Ropinirole for the treatment of restless legs syndrome

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Abstract: Dopaminergic agents, anticonvulsants, benzodiazepines, opiates, and iron supplementation comprise the classes of medications commonly used to treat restless legs syndrome (RLS), which is a disorder that is estimated to affect about 1 in 10 individuals worldwide and impacts an affected patient's sleep, mood, daytime function, and quality of life. RLS is characterized by an urge to move the legs that is worse at bedtime and at rest; the symptoms are temporarily relieved by leg movement. It is frequently accompanied by periodic limb movements during sleep (PLMS), which may independently disrupt sleep and may cause daytime drowsiness. Dopaminergic agents are considered to be first-line therapy in the management of RLS as well as PLMS. Ropinirole (Requip®, GlaxoSmithKline) is a dopamine agonist that was the first medication approved by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe primary RLS. Based on several large-scale clinical trials and open-label clinical series, this medication has been demonstrated to be effective and safe in treating the motor symptoms of RLS and improving sleep quality.

Keywords: ropinirole, restless legs syndrome, RLS, periodic limb movements

Restless legs syndrome

Restless legs syndrome (RLS) is a common neurologic disorder that is largely under-diagnosed and under-treated. RLS is characterized by an urge to move the legs that is worse at rest and at bedtime. The urge to move often presents as leg discomfort, but may range from mild irritation to disruptive, painful sensations. The symptoms typically occur near bedtime but may be present throughout the day in severe cases. Patients with RLS obtain symptom relief with movement, although the relief is temporary with rapid return of symptoms. RLS is present in childhood through old age. It is a chronic condition, but it may present with a relapsing-remitting course characterized by periods of remission that last weeks to sometimes years. RLS is typically and frequently associated with disturbed sleep, in which the patient experiences a delay in the onset of sleep and/or difficulty maintaining sleep. The latter is often characterized by fragmented sleep resulting from an inability to rapidly fall back asleep after awakenings throughout the night. The RLS morbidities of decreased functional alertness and emotional distress appear to be mostly secondary to the sleep disturbance associated with RLS (Kushida et al 2004). Other morbidities associated with RLS include disruption of bed-partner's sleep and increased risk of work-related or motor-vehicle accidents due to daytime fatigue or sleepiness.

Prevalence

The overall prevalence of RLS is estimated to be 10%. It appears to be more common in populations of Northern and Western European extraction, and less common in Asian (Kageyama et al 2000; Tan et al 2001) and Southern European (Turkey) populations (Sevim et al 2003). An early study using a population sample from Kentucky, US found that 10% of respondents experienced RLS symptoms 5 or more nights per month (Phillips et al 2000). The multinational RLS Epidemiology,

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Symptoms, and Treatment (REST) 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 (Hening et al 2004a). Interestingly, in this latter study, although 64.8% reported consulting a physician about their symptoms, only 12.9% reported receiving a diagnosis of RLS. The prevalence of RLS increases with age; however, the prevalence of RLS in children and the elderly has not been systematically investigated.

Phenotypes and genotypes

RLS can be divided into a more common, idiopathic, primary form and secondary forms associated with iron deficiency, pregnancy, and renal failure. The primary form of RLS appears to have a familial preponderance but with the exception of a monozygotic twin study that indicated concordance for RLS symptoms (Ondo et al 2000) and the identification of possible chromosomal loci at 12q, 14q, and 9p (Desautels et al 2001; Bonati et al 2003; Winkelmann et al 2006), the genetics of RLS remain unclear and it is considered to be a complex, heterogenetic disorder. In addition, early- and late-onset (over age 45) RLS has been described, with early-onset RLS occurring more commonly in families, progressing slower with age, and possessing a more limited relation to serum iron status compared to late-onset RLS (Allen and Earley 2000).

Etiology

The cause of RLS is unknown, but a defect in the dopamine-iron stores/transport mechanism is strongly suspected and a mechanism to explain the connection between iron deficiency and dopamine dysfunction in RLS has been proposed (Earley et al 2000a). Although not all imaging studies have found dopamine abnormalities (Eisensehr et al 2001), a mild reduction of dopamine function in the striatum region of the brain was detected by imaging studies using ligands targeted to pre- and post-synaptic dopamine sites (Turjanski et al 1999; Ruottinen et al 2000). Iron is a cofactor for the hydroxylation of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, and iron deficiency is frequently found in the major secondary forms of RLS (anemia, pregnancy, renal failure). RLS symptoms are associated with low iron stores (serum ferritin <50 mcg/L) (Sun et al 1998), and these symptoms are improved with subsequent iron supplementation. Additionally, studies examining cerebrospinal fluid (Earley et al 2000b), magnetic resonance imaging (MRI) (Allen et al 2001), and brains at autopsy (Connor et al 2003) have shown low iron levels in patients with primary RLS. Long-term dopaminergic treatment has been observed to reduce hyperalgesia in RLS patients, prompting a theory that implicates disturbed supraspinal pain modulation involving the basal ganglia and/or descending dopaminergic pathways in RLS pathophysiology (Stiasny-Kolster et al 2004). However, pain processing includes a complex, reciprocal interaction between dopaminergic and opioidergic systems, the mechanisms of which are not completely understood.

Diagnosis

Four essential diagnostic features of RLS were developed through a consensus conference at the National Institutes of Health in 2002 in conjunction with the International Restless Legs Syndrome Study Group (IRLSSG) (Allen et al 2003):

(1) A strong urge to move the legs, usually associated with uncomfortable sensations in the legs.

These sensations may be characterized by patients as vague, indescribable sensations to "creepy-crawly" feelings to irritating, painful symptoms. Sometimes the patient is unable to describe the symptom of leg discomfort and simply says that he or she has an urge or need to move the legs. These sensations are rarely found in the arms and trunk.

(2) Symptoms that start or become worse with rest.

Periods of recumbency, sitting, and rest, or situations in which leg movement is restricted can initiate or exacerbate RLS. For example, theater or airplane seats can be almost unbearable for a patient with severe RLS.

(3) A temporary or partial relief of symptoms with movement, such as stretching or walking.

Almost immediate alleviation of symptoms typically occurs with movement. However, this relief typically lasts only a few seconds to a few minutes, and prompts the RLS sufferer to repetitively flex and extend his or her legs or walk for short periods of time.

(4) A worsening of symptoms in the evening or at night.

RLS does have a circadian component; the symptoms frequently worsen as bedtime approaches.

Tools that can assist the clinician in the diagnosis include those for screening (Restless Legs Syndrome Questionnaire

[RLSQ]) (Allen and Earley 2001), severity assessment (International RLS [IRLS] Rating Scale (Walters et al 2003)), subjective sleep assessment (sleep logs or diaries), quality of life assessment (Atkinson et al 2004; Abetz et al 2005), and objective provocation/validation (suggested immobilization test [SIT] (Montplaisir et al 1998)). Ancillary testing is not necessary to establish the diagnosis of RLS, except in situations where secondary RLS (eg, ferritin and transferrin levels for iron deficiency, BUN and creatinine for renal failure) is suspected or when other possible disorders need to be excluded. These latter disorders include leg cramps and neuropathies, which can mimic RLS by sharing similar symptoms. Leg cramps may be differentiated from RLS in that the cramps typically affect specific muscle groups (eg, gastrocnemius), may be unilateral, can be associated with strenuous exercise and electrolyte imbalance, and may not temporarily be relieved by leg movement. Neuropathies are typically associated with medical conditions such as diabetes or back injury and do not have a circadian rhythmicity nor are relieved by leg movement. Further testing (eg, folate, B12, glycosylated hemoglobin, electromyography/nerve conduction velocity studies) may help to identify specific causes of neuropathies. Other disorders on the differential diagnosis include akathisia, vasculopathies, myelopathies, muscular pain-fasciculation syndromes, anxiety disorders, nocturnal epilepsy, rhythmic movement disorder, attention deficit-hyperactivity disorder, sleep starts, nocturnal paroxysmal dystonia, erythromelalgia, and myokymia. Polysomnography (sleep study) is generally not indicated in the evaluation of RLS unless periodic limb movement disorder or an RLS-associated sleep disorder is suspected.

RLS patients frequently have periodic limb movements (PLMs), characterized as stereotyped movements of the legs, typically big toe extension, ankle dorsiflexion, knee flexion, and hip flexion that occur on a repetitive basis during sleep (PLMS) or wake (PLMW) and can be present in all limbs though are most common in the legs. The current polysomnographic criteria for scoring PLMS consist of movements that are 0.5–5 seconds in duration, separated by 5–90 seconds, and are greater than 25% of toe dorsiflexion during calibration (The Atlas Task Force 1993; American Academy of Sleep Medicine 2005). A train of four of these movements that meet these criteria must be present in order for any of them to be counted as periodic limb movements. PLMS may be associated with arousals or awakenings from sleep, and it is suspected that these disturbances result in sleep fragmentation, which in turn may lead to daytime fatigue and sleepiness. However, this is controversial since the number of PLMS do not correlate with the level of daytime sleepiness (Montplaisir et al 1998). Nevertheless, PLMS greater than 15 per hour plus a clinical sleep disturbance or a complaint of daytime fatigue is diagnostic for periodic limb movement disorder (PLMD) in adults (American Academy of Sleep Medicine 2005). This is also not without controversy; since approximately 80% of individuals with RLS report significant PLMS (Montplaisir et al 1997), there is the belief that RLS and PLMD may not be distinct and separate entities, but rather comprise the same neurologic disease state.

Current therapies

RLS and PLMD are optimally treated with pharmacologic intervention; non-pharmacologic therapy such as exercise, warm baths, thermal biofeedback, leg vibration/massage, and acupuncture have had mixed success in limited studies (Kuo and Kushida 2003). However, the implementation of good sleep hygiene practices may be helpful as an adjunct to pharmacologic treatment (Table 1), as well as the management of concomitant conditions such as a peripheral neuropathy or vasculopathy. The primary pharmacologic treatment of RLS consists of dopaminergic agents, anticonvulsants, benzodiazepines, opiates, and iron supplementation. Of these classes of medications, dopaminergic agents have been the subject of the most recent and extensive investigation (Chesson et al 1999; Hening et al 1999, 2004b; Littner et al 2004). Dopamine agonists, in particular, are among the best-studied medications for RLS and are considered to be first-line therapy in the management of RLS.

Ropinirole

Ropinirole (Requip®, GlaxoSmithKline) is a non-ergoline dopamine agonist that was the first medication approved (May 4, 2005) by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe RLS.

Chemistry

The IUPAC chemical name of ropinirole hydrochloride is 4-(2-dipropylaminoethyl)-1,3-dihydroindol-2-one, and it is the hydrochloride salt of 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one monohydrochloride. It has an empirical formula of $C_{16}H_{24}N_2O{\cdot}HCl$ and its molecular weight is 296.84 (260.38 as the free base).

Table 1 General therapeutic guidelines for restless legs syndrome (RLS)

1. Consider discontinuing substances and medications that may potentially worsen RLS (caffeine, alcohol, nicotine, dopamine antagonists, tricyclic and selective serotonin release inhibitor [SSRI] antidepressants, lithium, first-generation antihistamines, beta-blockers).
2. Discuss good sleep hygiene practices (eg, standardizing sleep-wake schedules, bright light therapy) as an adjunct to pharmacotherapy.
3. Since treatment is symptomatic and not curative, discuss the possibility that the patient may need to take the medication indefinitely.
4. Dosage, timing, frequency, and side effect profiles (especially augmentation and rebound) of the medication should be carefully considered.
5. Age, severity/frequency of symptoms, and the impact of RLS on the patient's life are important considerations in the selection and timing of administration of the RLS medications.
6. A given medication should be started at the lowest possible dose and then slowly and carefully increased to its lowest effective dose based on titration instructions or schedules provided to the patient. The patient should be instructed to discontinue the medication and contact his or her physician with the appearance of any adverse effects.
7. Medication should be started in the early evening or bedtime; however, the patient should be given some latitude in the dosage and timing of his or her medication to adjust for the appearance of symptoms.
8. Combination therapy (eg, combining medications of several different classes) should be considered for patients who fail to respond to individual RLS medications.

Pharmacokinetics and metabolism

The majority of the following data were derived from the Internet-based version of the Physicians' Desk Reference (Thomason Healthcare 2005). Ropinirole is a non-ergoline derivative with high relative in vitro specificity and full intrinsic activity at the D2 and D3 dopamine receptor subtypes, and it binds with higher affinity to D3 compared with D2 or D4 receptor subtypes. It has moderate in vitro affinity for opioid receptors. Ropinirole and its metabolites have negligible in vitro affinity for dopamine D1, 5HT1, 5HT2, benzodiazepine, GABA, muscarinic, and alpha1-, alpha2-, or beta-adrenoreceptors. Ropinirole is rapidly absorbed after oral administration, and it reaches peak concentration in approximately 1–2 hours. The absorption of ropinirole is not affected by food; however, when ropinirole is taken with a high-fat meal, its T_{max} is increased by 2.5 hours and its C_{max} is decreased by approximately 25%. In clinical studies, over 88% of a radiolabeled dose was recovered in urine and the absolute bioavailability was 55%, indicating a first-pass effect. The clearance of ropinirole after oral administration to patients is 47 L/hour and its elimination half-life is approximately 6 hours. It is extensively metabolized by the liver to inactive metabolites and demonstrates linear kinetics over the therapeutic dosing range of 1–8 mg 3 times daily. The major cytochrome P_{450} isozyme involved in ropinirole metabolism is CYP1A2, and inhibitors or inducers of this enzyme have been shown to alter its clearance when coadministered with ropinirole. Steady-state concentrations are expected to be achieved within 2 days of dosing, and it is up to 40% bound to plasma proteins. Less than 10% of the administered dose is excreted as unchanged drug in urine. Although there are no gender effects on oral clearance, it is reduced by 30% in patients above 65 years compared to younger patients. Based on population pharmacokinetic analysis, the pharmacokinetics of ropinirole appear to be unchanged in patients with moderate renal impairment compared to an age-matched population. The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment.

Clinical efficacy in RLS

Ropinirole as a treatment for RLS was evaluated in 8 open-label trials and 11 randomized controlled trials between 1998 and 2006.

Open-label trials

There were four open-label clinical series examining the effects of ropinirole on RLS patients that were published in 1998 and 1999 (Estivill and de la Fuente 1999a; Estivill and de la Fuente 1999b; Galvez-Jimenez and Khan 1999; Ondo 1999). These involved small sample sizes of 5–16 subjects and varied in both the dose range of ropinirole (0.25–4 mg) and duration of treatment (1–10 months). Significant reductions in the subjective assessment of RLS symptom severity while on treatment were observed in all four studies. In the study by Ondo (1999), IRLS Rating Scale scores significantly improved from 18.6±2.4 to 7.7±3.5, which is a robust finding given that the population was difficult to treat since the patients used an average total number of 4.2±1.8 medications for their RLS symptoms prior to entering the study and many had levodopa-induced RLS rebound during the study. In one of the studies by Estivill and de la Fuente (1999b), significant improvement in the objective polysomnographic variables of sleep efficiency, total sleep time, and periodic limb movements were observed as well as subjective improvement in RLS symptoms, not only soon after the initiation of ropinirole treatment but also following a month of treatment.

Two other open-label clinical series were conducted to assess the long-term safety and tolerability of ropinirole in RLS (Bogan et al 2005b; Dreykluft et al 2005; Garcia-Borreguero et al 2005c); they were multi-center, 52-week trials, one conducted in the US and the other in Europe. Otherwise, the designs of these two trials were similar; patients were eligible for the trials if they had successfully completed a previous trial of ropinirole in RLS, and the ropinirole dose levels were titrated for efficacy, 0.5–4.0 mg/day. A total of 251/310 and 60/81 patients completed the two studies; the efficacy analyses included 308 and 81 patients (receiving a mean dose of 1.6 and 1.7 mg/day of ropinirole, respectively) and safety analyses included 309 and 81 patients, respectively. Rapid and extensive improvements in IRLS Rating Scale total scores were observed and were maintained throughout the studies, with mean baseline scores of 22.0 and 22.7 reduced to 10.9 and 9.8, respectively, at week 52 last observation carried forward (LOCF). Greater than 74% of patients were much or very much improved on the Clinical Global Impression-Improvement (CGI-I) Scale at week 52 LOCF compared with baseline, and sleep parameters as well as quality of life measures were improved. Combining the two studies, the most commonly reported adverse events (≥10%) were nausea, headache, and arthralgia, and the majority of the adverse events were mild to moderate in intensity, with the first occurrence largely in the initial 12 weeks of therapy. There were few reports of augmentation (3.9%), which is a known side-effect of dopaminergic agents and is a paradoxical increase in RLS symptom severity despite increased dose. This phenomenon manifests as worsened symptoms, spread of symptoms to other limbs, and/or symptom occurrence earlier in the day.

Two head-to-head, open-label comparisons of RLS treatments were conducted: ropinirole vs gabapentin and ropinirole vs levodopa sustained-release (SR). In the first randomized, 4-week, open-label trial, 8 patients received gabapentin (starting at 300 mg, titrated to symptom relief; mean dose, 800±397 mg) and 8 patients received ropinirole (starting at 0.5 mg, titrated to symptom relief; mean dose, 0.78±0.47 mg) (Happe et al 2003). Both IRLS Rating Scale severity and PLMS by polysomnography were significantly improved and, in the majority of patients, RLS symptoms were still improved after 6–10 months of follow-up. The second head-to-head study was a 14-week, open-label, randomized, crossover trial (6 weeks of first treatment condition, 1 washout week, 6 weeks of second treatment condition) comparing ropinirole vs levodopa SR in 11 RLS patients on chronic hemodialysis (Pellecchia et al 2004). Ropinirole was observed to be superior to levodopa SR in improving RLS severity (IRLS Rating Scale and CGI Scale) and sleep time; the authors concluded that ropinirole is more effective than levodopa SR in the treatment of RLS in patients on chronic hemodialysis.

Randomized controlled trials (Table 2)

The first controlled trial was published by Saletu et al 2000 (Saletu et al 2000a, 2000b); these investigators conducted a single-blinded, non-randomized, placebo-controlled, crossover trial investigating the acute effects of ropinirole on 12 patients diagnosed with RLS. In addition to self-rating and visual analog scales, polysomnography and a psychometric test battery were used to objectively assess sleep, cognition, mood, and periodic limb movements. Compared with placebo, ropinirole significantly improved subjective and objective measures of sleep quality, fine motor activity, reaction time, and PLMS per hour of sleep.

Adler and colleagues conducted a double-blind, placebo controlled, crossover study of ropinirole in 22 patients with RLS (Adler et al 2004). Patients were treated with either ropinirole (0.5–6 mg/day for 4 weeks, had a 1-week washout, and then crossed-over to the other arm for 4 weeks. There was a significant improvement in the IRLS Rating Scale from 25±7 during placebo treatment to 13±12 during ropinirole treatment. Eight of the 22 patients had complete resolution of their RLS symptoms during the ropinirole treatment. As an additional efficacy measure, global change scores (–3 markedly worse to +3 markedly improved) were significantly higher at the end of ropinirole vs placebo treatment. The most common adverse events for the ropinirole group vs the placebo group were nausea (27.3 vs 4.5%) and dizziness (22.7 vs 0%). The mean daily dose was 4.6±2.0 mg/day, with 14 out of 22 patients receiving the full 6 mg/day, which was a relatively high ropinirole dose; however, the patients tolerated this dose well with only one patient prematurely discontinuing ropinirole treatment due to adverse events (dizziness, nausea, and vomiting).

Trenkwalder and colleagues conducted a study named TREAT RLS 1, a 12-week, multi-center, double-blind, randomized, placebo-controlled trial involving 284 RLS patients from 10 European countries (Trenkwalder et al 2004). Patients were randomized (1:1) to receive either ropinirole 0.25–4.0 mg once daily or placebo. Significant

Table 2 Summary of ropinrole efficacy data from controlled trials

Author (y)	Type	N, Ages, Length	Results* of ropinrole group (compared with results of placebo group)
Saletu B (2000a) Saletu M (2000b)	SB/N/CR	12, 35–74 y, 1 n per treatment	Improved TST, SE, NREM Stage 2 sleep, stage shifts, fine motor activity, reaction time, PLMS index
Adler (2004)	DB/R/CR	22, 40–83 y, 4 w per treatment	Improved IRLS Rating Scale scores, global change scores, and RLS frequency by diary
Trenkwalder (2004)	DB/R/CT	284/28–78 y,12 w	Improved IRLS Rating Scale scores and greater proportion of much or very much improved scores on CGI-I Scale; improved sleep adequacy, sleep quantity, daytime somnolence, and sleep disturbance on MOS Sleep Scale; improved quality of life on RLS QoL Questionnaire
Walters (2004)	DB/R/CT	267/29–79 y/12 w	Improved IRLS Rating Scale and CGI-I Scale scores at week 1 and 12; improved somnolence, sleep disturbance, adequacy, and quantity on MOS Sleep Scale; improved mental health, social functioning, and vitality on MOS SF-36
Allen (2004a)	DB/R/CT	65/30–79 y/12 w	Improved PLMS, PLMW, and PLMs with arousals; improved latency to sleep and increased NREM stage 2 sleep; improved sleep adequacy on MOS Sleep Scale
Tompson (2004)	SB/R/CT	28/NA/7 w	Greater reduction in PLMs per hour by actigraphy (formal statistical analysis not conducted)
Kelly (2005)	DB/R/CT	37/NA/7 w	70% of patients tolerated each ropinirole dose; 43.2% tolerated maximum dose of 4.0 mg
Bliwise (2005)	DB/R/CT	54/mean=50.8 y/2 w	Improved IRLS Rating Scale scores and PLMS by polysomnography
Montplaisir (2004a; 2004b)	SB+DB/R/CT	202+92/18–79 y/24 w+12 w	3x greater odds of relapsing while on placebo vs ropinirole; improved overall life impact score of RLS QoL Questionnaire; role physical, vitality, social functioning, and mental health on MOS SF-36; improved sleep disturbance, daytime somnolence, and sleep quality on MOS Sleep Scale
Bogan (2006)	DB/R/CT	381/18–79 y/12 w	Improved IRLS Rating Scale and CGI-I Scale scores; improved sleep disturbance, quantity, and adequacy on MOS Sleep Scale; improved PLMS per hour by actigraphy; improved anxiety on HADS; improved quality of life on the Johns Hopkins RLS Quality of Life Questionnaire
Kushida (2006)	DB/R/CT	363/18–79 y/12 w	Improved IRLS Rating Scale and CGI-I Scale scores in this flexible-dose study

*statistically significant (unless otherwise noted).

Abbreviations: CGI-I, Clinical Global Impression-Improvement; CR, controlled trial, crossover design; CT, controlled trial, parallel-group design; DB, double blind; HADS, Hospital Anxiety and Depression Scale; IRLS, International Restless Legs Syndrome; MOS SF-36, Medical Outcomes Study Short Form-36; NA, not available; n, night; N, non-randomized; NREM, non-rapid eye movement sleep; PLMs, periodic limb movements; PLMS, periodic limb movements in sleep; PLMW, periodic limb movements in wake; QoL, Quality of Life; R, randomized; SB, single blind; SE, sleep efficiency; TST, total sleep time; w, weeks; y, years.

improvement in the IRLS Rating Scale (primary efficacy endpoint) at a mean ropinirole dose of 1.90±1.13 mg/day at week 12 was found compared with placebo, and significantly more patients in the ropinirole group (53.4%) showed improvement in the CGI-I Scale at week 12 compared with the placebo group (40.9%). The clinical benefit of ropinirole was evident by week 1 as reflected by significant differences in both the IRLS Rating Scale and CGI Scale, and the most common adverse events for the ropinirole group vs the placebo group were nausea (37.7 vs 6.5%) and headache (19.9 vs 16.7%). Ropinirole was effective despite the presence of a placebo effect that the authors concede "was larger than expected;" the IRLS Rating Scale total score at week 12 was 13.5±9.3 for the ropinirole group and 17.1±9.4 for the placebo group. However, the authors point out that similar placebo effects are common in trials in other diseases in which subjective tools are used to assess efficacy and that patients may have had enhanced treatment expectations due to such reasons as the poorly recognized status of RLS.

A companion study to the TREAT RLS 1 study was the TREAT RLS 2 study conducted by Walters and colleagues (Walters et al 2004). The same experimental design and endpoints were used in both studies, with a total of 267 RLS patients participating in this study. The mean (±standard error) adjusted IRLS Rating Scale score change between baseline and week 12 was significantly greater for patients receiving ropinirole (–11.2±0.76) than for those receiving placebo (–8.7±0.75). Significantly more patients in the ropinirole group responded as "much" or "very much" improved on the CGI-I Scale compared with those in the placebo group (59.5 vs 39.6%, respectively) at week 12. Significant improvements in the IRLS Rating Scale and CGI-I Scale scores were also found at week 1. Patients also showed significant improvement in all four domains of the Medical Outcomes Study (MOS) sleep scale, the overall life-impact score on the RLS Quality of Life (QoL) questionnaire, and three of the eight domains of the MOS Short Form (SF)-36 Health Survey. The two most common severe adverse events reported in >2% of the patients were nausea (8 patients receiving ropinirole, none receiving placebo) and headache (5 patients in each group); adverse events led to the discontinuation of <10% of patients in each treatment group. Similar to the TREAT RLS 1 study, a large placebo effect that lessened the treatment difference was observed in this study; however, the same explanations used to account for this effect in the former study is applicable to this study as well. The authors also point out that the single-dosing schedule at 1–3 hours before bedtime may have lessened the relative treatment effect of ropinirole, particularly for severely affected patients who had symptom onset before dosing. Although a more flexible dosing schedule would have undoubtedly enhanced the difference in treatment groups, the beneficial effects of ropinirole were documented across several measures of efficacy, sleep parameters, and quality of life in these two large-scale companion studies.

A 12-week, multi-center, double-blind, randomized, placebo-controlled trial was conducted by Allen and colleagues, in which they assessed 65 patients with both RLS and PLMS (Allen et al 2004a). Patients received flexible dosing of ropinirole (0.25–4 mg/day) and placebo that occurred once daily near bedtime. The PLMS per hour were significantly decreased for patients receiving ropinirole (48.5–11.8) at a mean dose of 1.8 mg/day vs those receiving placebo (35.7–34.2). PLMS with arousals per hour and PLMW per hour similarly significantly decreased for those receiving ropinirole; these measures increased for those receiving placebo. Sleep adequacy by the MOS sleep scale was significantly improved with ropinirole treatment, and significantly increased stage 2 sleep amounts and the patient's ability to initiate sleep compared to placebo were observed; however, a significantly greater increase in stages 3 and 4 sleep was observed in the placebo group. The authors posit that since PLMS mainly disrupt stage 2 sleep, effective treatment of RLS may be expected to increase stage 2 sleep, and that sleep deprivation over several nights results in an increased drive for sleep, expressed by the increased stages 3 and 4 sleep. The most common adverse effects reported during treatment were headache (34.4%) and nausea (31.3%).

Two randomized, placebo-controlled, forced-titration studies, primarily to assess the pharmacokinetics, safety, and tolerability of ropinirole, were conducted. The studies randomized RLS patients in a 2:1 ratio to ropinirole at a dose range of 0.25–4.0 mg/day over 7 weeks (maximum dose dependent on tolerability) or placebo. In the first study (ropinirole, 18 patients; placebo, 10 patients) (Allen et al 2004b; Kelly and Mistry 2004; Tompson and Della Pasqua 2004), based on a logistic model and factoring pharmacokinetic variability, 50% of patients were predicted to respond on either IRLS Rating Scale score or PLMS/hr at doses of ropinirole >1.5 mg/day. Ropinirole produced a greater reduction in PLMS/hr by actigraphy compared with placebo, particularly in the first third of the night when the PLMS were observed to be most prevalent. In the second study (ropinirole, 37 patients; placebo, 17 patients) (Kelly

and Mistry 2005), 29 (78.4%) of the ropinirole-treated patients completed the study, at least 70% of the patients tolerated each ropinirole dose, and 16 (43.2%) tolerated the highest dose of 4.0 mg. The two most frequently reported adverse events were nausea (59.5%) and headache (43.2%); the majority of the 237 adverse events reported in 35 patients receiving ropinirole (compared to 39 adverse events reported in 13 patients receiving placebo) were mild or moderate in intensity (224/237, 94.5%) and there were no unexpected or serious adverse events. As expected with a forced-titration regimen, the incidence of adverse events was high, but the high percentage of patients tolerating each ropinirole dose level and the improvement in RLS and PLMS suggest that this dosing regimen is generally well tolerated and effective in these patients.

Bliwise and colleagues (2005) conducted a short-term (2-week), double-blind, randomized, placebo-controlled trial on 22 RLS patients (ropinirole, 9; placebo, 13) who had long-standing RLS (mean duration of symptoms, 26.1 years) and had successfully undergone 4 weeks of open-label titration and dose adjustments with ropinirole for RLS symptoms. At a mean dose of 1.4 mg, ropinirole significantly decreased RLS severity and PLMS without changing sleep parameters.

An international, multi-center study evaluated 106 out of a total of 202 RLS patients aged 18–49 years who received 24 weeks of ropinirole at a dose range of 0.25–4.0 mg/day in a single-blind fashion (Haan et al 2004; Karrasch et al 2004; Montplaisir et al 2004a, 2004b). At the end of this single-blind phase, 92 patients meeting criteria for treatment continuation were randomized to 12 weeks of double-blind treatment with either ropinirole or placebo. The primary endpoint was the proportion of patients relapsing (IRLS Rating Scale score of ≥15 that had worsened by at least 6 points compared to the start of double-blind treatment or withdrawal due to lack of efficacy) during the double-blind phase. The odds of a patient relapsing while on placebo were three times greater than those of a patient receiving ropinirole. During the double-blind phase, significant improvements were found in those receiving ropinirole compared to those receiving placebo in quality of life and four domains of the SF-36; patients switching to placebo during the double-blind phase experienced significant worsening in sleep disturbance, daytime somnolence, and sleep quality of the MOS sleep scale. Most of the adverse events were mild or moderate in severity, and nausea and headache were the most common adverse events. Three patients (1.5%) experienced augmentation (reported as hyperkinesias) during ropinirole treatment, but it subsequently and spontaneous resolved with continued ropinirole treatment (Karrasch et al 2004).

Bogan and colleagues conducted a 12-week, multi-center, double-blind, randomized, placebo-controlled trial called TREAT RLS US in 308 patients aged 18–79 years with RLS (Bogan et al 2006). Patients received flexible dosing of ropinirole (0.25–4 mg/day) and placebo that occurred once daily 1–3 hours before bedtime. At week 12 LOCF, the mean IRLS Rating Scale total score in the ropinirole group had significantly decreased from 22.0±4.99 at baseline to 8.4±7.32 compared with a reduction in the placebo group from 21.6±4.79 to 11.9±9.20. Significantly more patients in the ropinirole group were rated as responders (much or very much improved) on the CGI-I Scale at week 12 LOCF compared with those receiving placebo. Similar significant findings in IRLS Rating Scale and CGI-I Scale scores were found at week 1 LOCF. A post-hoc analysis showed that there was a significant improvement in IRLS Rating Scale score from baseline to day 3 OC (observed case); indicating that the effect of ropinirole on RLS may be as early as 72 hours after administration (Bogan et al 2005a). Ropinirole significantly improved IRLS Rating Scale scores at every subsequent measurement starting at day 3 through week 12 (Sethi and Carson 2005). Significant improvement in subjective measures of sleep (disturbance, quantity, and adequacy), quality of life, and anxiety were observed in the ropinirole group. The PLMs index as measured by actigraphy was significantly decreased from baseline to week 6 in 110 patients in the ropinirole group compared to 113 patients in the placebo group (Rye et al 2005). The two most common adverse events that were reported in at least 5% of patients were nausea and headache.

A 12-week, multi-center, double-blind, randomized, placebo-controlled, flexible-dose study was conducted to investigate the efficacy of ropinirole in RLS patients requiring extended treatment coverage (Kushida and Tolson 2006). Patients received ropinirole (0.5–6.0 mg/day) in divided doses, with the first dose taken 1 hour before their usual onset of symptoms and the second dose 3–8 hours after the first dose. A total of 363 patients were randomized, with 359 patients comprising the intention-to-treat population. At week 12 LOCF, the mean total daily dose was 3.1±1.97 mg for ropinirole and, compared with placebo, the improvement from baseline in IRLS Rating Scale total score was significantly greater for ropinirole and more ropinirole-treated patients were classified as responders.

These results prompted the investigators to conclude that ropinirole is an effective treatment for RLS patients requiring extended treatment coverage.

Expert opinion

The eleven controlled trials in the preceding section had sample sizes from 12 to 363 subjects, lasted from 4 to 36 weeks in duration, consisted of both parallel and crossover designs, and included one with an open-label period (Table 2). The strengths of the later trials were that they used several validated, independent instruments to assess RLS symptoms and severity (eg, RLSQ, IRLS Rating Scale, CGI-I Scale) and for the most part had large sample sizes and longer treatment periods.

Several conclusions could be reached upon review of these studies and by post-hoc analyses conducted on a combination of the data from some of the above studies:

1. Ropinirole effectively treats the RLS symptoms and the major consequences associated with RLS. Specifically, it is highly effective in improving the symptoms of RLS, the sleep disturbance likely resulting from the symptoms, and the quality of life of RLS patients (Ferini-Strambi et al 2004). Ropinirole is also effective in controlling PLMS, which are frequently associated with RLS.
2. The onset of action of ropinirole treatment is rapid. Even at low doses (0.25–0.5 mg/day) during the first week of treatment, ropinirole was effective in significantly reducing the severity of RLS (Becker et al 2004; Allen et al 2005a). RLS symptom improvement may be seen after as few as 2 nights of ropinirole treatment (Ziman et al 2006b).
3. An initial response to ropinirole occurred in some patients at 0.25 mg/day; however, by week 12, a considerable proportion of patients benefited from titration to higher doses that were both efficacious and tolerable (ie, most patients titrated to and responded at a mean dose of up to approximately 2 mg/day) (Garcia-Borreguero et al 2005a, 2005b).
4. The benefits of ropinirole appear to be maintained in the long-term (Ferini-Strambi et al 2004; Tidswell et al 2004). Two open-label clinical series each lasting 52 weeks showed continued efficacy of ropinirole in reducing RLS severity.
5. Similar clinical responses to ropinirole are observed for both early- and late-onset (over age 45 years) RLS phenotypes (see section on Phenotypes and genotypes). Allen and colleagues suggest that the two phenotypes involving different biological processes may have a common final expression of dopaminergic pathology responsive to ropinirole (Allen et al 2005b; Sethi and Hosford 2006).
6. Ropinirole is effective in controlling both evening and nighttime RLS symptoms (Lee and Earl 2006).
7. Subjective sleep quality and quantity as well as objective RLS motor symptoms are significantly improved by ropinirole; the subjectively experienced improvements in sleep with ropinirole may be mediated via improvements in the underlying RLS-associated motor symptoms (Allen et al 2004d, 2004c). Reduced daytime alertness, a consequence of chronic sleep disruption, may improve in RLS patients with moderate-to-severe RLS receiving ropinirole (Lee et al 2006).
8. Ropinirole treatment produced greater improvements in mood symptoms in patients with RLS compared to those on placebo. Mood was assessed by the Hospital Anxiety and Depression Scale (HADS), the Profile of Mood States (POMS), and item 10 of the IRLS Rating Scale (related to mood symptoms) (Thomas et al 2006).
9. Ropinirole is well tolerated with adverse events generally mild or moderate. The side effect profile of ropinirole is comparable to other non-ergoline derivatives, with the main side effects related to its dopaminergic activity. Nausea, dizziness, headache, and somnolence are the common side-effects reported in the clinical trials of ropinirole. From data from 616 patients (ropinirole, 309; placebo, 307), the most common adverse event was nausea (ropinirole, 37.9%; placebo, 8.1%) and most of the patients reported the nausea to be mild or moderate (ropinirole, 85%; placebo, 100%). The overall withdrawal rates were low (ropinirole, 2.3%; placebo, 0.3%), indicating that these events did not limit treatment. Most adverse events occurred first in the initial 2-week interval of the study and ongoing decreases in incidence were observed in the subsequent 2-week intervals (ie, maintenance stages of the studies) (Montagna et al 2004). Augmentation and tolerance commonly occur with dopaminergic treatment of RLS, but are reported at a lower frequency in studies with ropinirole compared to those with levodopa. A possible association of dopaminergic agonists and pathologic gambling has been reported in patients with Parkinson's disease (PD); however, further study is warranted to study this phenomenon and to determine if it is a side effect of dopamine agonists or a symptom of advanced PD (Driver-Dunckley et al 2003; Dodd et al 2005). Similarly, daytime sleepiness to the level of "sleep

attacks" has been reported in conjunction with automobile accidents in PD patients taking dopamine agonists (Frucht et al 1999; Ondo et al 2001; Pal et al 2001). In RLS patients, Bassetti reported a single case of an RLS patient with multiple sleep attacks while taking pergolide at a dose of 0.25 mg/day (Bassetti et al 2002); there appears to be no report of sleep attacks in RLS patients taking non-ergoline dopamine agonists. Although dopamine agonists have been associated with sleep attacks, there is no consensus on whether a causal relationship exists (Plowman et al 2005); this phenomenon may be apparent more in PD patients due to the tendency towards daytime sleepiness in PD patients independent of treatment (Rye et al 2000) and the higher doses of dopaminergic agents needed to control PD compared with RLS.

10. The safety of ropinirole is not established in pediatric patients, so children should be considered for treatment only if there is significant impairment of their daytime alertness levels, cognition, school performance, behavior (eg, moodiness or irritability due to drowsiness), and/or quality-of-life. There are no studies of ropinirole in human pregnancy; it is classified as a pregnancy category C drug. A pregnant woman with RLS should definitely be informed that her RLS symptoms will typically resolve within one month of delivery.

Recommendations

Indications of use

Ropinirole is effective in treating RLS as well as PLMS. Treatment with ropinirole should be considered even in RLS patients who have failed other therapies, since it has been shown to be effective in improving RLS symptoms in this subgroup of patients (Ziman et al 2006a).

Dosing

It is important to take ropinirole prior to symptom onset, since the action of dopamine agonists generally starts 90–120 minutes after ingestion (Silber et al 2004). Further, for daily RLS, ropinirole may be started at 0.25 mg per day at 2 hours before RLS symptom onset, and then increased by 0.25 mg every 2 to 3 days until symptom relief is achieved (Silber et al 2004). Starting dose should be individualized based on RLS severity and age. In general, the effective dose for ropinirole is typically 2 mg or less, although some patients may require doses as high as 6 mg/day.

Adverse events

The common side-effects of nausea, dizziness, headache, and somnolence are typically worse in the first two weeks of treatment and may require dose reduction but rarely discontinuation of drug. The patient should be warned and monitored for sleep attacks; the presence of this adverse event should warrant immediate reduction or discontinuation of the drug. The probability of developing augmentation or tolerance is low; if they occur, decreasing or stopping this medication, or switching to another medication, may be necessary.

In conclusion, ropinirole is effective and well tolerated in the treatment of patients with RLS; it has rapid onset of action and long-term benefit with adverse events in the mild to moderate range.

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