Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Ropinirole in restless legs syndrome and periodic limb movement disorder

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
13 April 2010
Number of times this article has been viewed

Daniel Erichsen[1]
Raffaelle Ferri[2]
David Gozal[1]

[1]Department of Pediatrics, University of Chicago, Chicago, IL, USA;
[2]Department of Neurology, Oasi Institute IRCCS, Troina, Italy

Abstract: Restless legs syndrome and periodic limb movement disorder of sleep are now recognized as prevalent, distinct, yet overlapping disorders affecting all age groups. Although delineation of the mechanisms underlying these disorders continues to be the focus of very intense research efforts, it has become apparent that there is a prominent role for dopaminergic agents in the clinical management of these patients. Among the various dopaminergic drugs, ropinirole has undergone relatively intense and critical scrutiny, and appears to provide a safe and efficacious treatment option for patients with these two conditions. The more recent development of a controlled formulation for this drug is likely to yield additional benefits such as improved adherence and reduced fluctuations in daytime and nighttime symptoms. However, there is not enough evidence at this time to support such assumption.

Keywords: dopaminergic drugs, restless legs syndrome, ropinirole, period limb movement disorder

Restless legs syndrome

Restless legs syndrome (RLS) is a common condition characterized by a tetrad of diagnostic criteria that include: (a) leg restlessness, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (b) beginning or worsening of this unpleasant sensation during rest or inactivity such as lying or sitting; (c) partial or total relief of the unpleasant sensations by movement, and (d) worsening or occurrence of the unpleasant sensations in the evening or night compared to daytime.[1,2] RLS is thought to affect approximately 3% to 12% of the population,[3] and is common across the age spectrum from childhood to advanced ages in adults.[4] Although RLS has not been directly associated with significant bodily harm, it is an important cause of sleep deprivation and fragmentation, may induce depression, and can significantly hamper the ability to travel by car or flight. As further discussed below, RLS can be primary or develop as a consequence of several common conditions or disorders.

The term "restless legs syndrome" was first used by the Swedish neurologist Karl-Axel Ekbom in 1945, and constituted the first modern evidence-based approach to a phenomenon that until that point had been erroneously presumed to be part of the phenotypic expression of hysteria.[1] Even though the underlying biochemical and neurophysiologic mechanisms of RLS are currently only partially understood, there have been some recent advances in clarifying the etiology of this frequent condition.

Dopamine plays an important role in many movement disorders, such as Parkinson's disease,[5] Huntington's disease,[6] Wilson's disease,[7] and perhaps also in the regulation of sleep.[8] In addition to the known contribution of dopaminergic pathways to the

Correspondence: David Gozal
Department of Pediatrics, University of Chicago, 5721 S. Maryland Avenue, MC 8000, Suite K-160 Chicago, IL 60637, USA
Tel +1 (773) 702 6205
Fax +1 (773) 702 4523
Email dgozal@uchicago.edu

pathophysiology of several movement disorders, there are several lines of evidence that support a role for dopamine in the pathogenesis of RLS. For example, it is now well described that dopamine antagonists will worsen symptoms in patients with RLS, and conversely, dopamine agonists are associated with beneficial effects.[9] Furthermore, the findings reported from studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) would lend support to this theory.[10] Indeed, Allen and co-workers showed the presence of abnormal receptor binding and transport of dopamine in patients with period limb movement disorder (PLMD), a condition that is highly prevalent in RLS patients.[11] In addition, Staedt and collaborators found evidence for decreased dopamine D2-receptor binding in patients with period limb movements of sleep (PLMS) compared to control subjects.[12,13] However, there was no linear correlation between the severity of symptoms and the degree of receptor binding. Notwithstanding, patients reporting the highest frequency of sleep disruption also had the lowest level of receptor binding.[12,13] PET studies comparing patients with RLS and PLMS to control subjects have also demonstrated decreased dopamine receptor binding in the striatum and decreased F-DOPA uptake in the putamen.[14] Michaud et al used SPECT approaches and reported that presynaptic D2-receptor binding was decreased in patients with RLS compared to control subjects.[15] Therefore, although the exact role of dopamine in RLS remains to be elucidated, the cumulative findings emanating from these studies strongly support the presence of altered dopaminergic pathways in RLS patients.

Secondary RLS is commonly seen in conditions such as iron deficiency with or without anemia, in patient undergoing dialysis for uremic renal failure, and is also frequently observed in pregnancy. The common feature among these secondary causes of RLS would implicate a deficiency in iron or in iron stores,[16] and as such a great deal of interest has developed on the role of iron metabolism in the context of RLS. For example, oral iron supplementation decreased RLS scores when serum ferritin levels were below 0.45 pg/mL, but did not seem to have such beneficial effect on RLS symptoms when ferritin levels were higher, albeit decreased compared to control subjects.[17] Despite such findings, serum ferritin levels were correlated with RLS score.[17,18] However, such association could not be reproduced in a larger epidemiologic study.[19] Earley and co-workers suggested that iron deficiency in the central nervous system, rather than in the peripheral blood was correlated with RLS symptoms based on CSF studies from 16 patients and 8 control subjects.[20] Indeed, CSF levels of ferritin were significantly lower in the study group (mean 1.11 ± 0.25 ng/mL vs 3.50 ± 0.55 ng/mL, $P = 0.0002$) versus controls.[20] Also, imaging studies using T2-weighted MRI and post-mortem brain studies have found decreased levels of iron in the substantia nigra.[21,22] Snyder et al assessed neuronal staining patterns of ferritin in the human brain, and found increased mitochondrial levels of ferritin in the substantia nigra of patients with RLS compared to controls. The authors suggested that decreased cytosolic levels of iron could be a key factor in the pathophysiology of RLS.[23]

Despite such a priori compelling findings, iron replacement therapy has been tried in RLS with variable outcomes. For example, a single 1000 mg intravenous iron infusion was effective in achieving symptomatic improvements or RLS for an average of 6 months. However, long-term compliance was poor, and only 10 patients were included in this study.[24] In a 12-months, double-blind, placebo-controlled study, 60 patients with RLS and iron deficiency were randomized to receive either intravenous iron sucrose ($n = 29$) or placebo ($n = 31$). The RLS score at 11 weeks served as the primary endpoint and although lower in the treatment group, it did not achieve statistical significance. Other, significant findings were fewer withdrawals from the study in the iron sucrose arm ($n = 9$ in treatment vs $n = 21$ in placebo group, $P < 0.0006$) and a higher proportion of responders (>50% reduction of RLS scores) in the treatment group ($P = 0.02$).[25] A similar, albeit smaller study failed however to show any significant benefit of intravenous iron sucrose compared to placebo.[26] In an animal model, liver and serum iron levels were shown to have a diurnal variation with a 30% to 40% increase in liver iron and a 20% to 30% decrease in serum iron during the active dark phase. An iron deficient diet eliminated this circadian variation, and also decreased central iron stores, particularly during the inactive light phase.[27] Earley and co-workers found that lymphocytes of patients with RLS exhibited increased expression of transferrin receptors as well as ferroportin.[28] Since ferroportin is implicated in cellular iron excretion and elevated transferrin is a sign of intracellular depletion, these findings suggest the presence of a disrupted turnover of iron in RLS. In a patient with RLS and normal serum ferritin, a bone marrow biopsy was consistent with medullary iron depletion.[29] In an attempt to explain the relation of iron stores and dopamine function in the central nervous system it has been proposed that low central iron stores could affect the function of tyrosine hydroxylase. This enzyme, which serves as the rate limiting step in dopamine synthesis, requires iron as a co-factor, and therefore relative unavailability of iron in the brain could reduce dopamine release. A recent study showed a significant difference in the levels of tyrosine hydroxylase expression in post-mortem brain studies of RLS patients when compared to controls.[30]

Although the symptoms of RLS are most prominent in the peripheral portions of the lower limbs, it is the central nervous system, rather than peripheral nervous system, that appears to be involved in RLS pathogenesis.[31] Metoclopramide, a dopamine antagonist that crosses the blood–brain barrier, can markedly worsen symptoms of RLS and neutralize the therapeutic effect of dopamine agonists.[32] However, dopamine antagonists that do not cross the blood–brain barrier, such as domperidone, are void of RLS-exacerbating effects.[33] Functional magnetic resonance imaging (fMRI) has been used to study what sites of the brain are involved in involuntary leg movements in RLS. Sites that are activated prior to involuntary movements include the cerebellum, thalamus, inferior olive and red nucleus. These structures receive input from a spinal gait generator, and have been suggested to form a neuronal loop that induces the symptoms of RLS. The cerebral cortex, however, was not activated prior to involuntary movements, suggesting that only deeply located dopaminergic loci were primarily involved.[34]

There is a well described familial clustering of RLS. The concordance rate among identical twins has been reported to be 80%,[35] and more than half of all patients have a first-degree relative with RLS.[36] It is also known that familiar cases of RLS tend to present at an earlier age, and have a more indolent course than sporadic cases.[37] The mode of inheritance, however, remains to be fully understood. Genetic linkage studies have suggested a locus on chromosome 12q and autosomal recessive transmission.[38] However, autosomal dominant transmission with loci on chromosome 14q, 9p, 20p and 2q has also been proposed.[39–42] Two large scale genome-wide association studies involving a German/Canadian and Icelandic/American populations have thus far attempted to locate candidate genes implicated in RLS pathophysiology.[43,44] Although several genes (eg, MEIS1, BTBD9, MAP2K5, LBXCOR1) were identified as potential candidate genes, their functions are highly heterogenic, and as such, the implications of these findings are difficult to interpret.[43,44] Of note, the strongest association between candidate genes and phenotype was found for PLMS, rather than for RLS, at least in the Icelandic/American study.[44]

Periodic limb movements in sleep

PLMS is a condition characterized by episodes of repetitive movements of the lower limbs involving toe extension and dorsiflexion of the ankle during sleep.[45] PLMS is intimately associated with RLS, affecting about 80% of RLS patients, but also occurs commonly in other sleep and movement disorders, such as obstructive sleep apnea syndrome, idiopathic insomnia or hypersomnia, Parkinson's disease, and Gilles de la Tourette syndrome.[46–48] The standard criteria to diagnose PLMS include 4 consecutive stereotypical movements lasting 0.5 to 10 seconds, separated by 10 to 90 seconds.[49,50] PLMD is the occurrence of PLMS with the addition of an otherwise unexplained sleep complaint.[51,52]

The prevalence of PLMS is reported to be 4% to 11% in adults with increasing occurrence in the elderly.[53] The prevalence in the pediatric age group is lower, with RLS being reported in 2% of children in the community, and PLMD being reported in 5.6% of children referred to a sleep center.[54,55] Asymptomatic PLMS seems to be rare in children, but becomes increasingly common with advancing age,[56] and preliminary evidence suggests that asymptomatic PLMS might explain some cases of an otherwise unexplained complaint of insomnia.[57]

As with RLS, subcortical structures seem to be responsible for the abnormal movements. PLMS have been documented in patients with spinal cord transection.[58] Also, the absence of pre-motor cortical potentials preceding PLMS further suggests a role for central subcortical structures rather cortical or spinal mechanisms.[59,60] However, even if there seems to be no PLMS phase-locked EEG activity preceding the events, independent more recent studies have demonstrated the existence of temporal alignments between EEG activity and PLMS events;[61,62] thus, the involvement of cortical structures cannot be excluded with certainty. We should also note that PLMS may be induced by electronic stimulation of the peroneal nerve at the level of the fibular head.[59]

PLMS events are also accompanied by important transient autonomic changes involving heart rate[61–64] and blood pressure,[65,66] and such sympathetic activation has led to preliminary evidence implicating PLMD and an increased risk for cardiovascular and cerebrovascular morbidities.[67]

The role of iron stores and dopamine has been less thoroughly investigated in PLMS than in RLS, and in most studies there is significant overlap between the two entities. However, some common pathophysiological features seem to coincide in both conditions. For example, central nervous system iron deficiency,[67,68] and relative reductions in dopamine availability, such as occurs during late evenings and early nights, coincident with the circadian nadir of dopamine.[69,70] Further studies have suggested a dysfunction in a hypothalamically located dopaminergic nucleus (A11) to be responsible for symptoms of RLS as well as PLMS.[71] Finally, dopamine preparations are effective treatment options in both conditions.

Ropinirole

Dopamine agonists are currently considered as the first-line treatment in RLS. Ropinirole was the first FDA-approved pharmacological agent for moderate to severe primary RLS.[72] Ropinirole is classified as a non-ergolide dopamine agonist, and has affinity for the D2 and D3 receptor subtypes, but minimal affinity for the D1 receptor subtype. In addition, ropinirole has no affinity or very low affinity for receptors of other common neurotransmitters. Ropinirole binds to both central and peripheral dopamine receptors with variable activity and binding sites. Centrally, its affinity and activity at the D3 receptor is 20 times higher than at the D2 receptor and it binds to post-synaptic receptors.[73–75] The putative mechanism of action in the central nervous system is similar to that of endogenous dopamine, both in terms of post-synaptic effects and inhibitory feedback, thereby limiting further dopamine release. In the periphery, ropinirole binds to pre-synaptic D2 receptors eliciting a sympathomimetic response. This effect of ropinirole may be associated with increases in blood pressure and nausea, both of which can be attenuated by proceeding with slow increases in dosage till reaching therapeutic levels.[76,77]

Approximately 90% of radioactively labeled ropinirole is excreted in the urine, whether the drug was intravenously or orally, which suggests near complete absorption from the gut and a primarily renal disposition of the drug, which is however metabolized by the liver through N-depropylation.[78] The N-despropyl metabolite is then further metabolized to form 7-hydroxy and carboxylic acid derivatives, which are then excreted in urine.[78] Time to maximal plasma concentration (T_{max}) ranges from 0.5 to 4 hours, with maximal plasma concentration (C_{max}) generally occurring at 1.5 hours. Oral ropinirole has a bioavailability of approximately 50% and the elimination half-life is about 3 hours.[79] As with other lipophilic amines, absorption for ropinirole is fast and the distribution volume is extensive. At steady state, oral ropinirole has a volume of distribution of about 7.2 L/kg. Plasma protein binding is 10% to 40% at all plasma concentrations.[80,81] The metabolites are not active and all pharmacological properties can be attributed to the original compound. The liver enzyme CYP1A2 and to a much lesser extent CYP1A3 of the cytochrome P450 system are responsible for the metabolism of ropinirole.[78,82,83] This is clinically important, since there is great inter-individual variability in the activity of CYP1A2. Also, CYP1A2 can be induced by smoking and other drugs.[84] Irrespective of the dosage, the terminal elimination half-life of ropinirole ranges from 2 to 10 hours, with a mean of 6 hours, and as mentioned above, the drug metabolites are excreted in the urine.[78,85]

Administering ropinirole 3 times daily compared to once daily resulted in a 2-fold increase in C_{max} and in the area under the concentration time-curve (AUC). However, clearance of the drug was not significantly different under the two dosage regimens. Administration of single doses of 2 to 12 mg ropinirole increased the C_{max} and AUC in a proportional fashion, supporting the presence of a linear pharmacokinetic profile.[85] Although the effect is small, food intake does affect plasma concentration of ropinirole. A fat-rich breakfast decreased the C_{max} by 25%, and delayed the T_{max} by 2.6 hours, compared to fasting. Also a 13% decrease in AUC was noted. Although significant, these effects are unlikely to impose a significant clinical impact.[86]

Compared to younger subjects, clearance of ropinirole was slower in persons older than 65 years. Also, women taking hormonal replacement therapy had slower clearance. However, mild renal impairment, gender, common co-morbitites and common drugs did not seem to markedly affect ropinirole clearance. Ciprofloxacine, an inhibitor of CYP1A2 did increase plasma levels of ropinirole when these two drugs were co-administered. In contrast, theophylline which is a substrate for CYP1A2 did not affect plasma levels of ropinirole.[87,88] In summary, ropinirole has a good safety profile, it has a linear pharmacokinetic profile and high bioavailability, and a wide therapeutic window with few reported side effects. It can be used in most age groups, even though it has yet to be tested in children.

Clinical trials

There have been several studies investigating the effectiveness of ropinirole in RLS. However, in this review only randomized, placebo-controlled trials were included.

The role of ropinirole in RLS plus PLMS was studied in a double-blinded, placebo-controlled 12-week trial.[89] Primary RLS was diagnosed based on the international RLS study group (IRLSSG) criteria. Additional criteria include a PLMS index (PLMS-I) $>$ 5 per hour total sleep time (hrTST), an IRLS score $>$ 15, and a subject report of at least 15 nights with RLS symptoms in the 30 nights preceding the study. Of the 65 patients who met inclusion criteria, 59 subjects completed polysomnography (PSG) assessments, and were included in the study. Of these, 29 patients (17 women; mean age: 55.4 ± 10.3 years, range: 37 to 76) were randomized to the ropinirole group and 30 subjects (17 women; mean age: 53.3 ± 12.5 years, range: 30 to 79) were assigned to the placebo group. In the ropinirole-treatment arm, PLMS-I decreased from 48.5/hrTST to 11.5/hrTST, a significant improvement compared to the placebo group (35.7/hrTST to 34.2/hrTST; adjusted treatment difference: −27.2/hrTST; 95% confidence interval [CI] −39.1 to −15.4/hrTST; $P < 0.0001$). Similarly, the PLMS-I that was associated with arousals decreased from 7.0/hrTST to 2.3/hrTST in the treatment group versus an increase from 4.2/hrTST to 6.0/hrTST in the placebo group (adjusted treatment difference: –4.3/hrTST; 95% CI: –7.6 to –1.1/hrTST: $P = 0.01$). Interestingly, the PLM index during wakefulness (PLMW) also decreased from 56.5/hr to 23.6/hr with ropinirole, while it actually increased (from 46.6/hr to 56.1/hr) with placebo (adjusted treatment difference: –39.5/hr; 95% CI: −56.9 to −22.1/hr; $P < 0.0001$). Ropinirole also was superior to placebo in initiating sleep ($P < 0.05$) and NREM stage 2 sleep ($P < 0.001$). The placebo group, however, had an increase in NREM stage 3 and 4 sleep ($P < 0.01$). Sleep adequacy, as measured by the subjective Medical Outcomes Study sleep scale, was improved in the ropinirole group compared to the placebo group (adjusted treatment difference: 12.1; 95% CI: 1.1 to 23.1; $P < 0.04$). No significant negative outcomes were reported for either group. The results of this study suggested that ropinirole was safe and effective in treating symptoms of RLS with PLMS both during sleep and wake.

A smaller double-blind, placebo-controlled, crossover study that included 22 patients (16 women; mean age: 60 ± 13 years, range 40 to 83 years) with a diagnosis of primary RLS based on the IRLSSG criteria has also been published.[90] The main outcomes were the changes in the IRLS and ESS scales, and also included biweekly entries in an RLS diary. The patients were randomized to either 4 weeks of ropinirole (0.5 to 6.0 mg/day) followed by 4 weeks of placebo or vice versa. To exclude interference of ongoing medications, all subjects discontinued RLS medications 2 weeks prior to the baseline visit. The mean doses of ropinirole and placebo were 4.6 mg/day (range: 1 to 6 mg) with 14 of the 22 subjects taking 6 mg/day (vs 5.9 mg/day placebo). Mean RLS scores were 13 ± 12 in the ropinirole treatment period compared to 24.7 ± 7.2 in the placebo treatment period ($P < 0.001$) at the end of the 4 weeks. Complete resolution of symptoms (RLS score = 0) was achieved in 36% (8 of 22) in the ropinirole group as compared to none in the placebo group. However, there were no changes in ESS scores after either ropinirole or placebo. 19 patients completed RLS diaries and the mean rate of RLS was 23% in the placebo group compared to 12% in the treatment group. Two subjects discontinued their participation in the ropinirole group during treatment (one because of lack of response and the other because of nausea, vomiting and dizziness). One patient abandoned during placebo treatment because of syncope. The overall efficacy was a 50% reduction of RLS symptoms while receiving ropinirole based on RLS scores and the diary.

An international multi-center, randomized, placebo-controlled, double-blind study assessed the effectiveness and safety of ropinirole in RLS.[91] Centers from America, Europe and Australia recruited a total of 267 patients with moderate-to-severe RLS as per IRLSSG criteria with a baseline score of > 15 and RLS symptoms being present during at least 15 of the 30 days prior to the study. Patients discontinued all drugs known to affect RLS or sleep for 7 days or more before the baseline visit. Patients were then randomized to receive either ropinirole (0.25 to 4 mg/day) or placebo 3 hours before bedtime once daily. A total of 131 patients (76 females; mean age: 54.9 ± 10.8 years, range 29 to 77 years) were included in the treatment group and 136 patients (83 females; mean age: 56.0 ± 11.2 years, range 29 to 79 years) in the placebo group. Primary outcome was defined as the change in IRLS score at 12 weeks. Secondary outcomes included the IRLS score at 1 week and changes in Clinical Global Impression-Improvement (CGI-I) score at 1 and 12 weeks. Scores on RLS Quality of Life questionnaire and Medical Outcomes Study scale were also assessed. IRLS scores at 12 weeks were significantly better in the ropinirole treatment arm compared to the placebo group (–11.2 ± 0.76 vs –8.7 ± 0.75; adjusted treatment difference: –2.5; 95% CI: –4.6 to –0.4; $P < 0.02$). No severe adverse effects were reported. Thus, ropinirole emerged as superior to placebo in improving RLS symptoms as well as quality of life, and was globally well tolerated.

An European multi-center, randomized, placebo-controlled study has also evaluated the efficacy and safety of ropinirole in RLS.[92] The study duration was 12 weeks and 284 patients from 10 countries participated in the study. Inclusion criteria included an IRLS score of 15 or above. Treatment consisted of ropinirole 0.25 to 4 mg daily and was compared to placebo. A total of 146 subjects (88 females; mean age: 54.0 ± 11.1 years, range 30–78 years) was randomized to the treatment group and 138 (91 females; mean age: 56.2 ± 11.2 years, range 28 to 77 years) to the placebo group. The primary outcome endpoint was the change in IRLS score at 12 weeks. Changes in Clinical Global Impression (CGI) scale, improvements in sleep, health related quality of life and other outcomes were also assessed. From the randomization baseline, 76.7% (112/146) in the ropinirole group and 79.0% (109/138) in the placebo group completed the study. Improvements in IRLS scores at 12 weeks were significantly greater in the ropinirole group (−11.04 ± 0.72) versus placebo (−8.03 ± 0.74; adjusted treatment difference: −3.01; 95% CI: −5.03 to −0.99; $P = 0.0036$). A significantly higher percentage of subjects in the ropinirole group had improvements on the CGI scale (53.2% vs 40.9%; adjusted odds ratio = 1.7; 95% CI: 1.02 to 2.69; $P = 0.0416$). These improvements in IRLS score and on the CGI scale were noted at week 1. Improvements in sleep quality and quality of life were also greater in the treatment group. Adverse outcomes included headache and nausea, but no severe adverse effects were reported. In summary, ropirinole improved symptoms and quality of life in patients with RLS and was not associated with serious adverse effects.

Another randomized, placebo-controlled 6-week duration study to assess the efficacy of ropinirole in RLS patients included 22 patients (13 women; mean age: 50.8 years, range: 46. 5 to 55.2) that had undergone 4 weeks open-label titration prior to baseline.[93] Nine subjects were randomized to the ropinirole group and 13 to the placebo group. Treatment consisted in a dosage ranging from 0.25 mg to 6 mg ropinirole at bedtime vs placebo at bedtime. Primary efficacy end points at 2 weeks in addition to the 4 weeks of titration were PLMS assessed by nocturnal PSG, and differences in the score on the IRLSSG rating scale. In the treatment group, a significant decrease in PLMS and RLS symptoms was noted. The mean administered dose of ropinirole was 1.4 mg. The PLMS-I during NREM sleep in the treatment group was 19.7/hrTST (range 0 to 45.6/hrTST) at week 4 and 19.8/hrTST (range 0 to 44.4/hrTST) at week 6. PLMS-I in the placebo group was 19.2/hrTST (range 4.6 to 33.9/hrTST) at week 4 and 76.4/hrTST (37.3 to 115.5/hrTST) at week 6, indicating a significant worsening after transition to the placebo. All patients completed the study. No severe adverse effects were reported although dose-related side-effects included nausea, headache and daytime somnolence. The authors concluded that ropinirole is more effective than placebo at reducing PLMS in RLS patients.

To study the effectiveness and tolerability of ropinirole in RLS, a multicenter, double-blind, placebo-controlled study was conducted over 12 weeks.[94] 381 patients with RLS were included. 187 were randomized to receive placebo (109 female; mean age 52.2 ± 12.8 years, range 18 to 79 years) and 194 to receive (123 female; mean age 52.4 ± 13.1 years, range 19 to 78 years) 0.25 to 4.0 mg ropinirole as needed, once daily, 1 to 3 hours before bedtime. Primary outcome was the change in IRLS score at 12 weeks. Secondary outcome included the changes in CGI-I score. About 87.7% (164/187) of the subjects in the treatment group and 86.1% (167/194) in the placebo group completed the study. Ropinirole significantly improved IRLS scores compared to placebo at week 12 (adjusted mean treatment difference: −3.7; 95% CI: −5.4 to −2.0; $P < 0.001$). Mean changes in IRLS scores at 1 week and changes in CGI-I scale at week 1 and 12 were also significantly improved in the treatment group. Also, ropinirole was superior to placebo in subjectively assessed sleep disturbance and quantity, anxiety and quality of life. Of note, there was a trend towards decreased daytime sleepiness in the treatment group ($P = 0.10$). Similarly, 7 patients in the ropinirole group and 9 in the placebo group left the study due to adverse events of which none were unexpected or severe.

Ropinirole controlled release formulation

Ropinirole controlled release (CR), is a new developed formulation of the drug, that has yet to be specifically approved for RLS, but is approved for the treatment of Parkinson's disease. As with many other controlled release formulation drugs, ropinirole CR has a more constant serum concentration when compared to three times daily dosing of ropinirole. The peak to trough ratio (C_{max}/C_{min}) is 1.9 for ropinirole CR compared to 5 for standard ropinirole dosed three times daily. The C_{max} is around 12% lower, but the C_{min} and AUC are similar. Also, in the range of 2 to 8 mg daily, ropinirole CR behaves in a dose-dependent linear manner.[95] The side effect profile is similar to ropinirole immediate release (IR) and no new or unknown side effects have been identified thus far. Initial experience in the treatment of Parkinson's disease has failed to reveal any complications in switching from ropinirole IR or any other dopamine agonists to ropinirole CR.[96,97]

Data on ropinirole CR in RLS were gathered essentially from unpublished data available from GSK-GlaxoSmith-Kline.[98] We will briefly describe these data; however, as a cautionary note, it should be emphasized that such reports may be affected by potential bias because of the source of this information. We would also like to specify that there is no conflict of interest for any of the authors of this article in relation to the analysis of such data.

A phase II, open-label, uncontrolled clinical evaluation of ropinirole CR for RLS (CR-RLS) showed improvement in RLS symptoms with a mean decrease in IRLS of −19.3 and a mean change of PSQI of 4.3 from baseline, thus suggesting the potential efficacy of ropinirole in Japanese subjects affected by idiopathic RLS.[98] However, in the safety evaluation, adverse events on therapy were observed in 33 subjects (94%); of these a direct assignment of ropinirole CR to the side-effect was found in 29 subjects (83%). Most of the adverse events were mild or moderate in nature, and included nausea (43%), nasopharyngitis (34%), somnolence and vomiting (each 14%).

Other studies available are phase III trials. A 12-week, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of ropinirole CR for RLS (CR-RLS) in patients with RLS (SK&F-101468/205), found an adjusted mean IRLS change from baseline of ~15.4 after ropinirole vs ~9.6 after placebo ($P < 0.001$).[99] The percentage of responders on the CGI-I Scale was 79% after ropinirole CR vs 50% after placebo ($P < 0.001$). At least one adverse event was reported by 76% of patients taking ropinirole CR and 68% of those treated with placebo; the most common adverse events after ropinirole were nausea, headache, somnolence, dizziness and vomiting. Two patients treated with ropinirole CR showed serious (non-fatal) adverse events (vasovagal syncope and status asthmaticus) vs one patient treated with placebo (viral meningitis).

In the final report of the same study, these results were essentially confirmed. From these unpublished data, it was concluded that on-treatment adverse events were reported for 345 (89%) subjects, with the most frequently reported being nausea (26%) and headache (21%).[100] On-treatment severe adverse events were reported for 19 (5%) subjects; those reported for more than 1 subject were cellulitis (3 subjects, $<1\%$) and cholelithiasis (2 subjects, $<1\%$). No fatal severe adverse events were reported.

Another trial evaluated the safety and tolerability of converting from ropinirole immediate release (IR) to ropinirole CR in patients with RLS.[101] No substantial changes in IRLS or CGI-I were observed, and there were no new or unexpected adverse events or other safety results seen with conversions from ropinirole IR to ropinirole CR.

Finally, a study was conducted to confirm the effectiveness, safety, and tolerability of ropinirole CR in reducing RLS sleep disturbance and PLMS. In this study, sleep was recorded polysomnographically in a relatively small group of patients (n = 17).[102] PLMS index was found to be decreased after 12 weeks of treatment with ropinirole CR; however, the decrease was not significantly different from the changes seen in the placebo group.[102] However, the index of PLMS associated with arousals showed a more marked decrease while on treatment than in the placebo group. Notwithstanding such statements, statistical analyses were not provided. This is true also for other polysmnographic parameters as well as for subjective sleep evaluation items. For this reason, it is impossible to extrapolate any specific conclusions from this study.

Summary

The relatively high prevalence and increasing awareness to RLS and PLMD has prompted exploration of not only the theoretical pathophysiological mechanisms that underlie this condition, but has also instigated a large array of clinical trials with several agents such as iron or dopamine agonists. Among the latter, ropinirole IR has emerged as a relatively safe and efficacious therapeutic approach, albeit with some uncertainty as to its role in selected populations, such as children, for whom data are currently unavailable. Similarly, development of a controlled release formulation for ropinirole may provide additional advantages such as increased adherence and improved outcomes, but the data at the moment remain too limited to draw any definitive conclusions.

Disclosures

The authors declare no conflicts of interest.

References

1. Allen AP, Earley CJ. Restless legs syndrome: A review of clinical and pathophysiologic features. *J Clin Neurophysiol*. 2001;18:128–147.
2. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003;4:101–119.
3. Trenkwalder C, Hogl B, Winkelmann J. Recent advances in the diagnosis, genetics and treatment of resltess legs syndrome. *J Neurol*. 2009;256:539–553.
4. Simakajornboon HN, Kheirandish-Gozal L, Gozal D. Diagnosis and management of restless legs syndrome in children. *Sleep Med Rev*. 2009;13:149–156.
5. McRae A. Neurotransmitters and pharmacology of the basal ganglia. In: Jankovic J, Tolosa E, editors. Parkinson's Disease and Movement Disorders. Baltimore: Williams and Wilkins; 1998:491–592.
6. Brooks DJ. Functional imaging of movement disorders. In: Jankovic J, Tolosa E, editors. Parkinson's Disease and Movement Disorders. Baltimore: Williams and Wilkins; 1998:991–1016.
7. LeWitt PA, Pfeiffer RE. Neurologic aspects of Wilson's disease: clinical manifestations and treatment considerations. In: Jankovic J, Tolosa E, editors. Parkinson's Disease and Movement Disorders. Baltimore: Wiliams and Wilkin; 1998:47–66.
8. Bagetta G, De Sarro G, Priolo E, Nisticò G. Ventral tegmental area: site through which dopamine D2-receptor agonists evoke behavioural and electrocortical sleep in rats. *Br J Pharmacol*. 1988;95:860–866.
9. Winkelman JW. Considering the causes of RLS. *Eur J Neurol*. 2006;13 Suppl 3:S8–S14.
10. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disorders*. 2004;12:61–65.

11. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med*. 2004;5:385–391.
12. Staedt J, Stoppe G, Kogler A, et al. Dopamine D2 receptor alteration in patients with periodic movements in sleep (nocturnal myoclonus). *J Neurol Transm*. 1993;93:71–74.
13. Staedt J, Stoppe G, Kogler A, et al. Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alterations. *Eur Arch Psychiatry Clin Neurosci*. 1995;245:8–10.
14. Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. *Neurology*. 1999;52:932–937.
15. Michaud M, Soucy JP, Chabli A, Lavigne G, Montplaisir J. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. *J Neurol*. 2002;249:164–70.
16. Patrick LR. Restless legs syndrome: pathophysiology and the role of iron and folate. *Altern Med RBev*. 2007;12:101–12.
17. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing*. 1994;23:200–203.
18. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep*. 1998;21:371–377.
19. Berger K, von Eckardstein A, Trenkwalder C, Rothdach A, Junker R, Weiland SK. Iron metabolism and the risk of restless legs syndrome in an elderly general population – the MEMO study. *J Neurol*. 2002;249:1195–1199.
20. Earley CJ, Heckler D, Allen RP. IV iron treatment for RLS. *Sleep*. 2000;24:359.
21. Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology*. 2001;56:263–265.
22. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology*. 1999;61:304–309.
23. Snyder AM, Wang X, Patton SM, et al. Mitochondrial ferritin in the substantia nigra in restless legs syndrome. *J Neuropathol Exp Neurol*. 2009;68:1193–1199.
24. Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. *Sleep Med*. 2005;6:301–305.
25. Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. *Mov Disord*. 2009;24:1445–1452.
26. Earley CJ, HorskÃ A, Mohamed MA, Barker PB, Beard JL, Allen RP. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. *Sleep Med*. 2009;10:206–211.
27. Unger EL, Earley CJ, Beard JL. Diurnal cycle influences peripheral and brain iron levels in mice. *J Appl Physiol*. 2009;106:187–193.
28. Earley CJ, Ponnuru P, Wang X, et al. Altered iron metabolism in lymphocytes from subjects with restless legs syndrome. *Sleep*. 2008;31:847–852.
29. O'Keeffe ST. Iron deficiency with normal ferritin levels in restless legs syndrome. *Sleep Med*. 2005;6:281–282.
30. Connor JR, Wang XS, Allen RP, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain*. 2009;132:2403–2412.
31. Allen RP, Earley CJ. Restless legs syndrome: A review of clinical and pathophysiologic features. *J Clin Neurophysiol*. 2001;18:128–147.
32. Winkelmann J, Schadrack J, Wetter TC, Zieglgänsberger W, Trenkwalder C. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. *Sleep Med*. 2001;2:56–61.
33. Wetter TC, Stiasny K, Winkelman J, et al. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology*. 1999;52:944–950.
34. Bucher S, Seelosy K, Trenkwalder C, et al. Activation mapping of involuntary limb movements in the restless legs syndrome using functional magnetic resonance imaging. Proceedings of the 4th International Society for Magnetic Imaging in Medicine; 1996 April 27-May New York, USA. Dallas: Wiley; 1996:1331.
35. Ondo WG, Vuong KD, Wang Q. Restless legs syndrome in monozygotic twins: clinical correlates. *Neurology*. 2000;55:1404–1406.
36. Lazzarini A, Walters AS, Hickey K, et al. Studies of penetrance and anticipation in five autosomal-dominant restless legs syndrome pedigrees. *Mov Disord*. 1999;14:111–116.
37. Allen RP, La Buda MC, Becker P, Earley CJ. Family history study of the restless legs syndrome. *Sleep Med*. 2002;3(Suppl):S3–S7.
38. Winkelman J, Wetter TC, Collado-Seidel V, et al. Clinical characteristics and frequency of the hereditary restless legs syhdrome in a population of 300 patients. *Sleep*. 2000;23:597–602.
39. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain*. 2003;126:1485–1492.
40. Pichler I, Marroni F, Volpato CB, et al. Linkage analysis identifies a novel locus for restless legs syndrome on chromosome 2q in a South Tyrolean populatio isolate. *Am J Hum Genet*. 2006;79:716–723.
41. Chen S, Ondo WG, Rao S, Li L, Chen Q, Wang Q. Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p. *Am J Hum Genet*. 2004;74:876–885.
42. Winkelmann J, Lichtner P, KemLink D, et al. New loci for restless legs syndrome map to Chromosome 4q and 17p [abstract]. *Mov Disord*. 2006;21:304.
43. Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. *N Engl J Med*. 2007;357:639–647.
44. Winkelmann J, Schormair B, Lichtner P, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nat Geneet*. 2007;39:1000–1006.
45. Vetrugno R, D'angelo R, Montagna P. Periodic limb movements in sleep and periodic limb movement disorder. *Neruol Sci*. 2007;28(Suppl):S9–S14.
46. Baran AS, Richert AC, Douglass AB, May W, Ansarin K. Change in periodic limb movements index during treatment of obstructive sleep apnea with continuous positive airway pressure. *Sleep*. 2003;26:717–720.
47. Coleman RM, Pollack CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. *Ann Neurol*. 1980;8:416–421.
48. Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. *Sleep Med Rev*. 2006;10:169–177.
49. American Sleep Disorders Association. Recording and scoring leg movements. The Atlas Task Force. *Sleep*. 1993;16:748–759.
50. Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med*. 2006;7:175–183.
51. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003;4:101–119.
52. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 2nd ed. Diagnostic and Coding Manual. Westchester, Illinois: American Academy of Sleep Medicine; 2005.
53. Earley CJ, Allen RP, Beard JL, Connor JR. Insight into the pathophysiology of resless legs syndrome. *J Neurosci Res*. 2000;62:623–628.
54. Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents-the Peds REST study. *Pediatrics*. 2007;120:253–266.
55. Kirk VG, Bohn S. Periodic limb movements in children: prevalence in a referred population. *Sleep*. 2004;27:313–315.

56. Ancoli-Istrael S, Kripke DF, Klauber MR, et al. Periodic limb movements in sleep in community-dwelling elderly. *Sleep*. 1991;14:496–500.
57. Ferri R, Gschliesser V, Frauscher B, Poewe W, Högl B. Periodic leg movements and periodic leg movement disorder in patients presenting with unexplained insomnia. *Clin Neurophysiol*. 2009;120:257–263.
58. Lee MS, Choi YC, Lee SH, Lee SB. Sleep related periodic leg movements associated with spinal cord lesions. *Mov Disord*. 1996;11:719–722.
59. Lugaresi E, Cirignotta F, Coccagna G, Montagna P. Nocturnal myoclonus and restless legs syndrome. *Adv Neurol*. 1986;43:295–307.
60. Trenkwalder C, Bucher SF, Oertel WH. Bereitschaftspotential in idiopathic and symptomatic restless legs syndrome. *Electroencephalogr Clin Neurophysiol*. 1993;89:95–103.
61. Ferri R, Zucconi M, Rundo F, Spruyt K, Manconi M, Ferini-Strambi L. Heart rate and spectral EEG changes accompanying periodic and non-periodic leg movements during sleep. *Clin Neurophysiol*. 2007;118:438–448.
62. Ferrillo F, Beelke M, Canovaro P, et al. Changes in cerebral and autonomic activity heralding periodic limb movements in sleep. *Sleep Med*. 2004;5:407–412.
63. Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J. EEG and cardiac activation during periodic leg movements in sleep: support for a hierarchy of arousal responses. *Neurology*. 1999;52:786–791.
64. Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. *Sleep*. 2007;30:755–766.
65. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. *Neurology*. 2007;68:1213–1218.
66. Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. *Clin Neurophysiol*. 2007;118:1923–1930.
67. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep*. 2009;32:589–597.
68. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med*. 2004;5:385–391.
69. Hening WA, Walters AS, Wagner M, et al. Circadian rhythm of motor restlessness and sensory symptoms in idiopathic restless legs syndrome. *Sleep*. 1999;22:901–912.
70. Khaldy H, León J, Escames G, Bikjdaouene L, García JJ, Acuña-Castroviejo D. Circadian rhythms of dopamine and dihydroxyphenyl acetic acid in the mouse striatum: effects of pinealectomy and melatonin treatment. *Neuroendocrinology*. 2002;75:201–208.
71. 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*. 1998;13:271–275.
72. Kushida CA. Ropinirole for the treatment of restless legs syndrome. *Neuropsychiatr Dis Treat*. 2006;2:407–419.
73. Eden RJ, Costall B, Domeney AM, et al. Preclinical pharmacology of ropinirole (SK&F101468-A), a novel dopamine D2 agonist. *Pharmacol Biochem Behav*. 1991;38:147–154.
74. Coldwell MC, Boyfield I, Brown T, Hagan JJ, Middlemiss DN. Comparison of the functional potencies of ropinirole and other dopamine receptor agonists at human D2(long), D3 and D4 receptors expressed in Chinese hamster ovary cells. *Br J Pharmacol*. 1999;127:1696–1702.
75. Levant B, Ling ZD, Carvey PM. Dopamine D3 receptors: relevance for drug treatment of Parkinson's disease. *CNS Drugs*. 1999;12:391–402.
76. Jenner P. The rationale for the use of dopamine agonists in Parkinson's disease. *Neurology*. 1995;45(Suppl):S6–S12.
77. Brooks DJ, Torjanski N, Burn DJ. Ropinirole in the symptomatic treatment of Parkinson's disease. *J Neural Transm Suppl*. 1995;45:231–238.
78. Ramji JV, Keogh JP, Blake TJ, et al. Disposition of ropinirole in animals and man. *Xenobiotica*. 1999;29:311–325.
79. Dollery C. Ropinirole hydrochloride. In: Dollery C, editor. Therapeutic drugs. Vol 2, 2nd ed. Edinburgh: Churchill Livingstone; 1999:50–54.
80. Swagzdis JE, Wittendorf RW, DeMarinis RM, Mico BA. Pharmacokinetics of dopamine-2 agonists in rats and dogs. *J Pharm Sci*. 1986;75:925–928.
81. Jenner P, Tulloch I. The preclinical pharmacology of ropinirole-receptro interactions, antiparkinsonian activity and potential to induce dyskinesia. In: Olanow CW, Obeso JA, editors. Beyond the Decade of the Brain. Dopamine agonists in early Parkinson's disease. Royal Tunbridge Wells: Wells Medical; 1997:115–128.
82. Bloomer JC, Clarke SE, Henery RJ. In vitro identification of the P450 enzymes responsible for the metabolism of ropinirole. *Drug Metab Dispos*. 1997;25:840–844.
83. Beerahee A, Nichols A, Aluri J. Population pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of ropinirole in Parkinson patients. Report number BF-1019. Harlow (UK): SmithKline Beecham Pharmaceuticals. 1995.
84. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet*. 1999:36:425–438.
85. Hubble J, Koller WC, Atchinson P, et al. Linear pharmaceuticals behavior of ropinirole during multople dosing in patients with Parkinson's disease. *Clin Pharmacol*. 2000;36:641–646.
86. Brefel C, Thalamus C, Rayet S, et al. Effect on food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol*. 1998;45:412–425.
87. Tulloch IF. Pharmacologic profile of ropinirole: a nonergolinic dopamine agonist. *Neurology*. 1997;49(Suppl 1):S58–S62.
88. Jost WH. Ropinirole: current status of the studies. *J Neurol*. 2004;251(Suppl 6):S13–S18.
89. Allen R, Becker PM, Bogan R, et al. Ropinirole decrease periodic letg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep*. 2004;27:907–914.
90. Adler CH, Hauser RA, Sethi K, et al. Ropnirole for restless legs syndrome: a placebo-controlled crossover trial. *Neurology*. 2004;62:1405–1407.
91. Walters AS, Ondo WG, Dreykluft T, et al. Ropinirole is effective in the treatment of resless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord*. 2004;19:1414–1423.
92. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al. Ropinirole in the treatment of restless legs syndrome: results from a 12-week, randomised, placebo-controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry*. 2004;75:92–97.
93. Bliwise DL, Freeman A, Ingram CD, Rye DB, Chakravorty S, Watts RL. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. *Sleep Med*. 2005;6:141–147.
94. Bogan RK, Fry JM, Schmidt MH, et al. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc*. 2006;81:17–27.
95. Tompson DJ, Vearer D. Steady-State Pharacokinetic Properties of a 23-hour Prolonged-Release Formulation fo Ropinirole: Results of Two Randomised Studies in Patients with Parkinson's Disease. *Clin Ther*. 2007;29:2654–2666.
96. Stocchi F, Giorgi L. Efficacy of ropinirole 24-hour prolonged release compared with immediate release formulation in early Parkinson's disease (PD): the EASE-PD Monotherapy study. [abstract]. *Eur J Neurology*. 2006;13(Suppl 2):205.
97. Pahwa R, Stacy MA, Factor SA, et al. Ropinirole 24-hour prolonged release. Randomized, controlled study in advanced Parkinson disease. *Neurology*. 2007;68:1108–1115.
98. GlaxoSmithKline. Clinical evaluation of ropinirole CR-RLS tablets in restless legs syndrome (RLS) open-label, uncontrolled study. Study No. ROX107846, 2009;http://www.gsk-clinicalstudyregister.com/files/pdf/20158.pdf

99. GlaxoSmithKline. A 12-week, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of ropinirole controlled release for RLS (CR-RLS) in patients with restless legs syndrome. Study No. SK&F-101468/205 2008;http://www.gsk-clinicalstudyregister.com/files/pdf/19930.pdf
100. GlaxoSmithKline. A 52-Week, open-label study to assess the long-term safety of ropinirole extended release (XR) in patients with restless legs syndrome (RLS). Final report. Study No. SK&F-101468/206 2008;http://www.gsk-clinicalstudyregister.com/files/pdf/19931.pdf
101. GlaxoSmithKline. A 52 week open-label extension study of the long-term safety of ropinirole in subjects suffering from restless legs syndrome (RLS). Study No. SKF-101468/243 2005;http://www.gsk-clinicalstudyregister.com/files/pdf/22613.pdf
102. GlaxoSmithKline. A 12-week, multi-center, double-blind, placebo-controlled, parallel group, flexible dose polysomnography study of ropinirole controlled release for restless legs syndrome (CR-RLS) in RLS patients with sleep disturbance and periodic limb movements (PLM) during sleep. Study No. RRL103660. 2008;http://www.gsk-clinicalstudyregister.com/files/pdf/21024