of improvement with ropinirole was approximately 50% using the RLS Rating Scale and diary data. Only eight out of the 22 patients had complete resolution of symptoms during ropinirole treatment. It was well tolerated during the study, and the most common adverse effects reported were nausea and dizziness. The high average daily dose of ropinirole required for treatment in this study was likely to be as a result of administering the first dose too early in the evening, which may have produced some augmentation effects. Another explanation for this atypical result is that the study period was very short and the dosage was increased rapidly due to time constraints.

A multinational study evaluated 106 out of 202 RLS patients who completed 24 weeks of ropinirole treatment, titrated to a dose range of 0.25–4 mg/day in a single-blind condition; 92 of these patients were then randomized to 12 weeks of double-blind treatment with ropinirole or placebo [61]. The drug was administered once daily near bedtime. The primary end point was the proportion of patients relapsing during the double-blind phase. The odds of a patient relapsing while receiving placebo were approximately three-times greater than those of a patient receiving ropinirole. In addition, health-related quality of life measures showed a significant treatment difference in favor of ropinirole, and when compared with patients continuing to receive ropinirole, patients switching to placebo during the double-blind phase experienced significant worsening in sleep disturbance, daytime somnolence and sleep quality.

Ultimately, the most recently published study has been the most comprehensive and objective evaluation. Allen and colleagues studied 65 patients with RLS and PLMs in a double-blinded, placebo-controlled, parallel-group, 12-week assessment [62]. The dose of active medication or matching placebo was flexible, ranging from 0.25 to 4.0 mg/day. Drug administration occurred once daily near bedtime. Objective data were obtained from standard polysomnographic evaluations and subjective measures were gathered using the International Restless Legs Scale and the Medical Outcomes Study sleep scale. Ropinirole, at a mean dose of 1.8 mg/day, effectively reduced PLMs in sleep to normal levels (<5 PLMs/h) for more than half of the patients. At this dose, it also reduced PLMs with arousal to a trivial level (<2 PLMA/h) for most (78.6%) patients. More specifically, PLMs in sleep/h decreased from 48.5 to 11.8 in the ropinirole group compared with a decrease

from 35.7 to 34.2 in the placebo group. PLMs while awake /h were also considerably decreased with ropinirole treatment as compared with placebo. PSG studies further demonstrated that ropinirole treatment significantly improved both patients' ability to initiate sleep and the amount of Stage II sleep compared with placebo. Additionally, there were nonsignificant trends toward increases in total sleep time and sleep efficiency. Again, ropinirole was well tolerated, with no serious adverse effects. The most common adverse effects reported during treatment were headache (34.4%) and nausea (31.3%).

Safety & tolerability

The clinical safety of ropinirole is similar to other dopamine agonists. Most side effects are related to its dopaminergic activity. The most commonly reported side effects in clinical trials include nausea, headache, dizziness, somnolence, vomiting, abdominal pain, dyskinesia, orthostatic hypotension and worsening of RLS or PD symptoms [63]. Augmentation of symptoms, described as either a morning rebound exacerbation or an earlier appearance in the evening, has been attributed to some dopamine agonists, particularly levodopa. Although there have been some reports of augmentation associated with the use of ropinirole, the present data provide no clear suggestion to the extent of its impact at the lower doses commonly used for RLS.

The one adverse effect of dopamine agonists that appears to be receiving more attention is that of drowsiness or sleepiness. The initial report of irresistible and sudden sleepiness (i.e., sleep attacks) induced by dopamine agonists resulting in automobile accidents in PD patients spurred numerous investigations that have suggested that sleepiness in PD patients can occur with many different treatments [64–66]. The adverse effect of daytime drowsiness from treatment with dopamine agonists appears to be more common for PD patients than for RLS patients [67]. In clinical practice, patients should be monitored carefully for these symptoms, and they may need to be advised not to drive and to avoid other potentially dangerous activities. Given this caveat, however, monitoring of somnolence in patients treated with dopamine agonists has not been extensively researched, and its importance and severity remain unclear.

Although sleepiness has been reported as a side effect of dopaminergic agents in some RLS patients, ropinirole appears less likely to cause excessive daytime sleepiness in the treatment of RLS as compared with the treatment of PD. Part of this explanation may be due to the very different pathologies of these two disorders. PD patients also show a possible predisposition towards daytime sleepiness independent of treatment [68]. Finally, PD patients often take much higher doses of these dopaminergic agents than their RLS counterparts.

The long-term use of nonergoline dopamine agonists such as ropinirole will probably not result in serious adverse effects, such as pleuropulmonary fibrosis and cardiac valvulopathy, which have been attributed to some ergot-derived dopamine agonists. However, long-term postmarketing surveillance is still lacking.

Expert opinion & five-year view

Overall, recent studies of ropinirole have demonstrated its remarkable clinical efficacy in the treatment of both idiopathic and uremic RLS. Ropinirole treatment reduces the incidence of the motor symptoms of RLS, and it improves overall sleep, thus effectively treating the primary morbidity of RLS. Furthermore, improvements in sleep have been demonstrated with both objective and subjective assessments. The average daily dose of ropinirole for effective RLS treatment appears to be approximately 2.0 mg, given 1–3 h prior to bedtime.

Ropinirole has also been well tolerated, with no serious adverse effects. Nausea, headache and dizziness remain the most frequent side effects. The significance of augmentation remains unclear due to a lack of substantial data at this time. Treating RLS with the lowest effective dose of ropinirole should help to avoid some of these adverse effects. The issue of sleepiness secondary to medication effects, raised for the treatment of PD, has had quite limited study in relation to RLS. However, ropinirole appears less likely to cause excessive daytime sleepiness in the treatment of RLS as compared with the treatment of PD, for the reasons described above.

In the near future, large multicenter trials are needed to further investigate the role of dopamine agonists in RLS treatment. Specifically, emphasis should be placed on gathering more data on clinical efficacy, precise effects of treatment, and long-term benefits and treatment effects. Other focal points of study should be the issue of symptomatic augmentation and the potential problem of daytime sleepiness induced by treatment. There clearly remains an inadequate amount of knowledge regarding the long-term treatment outcomes and the extent of augmentation with dopamine agonists. Lastly, comparative studies of agents used in RLS therapy would be helpful in guiding treatment.

Key issues

- Restless legs syndrome (RLS) is a common neurologic condition characterized by uncomfortable and unpleasant sensations in the legs, which are relieved by movement. Although the etiology remains uncertain, current research indicates involvement of the dopamine system.
- Ropinirole is a nonergoline dopamine agonist which is approved for the treatment of the signs and symptoms of idiopathic Parkinson's disease.
- Treatment with ropinirole reduces the incidence of the motor symptoms of RLS and improves overall sleep quality.
- The ropinirole dosage required to treat the symptoms of RLS (0.25–3.0 mg) appears to be much smaller than what is necessary for Parkinson's disease therapy.
- Ropinirole is generally well tolerated, with no serious adverse effects.
- Further investigation through long-term clinical trials may soon lead to the approval of ropinirole for RLS therapy.

There remains a lack of information regarding various administration routes and special populations. The elderly constitute part of the population currently being studied, but systematic reviews may be necessary. In addition, given the current increased awareness of ADHD in children, it appears probable that more emphasis will be placed on evaluating associated disorders such as RLS and the medications used to treat them. The treatment of secondary

RLS with dopaminergic agents deserves more attention. Also, treatment of RLS with dopamine agonists will require further analyses of patients' symptoms and the various needs for once-daily dosing, multiple daily doses or only intermittent treatment. Finally, additional molecular genetic studies may help to identify genes that can predispose to this disorder, thus facilitating the development of new therapeutic strategies.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- 1 Allen RP, Hening WA, Montplaisir J *et al.* Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from The RLS Diagnosis and Epidemiology workshop at the National Institute of Health. *Sleep Med.* 4(2), 101–119 (2003).
- **Reviews the important considerations in confirming a diagnosis of restless legs syndrome (RLS).**
- 2 Atlas Task Force of the American Sleep Disorders Association. Recording and scoring of leg movements. *Sleep* 16, 748–759 (1993).
- 3 Montplaisir J, Boucher S, Poirier G, Lazure G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov. Disord.* 12, 61–65 (1997).
- 4 Ferini-Strambi L, Bonati MT, Oldani A, Aridon P, Zucconi M, Casari G. Genetics in restless legs syndrome. *Sleep Med.* 5(3), 301–304 (2004).
- 5 Trenkwalder C, Paulus W. Why do restless legs occur at rest? Pathophysiology of neuronal structures in RLS. Neurophysiology of RLS (part 2). *Clin. Neurophysiol.* 115, 1975–1988 (2004).
- **Second part of a current update on the pathophysiology of RLS.**
- 6 Ondo WG, He Y, Rajasekaran S, Le WD. Clinical correlates of 6-hydroxydopamine injections into A11 dopaminergic neurons in rats: a possible model for restless legs syndrome. *Mov. Disord.* 15, 154–158 (2000).
- 7 Michaud M, Dumont M, Selmaoui B, Paquet J, Fantini ML, Montplaisir J. Circadian rhythm of restless legs syndrome: relationship with biological markers. *Ann. Neurol.* 55(3), 372–380 (2004).
- **Proposes the role of a circadian factor in the development of RLS.**
- 8 Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. *Neurology* 52(5), 932–937 (1999).
- 9 Ruottinen HM, Partinen M, Hublin C *et al.* An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. *Neurology* 54(2), 502–504 (2000).
- 10 Eisensehr I, Wetter TC, Linke R *et al.* Normal IPT and IBZM SPECT in drug-naive and levodopa-treated idiopathic restless legs syndrome. *Neurology* 57(7), 1307–1309 (2001).
- 11 Earley CJ, Hyland K, Allen RP. CSF dopamine, serotonin, and bipterin metabolites in patients with restless legs syndrome. *Mov. Disord.* 16(1), 144–149 (2001).
- 12 Stiasny-Kolster K, Möller JC, Zschocke J *et al.* Normal dopaminergic and serotonergic metabolites in cerebrospinal fluid and blood of restless legs syndrome patients. *Mov. Disord.* 19(2), 192–196 (2004).
- 13 Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep* 21(4), 371–377 (1998).
- 14 Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology* 54(8), 1698–1700 (2000).
- 15 Allen RP, Barker PB, Wehr F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* 56(2), 263–265 (2001).
- 16 Connor JR, Boyer PJ, Menzies SL *et al.* Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology* 61(3), 304–309 (2003).
- 17 Earley CJ, Allen RP, Beard JL, Connor JR. Insight into the pathophysiology of restless legs syndrome. *J. Neurosci. Res.* 62(5), 623–628 (2000).
- 18 Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch. Intern. Med.* 160(14), 2137–2141 (2000).
- 19 The International Restless Legs Syndrome Study Group. The International Restless Legs Syndrome Study Group rating scale for Restless Legs Syndrome. *Sleep Med.* 4(2), 121–132 (2002).
- **Explains the use of the Idiopathic Restless Legs Syndrome Rating Scale and its validation for the evaluation of RLS.**
- 20 Ulfberg J, Nystrom B, Carter N, Edling C. Restless legs syndrome among working-aged women. *Eur. Neurol.* 46(1), 17–19 (2001).
- 21 Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov. Disord.* 16(6), 1159–1163 (2001).
- 22 Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. *Neurology* 54(5), 1064–1068 (2000).
- 23 Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* 5(3), 237–246 (2004).
- 24 Kageyama T, Kabuto M, Nitta H *et al.* Prevalences of periodic limb movement-like and restless legs-like symptoms among Japanese adults. *Psychiatry Clin. Neurosci.* 54(3), 296–298 (2000).
- 25 Tan EK, Seah A, See SJ, Lim E, Wong MC, Koh KK. Restless legs syndrome in an Asian population: a study in Singapore. *Mov. Disord.* 16(3), 729–732 (2001).
- 26 Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. *Sleep* 22(3), 297–300 (1999).
- 27 Chervin RD, Archbold KH, Dillon JE *et al.* Associations between symptoms of inattention, hyperactivity, restless legs, and periodic limb movements. *Sleep* 25(2), 213–218 (2002).
- **Examines the connections between RLS and attention deficit hyperactivity**

- disorder and the comorbid effects on sleep and daytime function.
- 28 Michaud M, Paquet J, Lavigne G, Desautels A, Montplaisir J. Sleep laboratory diagnosis of restless legs syndrome. *Eur. Neurol.* 48(2), 108–113 (2002).
- 29 Michaud M, Lavigne G, Desautels A, Poirier G, Montplaisir J. Effects of immobility on sensory and motor symptoms of restless legs syndrome. *Mov. Disord.* 17(1), 112–115 (2002).
- 30 Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 22(7), 961–968 (1999).
- **First comprehensive, evidence-based review of the literature for treatment options in the management of RLS and periodic leg movement disorder.**
- 31 Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 27(3), 557–559 (2004).
- 32 The Restless Legs Syndrome Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 27(3), 560–567 (2004).
- **Updated information and practice parameters on dopaminergic therapy for RLS.**
- 33 Stiasny K, Wetter TC, Winkelmann J *et al.* Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 56(10), 1399–1402 (2001).
- 34 Wetter TC, Stiasny K, Winkelmann J *et al.* A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 52(5), 944–950 (1999).
- 35 Trenkwalder C, Hundemer HP, Lledo A *et al.* Efficacy of pergolide in treatment of restless legs syndrome: The PEARLS study. *Neurology* 62(8), 1391–1397 (2004).
- 36 Danoff SK, Grasso ME, Terry PB, Flynn JA. Pleuropulmonary disease due to pergolide use for restless legs syndrome. *Chest* 120(1), 313–316 (2001).
- 37 Pritchett AM, Morrison JF, Edwards WD. Valvular heart disease in patients taking pergolide. *Mayo Clin. Proc.* 77(12), 1280–1286 (2002).
- 38 Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 52(5), 938–943 (1999).
- 39 Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome: an open label trial. *Neuropsychobiology* 50(1), 65–70 (2004).
- 40 Becker PM, Ondo W, Sharon D. Encouraging initial response of restless legs syndrome to pramipexole. *Neurology* 51(4), 1221–1223 (1998).
- 41 Lin SC, Kaplan J, Burger CD, Fredrickson PA. Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clin. Proc.* 73(6), 497–500 (1998).
- 42 Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur. J. Neurol.* 7(1), 127–131 (2000).
- 43 Stiasny K, Moller JC, Oertel WH. Safety of pramipexole in patients with restless legs syndrome. *Neurology* 55(10), 1589–1590 (2000).
- 44 Happe S, Sauter C, Klosch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology* 48(2), 82–86 (2003).
- 45 Adler CH, Sethi KD, Hauser RA *et al.* Ropinirole for the treatment of early Parkinson's disease. *Neurology* 49(2), 393–399 (1997).
- 46 Brooks DJ, Abbott RJ, Lees AJ *et al.* A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. *Clin. Neuropharmacol.* 21(2), 101–107 (1998).
- 47 Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, Fuell D. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Clin. Neuropharmacol.* 19(3), 234–245 (1996).
- 48 Lieberman A, Olanow CW, Sethi K *et al.* A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. *Neurology* 51(4), 1057–1062 (1998).
- 49 GlaxoSmithKline. Requip® Package Insert (2001).
- 50 Kuzel MD. Ropinirole: a dopamine agonist for the treatment of Parkinson's disease. *Am. J. Health Syst. Pharm.* 56(3), 217–224 (1999).
- 51 Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin. Pharmacokinet.* 39(4), 243–254 (2000).
- 52 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.* 27(4), 178–181 (2004).
- 53 Saletu B, Gruber G, Saletu M *et al.* Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. *Neuropsychobiology* 41(4), 181–189 (2000).
- 54 Saletu M, Anderer P, Saletu B *et al.* Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals, and respiratory variables. *Neuropsychobiology* 41(4), 190–199 (2000).
- 55 Estivill E, De la Fuente V. The efficacy of ropinirole in the treatment of chronic insomnia secondary to restless legs syndrome: polysomnography data. *Revista De Neurologia* 29(9), 805–807 (1999).
- 56 Ondo W. Ropinirole for restless legs syndrome. *Mov. Disord.* 14(1), 138–140 (1999).
- 57 Estivill E, De la Fuente V, Barraquer A, Cilveti R. Use of ropinirole as a treatment of 10 patients with restless legs syndrome. *14th European Congress on Sleep Research*, Madrid, Spain, 9–12 September. *J. Sleep Res.* 7(2), 80 (1998).
- 58 Galvez-Jimenez N, Khan T. Ropinirole and restless legs syndrome. *Mov. Disord.* 14(5), 890–892 (1999).
- 59 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* 75, 92–97 (2004).
- **Large, randomized, placebo-controlled study evaluating the effects of ropinirole on RLS using subjective outcome measures.**
- 60 Adler CH, Hauser RA, Sethi K *et al.* Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. *Neurology* 62, 1405–1407 (2004).
- 61 Montplaisir J, Karrasch J, Haan J, Kruger AJ, Volc D. The impact of ropinirole treatment on RLS symptoms and health-related quality of life (HRQOL) in patients with RLS: Results of a multinational 36-week study. *Sleep* 27, A293 (2004).
- 62 Allen R, Becker PM, Bogan R *et al.* Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep* 27(5), 907–914 (2004).

- Large, randomized, placebo-controlled trial evaluating the effects of ropinirole on RLS using both objective and subjective outcome measures.

63 Physicians' Desk Reference (2004).

64 Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 52(9), 1908–1910 (1999).

65 Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology* 57(8), 1392–1396 (2001).

66 Pal S, Bhattacharya KF, Apapito C, Chaudhuri KR. A study of excessive daytime sleepiness and its clinical significance in three groups of Parkinson's disease taking pramipexole, cabergoline and levodopa mono and combination therapy. *J. Neurol. Transm.* 108(1), 71–77 (2002).

67 Hobson DE, Lang AE, Martin WR *et al.* Excessive daytime sleepiness and sudden onset sleep in Parkinson's disease: a survey by Canadian Movement Disorders Group. *JAMA* 287(4), 455–463 (2002).

68 Rye DB, Bliwise DL, Dihenia B, Gureki P. Daytime sleepiness in Parkinson's disease. *J. Sleep Res.* 9(1), 63–69 (2000).

Affiliations

- Rajdeep S Kakar, MD, MPH
Stanford University Center of Excellence for Sleep Disorders Research, Stanford Sleep Disorders Center, Department of Psychiatry and Behavioral Sciences,
401 Quarry Road, Suite 3301,
Palo Alto, CA 94305, USA
Tel.: +1 650 723 6601
Fax: 1 650 725 8910
- Clete A Kushida, MD, PhD, RPSGT
Stanford University Center of Excellence for Sleep Disorders Research, Stanford Sleep Disorders Center, Department of Psychiatry and Behavioral Sciences,
401 Quarry Road, Suite 3301,
Palo Alto, CA 94305, USA
Tel.: +1 650 723 6601
Fax: 1 650 725 8910
clete@stanford.edu