Ropinirole Decreases Periodic Leg Movements and Improves Sleep Parameters in Patients with Restless Legs Syndrome

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Study Objectives: Polysomnographic study evaluating the efficacy of ropinirole for the treatment of patients with restless legs syndrome (RLS) suffering from periodic leg movements in sleep (PLMS).

Design: Double-blinded, placebo-controlled, parallel-group study.

Setting: 15 tertiary referral centers in the USA.

Participants: 65 patients with RLS and PLMS.

Interventions: Ropinirole (0.25-4.0 mg per day) or placebo for 12 weeks.

Measurements and Results: Data from 59 patients were included in the primary endpoint analysis. PLMS per hour decreased more with ropinirole (48.5 to 11.8), compared with placebo (35.7 to 34.2; adjusted treatment difference: -27.2; 95% confidence interval [CI]: -39.1, -15.4; P < .0001). Periodic limb movements with arousal per hour decreased from 7.0 to 2.5 with ropinirole but increased from 4.2 to 6.0 with placebo (adjusted treatment difference: -4.3, 95% CI: -7.6, -1.1; P = .0096). Periodic limb movements while awake per hour decreased from 56.5 to 23.6 with ropinirole but increased from 46.6 to 56.1 with placebo (adjusted treatment difference: -27.2; 95% CI: -39.1, -15.4; P < .0001). Ropinirole treatment significantly improved patients' ability to initiate sleep (P < .05) and the amount of Stage 2 sleep compared with placebo (P < .001). There were also nonsignificant trends toward increases in total sleep time and sleep efficiency. Sleep adequacy (measured on the subjective Medical Outcomes Study sleep scale) was significantly improved with ropinirole treatment (adjusted treatment difference: 12.1; 95% CI: 1.1, 23.1; P = .0316). In contrast, the placebo group showed a greater increase in Stage 3/4 sleep (P < .01). No serious adverse events occurred in either group.

Conclusions: Ropinirole is effective in the treatment of both the sleep and waking symptoms of RLS.

Abbreviations: IRLS, International Restless Legs Scale; LOCF, Last observation carried forward; PLMA, Periodic leg movements with arousal; PLMS, Periodic leg movements in sleep; PLMW, Periodic leg movements while awake; PSG, Polysomnogram; REM, Rapid eye movement; RLS, Restless legs syndrome; TST, Total sleep time

Key Words: Restless legs syndrome; RLS, periodic leg movements; sleep; polysomnogram; ropinirole; placebo-controlled, Ekbom syndrome

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INTRODUCTION

SLEEP DISTURBANCE IS A PROMINENT FEATURE OF RESTLESS LEGS SYNDROME (RLS), A NEUROLOGIC SENSORIMOTOR DISORDER THAT WAS FIRST DESCRIBED IN THE SCIENTIFIC LITERATURE BY KARL EKBOM IN 1945. The etiology of RLS is unknown, although there is evidence of both a brain-iron deficiency and central dopaminergic dysfunction. The medical community has increasingly recognized the importance of fully evaluating pharmacologic treatments for this condition, and the diagnostic criteria for RLS were updated at a workshop at the National Institutes of Health in 2003. Standards of practice providing evidence-based treatment guidelines are also available.

The four cardinal diagnostic features of RLS include (1) an urge to move the legs that is usually associated with paresthesias or dysesthesias, (2) symptoms that start or become worse with rest, (3) at least partial relief of symptoms with physical activity, and (4) worsening of symptoms in the evening or at night. The syndrome is defined by sensory disturbances involving an urge to move the legs, and it also has a primary motor symptom that is characterized, as first observed by Lugaresi et al., by the occurrence of periodic leg movements in sleep (PLMS). PLMS occur in approximately 80% to 90% of patients who have RLS and support the diagnosis of RLS. PLMS per hour reflect the underlying severity of the disorder and correlate significantly with the subjective report of RLS severity. PLMS are frequently associated with arousal from sleep (known as periodic leg movements with arousal [PLMA]). In addition, during the night, periodic movements have also been shown to occur while the patient is awake, which has led to the term periodic leg movements while awake (PLMW). PLMW occur prior to sleep onset and are a factor that increases latency to sleep onset. While the relation between PLMW and RLS severity remains to be established, we hypothesize that it will be at least as strong as that for PLMS, and for diagnosis, PLMW may be more accurate than PLMS. The results of 1 study have shown that PLMW have a sensitivity and specificity of 87% and 80%, respectively, for RLS diagnosis, whereas the corresponding values for PLMS were 78% and 76%, respectively.

In addition, a primary morbidity of RLS is sleep disturbance, with a clinically significant reduction in sleep efficiency resulting from the frequent brief arousals due to PLMS. Effective
treatment must therefore reduce the PLMS caused by RLS in order to reduce the severity of a primary source of morbidity of this disorder. The reduction of PLMS also provides objective documentation of treatment efficacy.

PLMS occur mostly during non-rapid eye movement (non-REM) sleep. PLMA disrupt the continuity of sleep by producing either awakening or a lighter stage of sleep (Stage 1) and accordingly reduce the amount of deeper non-REM sleep (particularly Stage 2). Thus, improvement of RLS with treatment should not only be documented by changes in the physiologic variables on a polysomnogram (PSG) of PLMS and PLMW, but also by improvements in PLMA, sleep latency, sleep efficiency, and amount of sleep, particularly the amount of Stages 2 to 4 of non-REM sleep.

While it is clinically well accepted that dopamine-receptor agonists provide effective treatment for primary RLS, the scientific evaluation using double-blind placebo-controlled studies has been limited. Two small studies of pergolide9,10 and 1 study of pramipexole11 have been carried out with PSG assessments. In these studies, PLMS decreased as expected with treatment, but although pergolide treatment resulted in increased total sleep time and sleep efficiency, no such effect was seen with pramipexole. This has raised the question of whether a primary D2/D3-receptor agonist improves sleep parameters to the same extent as the broader-spectrum D1-, D2-, and D3-receptor agonist pergolide. There have been several small open-label studies using PSG to evaluate the efficacy of the D2/D1-receptor agonist ropinirole in the treatment of RLS patients.12-14 Ropinirole, in these studies, improved PLMS, TST, and sleep efficiency, as well as subjective sleep quality. To date there have been no published, double-blind, placebo-controlled, PSG studies of ropinirole in patients with RLS. However, a large, double-blind, placebo-controlled trial that did not utilize PSG was recently completed and demonstrated significant improvements in RLS symptoms, sleep, and quality of life in the ropinirole group compared with the placebo group.15

The current study, named the Ropinirole Efficacy and Safety (RESET PLM) study, was designed to evaluate the efficacy of ropinirole in patients with RLS, measuring PLMS per hour as the primary outcome variable and PLMA per hour of sleep as a key secondary endpoint.

The sample sizes for this study were therefore calculated to provide adequate power for the evaluation of these objective measures of the treatment response to ropinirole. The study also included several secondary endpoints to evaluate the effects of ropinirole on patients’ subjective experiences of improvement in sleep and RLS symptoms (although the study was not designed to have sufficient power to detect significant differences on these endpoints). The Medical Outcomes Study (MOS) Sleep Scale was included to provide a measure that is more specific to sleep improvements, while the International Restless Legs Scale (IRLS), a physician-completed subjective questionnaire, was included to provide an overall clinical evaluation of RLS. This is the first such study using ropinirole and is also the largest published placebo-controlled PSG study of any treatment for RLS.

METHODS

Patients

Patients were recruited from 15 tertiary referral centers in the United States. Sixty-five patients between the ages of 18 and 79 years who met the International RLS Study Group criteria for RLS and had 5 PLMS per hour on a screening PSG were included in the study. Patients were also required to have a score of 15 or greater (indicating moderate severity) on the IRLS (ranging from 0 to 40)16 at baseline and report a minimum of 15 nights with RLS symptoms in the month prior to the study.

Patients were excluded from the study if they had daytime RLS symptoms requiring treatment, sleep disorders other than RLS, movement disorders, signs or symptoms of secondary RLS (eg, secondary to pregnancy, renal failure, iron-deficiency anemia, gastric surgery, or neuropathy), any unstable medical conditions (eg, severe cardiovascular disease or orthostatic hypotension), or conditions that could affect efficacy assessments (eg, diabetes, peripheral neuropathy, rheumatoid arthritis or fibromyalgia syndrome). Patients who had oxygen saturation values less than 80% at any time during the night or had more than 5 significant sleep-disordered breathing events per hour of sleep on the screening PSG were also excluded. Significant sleep-disordered breathing events were defined as apneas or hypopneas lasting for at least 10 seconds with a minimum of an 8% decrease in oxygen saturation.

Study Design

This was a double-blinded, placebo-controlled, parallel-group, 12-week study. Patients taking any medications affecting RLS or sleep entered a washout phase for a minimum of 7 days or 5 half-lives, whichever was longer, prior to the start of the study. Eligible patients were randomly assigned (1:1) at the baseline visit to receive either ropinirole or placebo for 12 weeks of double-blind treatment. The dose of active medication or matching placebo was flexible, ranging from 0.25 mg per day to 4.0 mg per day. Medication was titrated to an optimal dose, based on the investigator’s impression of individual efficacy and tolerability. For all patients, therapy was initiated at 0.25 mg per day of ropinirole or matching placebo for 2 days. At Day 2, the dose was then increased to 0.5 mg per day for 5 days. Thereafter, the dose could be increased in 0.5-mg increments at weekly intervals up to 3.0 mg per day, with a final increase from 3.0 mg per day to 4.0 mg per day. A stable dose was to be maintained for the last 4 weeks of the study. Treatment was administered 1 to 3 hours prior to bedtime, depending on patients’ symptoms. However, on nights when PSG assessments were carried out, treatment was administered 2 to 3 hours prior to PSG in order to allow pre-PSG assessments. Clinic visits were conducted at screening, baseline, Day 2, weekly for the first 8 weeks of the study, at Week 12, and 1 week after discontinuation of study medication (follow-up visit). PSG assessments were conducted for 2 consecutive nights prior to clinic visits at baseline, Week 6, and Week 12 or the last visit if a patient prematurely discontinued the study. The PSG values from the second night were used for all analyses.

PSG Measures

Sleep was recorded between approximately 11 PM (lights out) and 7 AM using a 12-channel paper PSG recorder, including 2 electroencephalogram channels (C3-A2, C4-A1), 2 electrooculo-
gram channels (left/right), submental electromyogram, nasal/thermal airflow by heat-sensitive thermistors, electrocardiogram, respiratory effort by chest and abdomen strain gauges, and oxygen saturation using finger pulse oximetry. Leg-movement activity was recorded separately from the anterior tibialis of each leg. PSG recordings were made on paper in order to avoid inter-PSG recorder software validity issues. The sleep electroencephalogram tracing was visually scored following standard procedures. PLMS were scored visually based on the recommendation of the American Sleep Disorders Association Atlas Task Force with the following criteria: (1) an electromyogram burst length between 0.5 and 5.0 seconds; (2) a movement amplitude of at least 25% of calibration movement; (3) an interval of 5 to 90 seconds between movements (PLMS); and (4) a minimum of 4 consecutive movements required for a group of movements to be scored as PLMS. PLMW were scored throughout all of the wake time during the nocturnal PSG using the criteria defined by Michaud. These criteria are the same as those used for scoring PLMS, except that the maximum duration was 10 seconds. Arousals during sleep were scored strictly according to the American Academy of Sleep Medicine published standards. An arousal was considered associated with a leg movement only if it started after the leg movement began, if it finished before the leg movement had ended, and if there were no other factors that might have contributed to the arousal, for example, any sleep-disordered breathing event during the time of the arousal. All records were centrally scored by registered polysomnographic technologists and reviewed in detail by a Diplomate of the American Board of Sleep Medicine experienced with PLMS and RLS.

**MOS Sleep Scale**

Patients were asked to complete the MOS sleep scale at baseline and at Week 12 (or at the time of withdrawal in the case of patients who withdrew prematurely). The MOS sleep scale was developed to provide a valid and reliable scale that included the most applicable theoretical constructs of sleep (ie, sleep initiation, maintenance, perceived adequacy, regularity, daytime somnolence, and respiratory impairments). The scale consists of a comprehensive battery that measures specific aspects of sleep in patients who may have varying comorbidities and is therefore appropriate for a medically diverse patient population. Four domains of the MOS scale were selected for analysis, as these were considered to be particularly relevant to RLS: sleep adequacy assesses whether the individual obtained the sleep he or she needs to feel rested upon waking in the morning during the past 4 weeks; sleep disturbance assesses whether the individual had trouble falling asleep or were awakened during her or his sleep or had sleep restlessness during the past 4 weeks; sleep quantity measures how many hours of sleep the individual obtained each night during the past 4 weeks; daytime somnolence assesses whether the individual felt drowsy or sleepy during the day, had trouble staying awake, or took longer than 5-minute naps during the day during the past 4 weeks. The 2 domains related to respiration in sleep were prospectively determined not to be relevant to the goals of this study and were therefore excluded from analyses. With the exception of sleep quantity, which was reported in hours, MOS measures were reported on a scale of 0 to 100, such that a high score reflected more of the attribute implied by the domain name (eg, greater sleep disturbance, greater sleep adequacy).

**International RLS Rating Scale**

The IRLS for each patient was completed at baseline, Day 2, Weeks 1 to 8, and Week 12 (or at the time of withdrawal in the case of patients who withdrew prematurely). This scale, which was developed and validated by the International RLS Study Group, comprises 10 questions relating to the frequency and severity of RLS symptoms and the impact that these symptoms have on daily activities and mood. Responses are graded in the range 0 to 4 (0 = absence of a problem, 4 = very severe problem), with a maximum total score of 40.

**Data Analyses**

Summary statistics of patient characteristics at baseline were provided to allow comparison of the treatment groups. The treatment effects were evaluated for change from baseline to Week 12, with the last observation used for patients who discontinued the study early. The analysis of variance for change from baseline included center grouping and the baseline score of the endpoint being tested as covariates. The primary and key secondary endpoints were prospectively defined as the endpoints on which primary inferences would be made. The primary outcome evaluation was for PLMS per hour, and PLMA per hour was a key secondary endpoint. Secondary analyses assessing sleep parameters were conducted for PLMW per hour, sleep latency, sleep efficiency, percentage of TST spent in Stage 2 sleep, percentage of TST spent in Stage 3/4 sleep, and the subjective rating on the MOS sleep scales. A secondary analysis was also conducted for the IRLS total score.

In addition, TST; percentage of TST spent in stage 1 sleep; non-REM sleep (minutes of Stages 2 and 3/4 combined); and absolute time spent in Stage 1, Stage 2, Stages 3/4, and Stages 2 and 3/4 combined were investigated retrospectively.

**RESULTS**

**Patients and Treatment**

Sixty-five patients entered the study and received at least 1 dose of study medication. The 32 patients randomly assigned to receive ropinirole had a mean age (SD) of 54.6 (12.1) years and 62.5% (20 of 32) were women, whereas the 33 patients randomly assigned to placebo had a mean age (SD) of 53.2 (12.9) years and 54.5% (18/33) were women. Fifty-five patients completed the study (28 of 32 in the ropinirole group and 27 of 33 in the placebo group), including PSG assessments.

Of the 65 patients who entered the study, 59 completed postbaseline PSG assessments and were therefore included in the analysis of the primary endpoints. Table 1 describes the demographics and baseline disease characteristics of the 59 patients (ropinirole, n = 29; placebo, n = 30) who were included in the analysis of the primary endpoints. Patients in the ropinirole and placebo groups who underwent postbaseline PSG were similar in terms of age, sex, age at onset of RLS, and family members with RLS.
The mean daily dose at Week 12 (last observation carried forward [LOCF]) was 1.8 mg per day (median 1.5 mg per day) in the ropinirole group, compared with a dose equivalence of 2.7 mg per day (median 3.0 mg per day) in the placebo group. The treatment received by 4 (12.5%) patients in the ropinirole group was titrated to the maximum dose of 4.0 mg per day compared with 12 (36.4%) patients in the placebo group.

**Objective Assessments**

Both the primary outcome variable (PLMS per hour) and the key secondary variable (PLMA per hour) showed large and statistically significant differences in favor of ropinirole over placebo for the change from baseline to Week 12 LOCF. PLMS per hour decreased from 48.5 to 11.8 in the ropinirole group compared with a decrease from 35.7 to 34.2 in the placebo group (Figure 1a). The adjusted treatment difference was -27.2 (95% confidence interval [CI]: -39.1, -15.4; \( P < 0.0001 \)). For patients who were treated with ropinirole, PLMS per hour were reduced to the normal level of 5 or fewer for 53.6% of patients and was 15 or fewer for 71.4% of patients at Week 12. In contrast, in the placebo group, PLMS per hour were reduced to 5 or fewer for 14.8% of patients and to 15 or fewer for 40.7% of patients at Week 12. PLMA per hour similarly decreased from 7.0 to 2.5 in the ropinirole group compared with an increase from 4.2 to 6.0 in the placebo group, with an adjusted treatment difference of -4.3 (95% CI: -7.6, -1.1; \( P = 0.0096 \); Figure 1b). In the ropinirole-treated group, 35.7% of the patients had no PLMA, and 78.6% fewer than 2 PLMA per hour at Week 12. The corresponding values in the placebo group showed that 14.8% of the patients had no PLMA and 25.9% had fewer than 2 PLMA per hour.

Analysis of PLMW per hour showed a mean decrease from 56.5 to 23.6 in the ropinirole group at Week 12 LOCF, compared with an increase from 46.6 to 56.1 in the placebo group (Figure 2). The adjusted treatment difference was statistically significant:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ropinirole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients, no.</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Women, no. (%)</td>
<td>17 (58.6)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>55.4 (10.3)</td>
<td>53.3 (12.5)</td>
</tr>
<tr>
<td>Range</td>
<td>37-76</td>
<td>30-79</td>
</tr>
<tr>
<td>Age at onset of RLS, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>38.8 (17.1)</td>
<td>35.5 (15.6)</td>
</tr>
<tr>
<td>Range</td>
<td>13-68</td>
<td>12-68</td>
</tr>
<tr>
<td>Patients with first-degree relatives with RLS/PLMS, no. (%)</td>
<td>14 (48.3)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Patients with prior RLS treatment, no. (%)</td>
<td>16 (55.2)</td>
<td>15 (50.0)</td>
</tr>
<tr>
<td><strong>Baseline disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLMS, no./h (SD)</td>
<td>48.5 (31.7)</td>
<td>35.7 (23.6)</td>
</tr>
<tr>
<td>PLMA, no./h (SD)</td>
<td>7.0 (8.0)</td>
<td>4.2 (3.9)</td>
</tr>
<tr>
<td>PLMW, no./h (SD)</td>
<td>56.5 (43.9)</td>
<td>46.6 (41.2)</td>
</tr>
<tr>
<td>TST, min (SD)</td>
<td>386.9 (59.5)</td>
<td>393.4 (50.0)</td>
</tr>
<tr>
<td>Stages 2 and 3/4 sleep, min (SD)</td>
<td>244.7 (50.4)</td>
<td>264.0 (53.2)</td>
</tr>
<tr>
<td>Sleep efficiency, % of TST (SD)</td>
<td>81.2 (11.6)</td>
<td>81.9 (10.1)</td>
</tr>
<tr>
<td>Sleep latency, min (SD)</td>
<td>16.7 (16.4)</td>
<td>8.9 (8.5)</td>
</tr>
</tbody>
</table>

*Primary analysis population included all patients who underwent a postbaseline polysomnography assessment.

RLS refers to restless legs syndrome; PLMS, periodic limb movements of sleep; PLMA, periodic limb movements with arousal; PLMW, periodic limb movements during wake; TST, total sleep time.
-39.5 (95% CI: -56.9, -22.1; $P < .0001$). Of the patients receiving ropinirole, 25.0% had no PLMW, and 50.0% had fewer than 10 PLMW per hour at Week 12 LOCF, whereas in the placebo group 11.1% of patients had no PLMW, and 14.8% had fewer than 10 PLMW per hour at Week 12 LOCF.

Among the other PSG sleep variables, the change in the ability to initiate sleep, as measured by sleep latency, was significantly greater in the ropinirole group compared with the placebo group. The average sleep latency in the ropinirole group was decreased from 16.7 to 6.6 minutes compared with an increase from 8.9 to 14.4 minutes in the placebo group, with an adjusted treatment difference of -9.8 minutes (95% CI: -17.2, -2.4; $P = .0106$). For sleep latency, diagnostic plots of the original model suggested that the underlying normality assumption of the model was invalid. Therefore nonparametric techniques were used to analyze the data. The use of nonparametric techniques did not alter the conclusion and indicated a similar and statistically significant benefit of ropinirole over placebo, while taking center group and baseline score into account (difference = -9.73, $P = .0025$).

Significant differences were seen between the groups in terms of changes in the minutes and percentage of time spent in stage 2 sleep, which increased in the ropinirole group but decreased in the placebo group (95% CI: 26.9, 76.3; $P = .0001$). In contrast, an increase in minutes of stage 3/4 sleep was seen in the placebo group compared with a smaller increase from baseline in the ropinirole group (95% CI: -47.3, -9.6; $P = .0038$). Although not significant, TST and sleep efficiency showed a trend toward a larger increase from baseline with ropinirole versus placebo, whereas there was a larger decrease in the percentage of Stage 1 sleep in the placebo group than in the ropinirole group. There was also an increase in the total minutes of combined non-REM Sleep stages 2 and 3/4 in the ropinirole group compared with placebo.

### Table 2—Polysomnographic measures of sleep: change from baseline to Week 12 last observation carried forward

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted* mean (SEM) change from baseline</th>
<th>Adjusted* treatment difference</th>
<th>95% confidence interval</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep stage, in minutes, as a percentage of TST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>Ropinirole (n = 29)</td>
<td>Placebo (n = 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mins</td>
<td>-7.9 (4.8)</td>
<td>-12.1 (4.5)</td>
<td>4.2</td>
<td>(-9.0, 17.4)</td>
</tr>
<tr>
<td>% TST</td>
<td>-2.7 (1.3)</td>
<td>-3.4 (1.2)</td>
<td>0.7</td>
<td>(-2.8, 4.2)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>mins</td>
<td>32.9 (8.8)</td>
<td>-18.7 (8.5)</td>
<td>51.6</td>
</tr>
<tr>
<td>% TST</td>
<td>4.6 (2.0)</td>
<td>-5.4 (1.9)</td>
<td>10.0</td>
<td>(4.6, 15.4)</td>
</tr>
<tr>
<td>Stages 3/4</td>
<td>mins</td>
<td>2.7 (6.8)</td>
<td>31.1 (6.5)</td>
<td>-28.5</td>
</tr>
<tr>
<td>% TST</td>
<td>-0.2 (1.5)</td>
<td>7.6 (1.5)</td>
<td>-7.9</td>
<td>(-12.1, -3.7)</td>
</tr>
<tr>
<td>Deep sleep—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stages 2 and 3/4 combined</td>
<td>mins</td>
<td>37.0 (9.9)</td>
<td>11.0 (9.6)</td>
<td>26.0</td>
</tr>
<tr>
<td>% TST</td>
<td>4.6 (1.8)</td>
<td>2.0 (1.8)</td>
<td>2.6</td>
<td>(-2.6, 7.8)</td>
</tr>
<tr>
<td>REM</td>
<td>mins</td>
<td>3.5 (7.1)</td>
<td>5.9 (6.8)</td>
<td>-2.5</td>
</tr>
<tr>
<td>% TST</td>
<td>-0.7 (1.6)</td>
<td>0.9 (1.5)</td>
<td>-1.6</td>
<td>(-6.1, 2.8)</td>
</tr>
<tr>
<td>TST, min</td>
<td>28.0 (9.0)</td>
<td>11.0 (8.7)</td>
<td>20.5</td>
<td>(-4.6, 45.6)</td>
</tr>
<tr>
<td>Sleep efficiency, %, as percentage of TST</td>
<td>5.2 (1.8)</td>
<td>1.0 (1.8)</td>
<td>4.3</td>
<td>(-0.8, 9.4)</td>
</tr>
<tr>
<td>Sleep latency, minutes to sleep onset</td>
<td>-6.1 (2.6)</td>
<td>3.7 (2.5)</td>
<td>-9.8</td>
<td>(-17.2, -2.4)</td>
</tr>
</tbody>
</table>

*Adjusted for center group and baseline score.
TST refers to total sleep time; REM, rapid eye movement; mins refers to minutes.
Subjective Assessments

Subjective assessments of sleep using the MOS sleep scale found that sleep adequacy was significantly improved in the ropinirole group compared with the placebo group (Table 3). The adjusted treatment difference between the ropinirole and placebo groups in terms of sleep adequacy at Week 12 LOCF was 12.1 (95% CI: 1.1, 23.1; P = .0316). The other 3 domains that were analyzed did not show statistically significant differences between the ropinirole and placebo groups (possibly due to insufficient numbers of patients), although improvements were consistently greater with ropinirole than placebo.

The IRLS results were not significantly different between the ropinirole and placebo groups, although a difference in favor of ropinirole was noted (adjusted treatment difference at Week 12 LOCF was -1.2 (95% CI: -5.2, 2.9; P = .5645).

Safety and Tolerability

No serious adverse events occurred in either group during the 12 weeks of treatment. The most common adverse events reported during treatment were headache (occurring in 34.4% of the ropinirole group versus 18.2% of the placebo group) and nausea (31.3% in the ropinirole group versus 15.2% in the placebo group). Dizziness, vomiting, and hyperkinesias were reported by more than 10% of the patients receiving ropinirole (Table 4). Somnolence also exceeded 10% in both groups and was similar between groups (15.6% in the ropinirole group versus 12.1% in the placebo group). One patient in the ropinirole group withdrew from the study due to an adverse event (worsening of headache). Five patients (4 in the ropinirole group and 1 in the placebo group) experienced worsening of RLS symptoms, which were coded as hyperkinesias. Hyperkinesia is a coded term in the World Health Organization Adverse Reaction Terminology adverse-event dictionary. The worsening of RLS symptoms has been linked to augmentation. All 4 patients with hyperkinesia in the ropinirole group completed the study, and in 1 of these patients the hyperkinesia resolved with continued treatment. The patient from the placebo group who experienced resolution of the hyperkinesia withdrew from the study (at Week 6) due to insufficient treatment efficacy. There were no reports of hallucinations, but there was 1 report of nocturnal body jerks in the ropinirole group; this was coded as a dyskinesia.

DISCUSSION

This is the largest double-blind, placebo-controlled, published PSG evaluation of any treatment for RLS. These data document that, compared with placebo, treatment with ropinirole significantly reduces the primary motor disturbance of RLS, as measured by periodic limb movements during sleep (PLMS) and during the resting or awake state in the sleep period (PLMW). Ropinirole treatment also produced a significant reduction in the major RLS sleep disturbance of arousals associated with the PLMS. Ropinirole, at a mean dose of 1.8 mg per day, effectively reduced PLMS to normal levels (< 5 PLMS per hour) for more than half of the patients and reduced PLMA to an inconsequential level (< 2 PLMA per hour) for the large majority (78.6%) of patients.

Decreases in PLMS have been shown in double-blind placebo-controlled trials for carbidopa/levodopa and the dopamine-receptor agonists pergolide and pramipexole. In the current study, PLMW were also shown to be significantly decreased in patients receiving ropinirole compared with those receiving placebo. Changes in PLMW were also reported in a small study using pramipexole (N = 10), but they were not measured in the carbidopa/levodopa or pergolide studies. PLMW are considered to represent a continuation into waking of the same motor expression of RLS symptoms seen in sleep and represent a motor response to the sensory symptoms of RLS.

RLS preferentially reduces the amount of Stage 2 sleep (the most prevalent stage of sleep), as PLMS, which may lead to arousals during sleep, are more pronounced during Stage 2 sleep than during any other sleep stage, except stage 1. In contrast,
PLMW disrupt sleep onset, resulting in prolonged sleep latency. Consequently, sleep latency, arousals with PLMS, and minutes of Stage 2 sleep provide sensitive indicators of any RLS treatment benefit.

Sleep deprivation over several nights results in an increased drive for sleep, expressed by increased slow-wave sleep (Stages 3/4). The PLMs of RLS mainly disrupt Stage 2 sleep\(^{24}\) (resulting in decreased Stage 2 sleep). Effective treatment of RLS might therefore be expected to result mainly in increases in the time spent in Stage 2 sleep.

The PSG data in our study showed that effective treatment reduces PLMs and may reverse the sleep changes that occur in RLS. Treatment with ropinirole increased Stage 2 sleep, with only a marginal increase in minutes of Stage 3/4 sleep, thereby resulting in an overall improvement in sleep. The patients treated with ropinirole also reported improved sleep adequacy, suggesting that they felt more rested when they awoke. In contrast, the placebo group had a statistically significant increase in minutes of Stage 3/4 sleep, without subjective improvement in sleep adequacy. These findings support the suggestion that effective treatment of RLS would result in increases in Stage 2 sleep.

The differences between the ropinirole and placebo groups favored ropinirole and were statistically significant for decreased arousals from the leg movements (PLMA per hour), decreased sleep latency, and increased Stage 2 sleep, which represent primary targets for sleep disruption by periodic limb movements. Similar increases in sleep, occurring mostly in Stage 2, have previously been reported by Saletu et al, in an unblinded study of ropinirole in RLS.\(^{13}\) Therefore, it appears that the increase in minutes of Stage 2 sleep is likely to be a sensitive electroencephalographic sleep-stage measure of the pharmacologic treatment efficacy for RLS.

Other sleep measures generally linked to restorative sleep, include TST, non-REM time (excluding Stage 1 sleep), and sleep efficiency. On these measures, there were no statistically significant differences between the ropinirole and placebo groups (possibly due to the sample size in this study), although a trend toward a greater increase with ropinirole compared with placebo was observed for these 3 variables.

Studies of ropinirole have looked at the effects of higher doses than those used in the current study,\(^{25}\) and, although the dose used in our study was clearly sufficient for clinical improvement on multiple PSG parameters, it remains possible that an increased dose might have produced more substantial improvements in sleep and subjective measures of improvement, such as can be seen on the IRLS scale.

As noted previously, improved sleep has also been shown in double-blind placebo-controlled trials for pergolide but not for pramipexole.\(^{9,11}\) Nevertheless, it is not clear whether this represents a clinical difference between these medications or is a consequence of the pramipexole study design.

The use of subjective outcome measures in the assessment of treatment effects often results in a relatively high placebo effect, which makes it more difficult to demonstrate treatment efficacy. This also seemed to be true in our study. In light of this, and the fact that our study was powered to detect treatment differences in terms of objective PSG measures, it is not surprising that the differences between the ropinirole and placebo groups on the IRLS and some of the MOS sleep domains did not reach statistical significance. However, it is important to note that recent placebo-controlled studies of ropinirole that were adequately powered to detect such differences have shown statistically significant benefits of ropinirole on the IRLS and all of the sleep domains of the MOS scale.\(^{15,26}\)

There were no differences between the treatment groups in terms of the amount of REM sleep. PLMS in patients with RLS are, in general, much less frequent and are often absent in REM sleep.\(^{24}\) It appears that REM sleep remains mostly intact in patients with RLS, and, therefore, changes as a result of treatment were not expected.

Overall, this study demonstrates the remarkable clinical efficacy of ropinirole in the treatment of both the sleep and waking motor symptoms of RLS. The motor symptoms of RLS were effectively normalized for more than half of the subjects treated. Ropinirole treatment reduced the motor symptoms and improved overall sleep, thus effectively treating the primary morbidity of RLS. Furthermore, improvements in sleep were demonstrated with both objective and subjective assessments. Ropinirole was also well tolerated, with no serious adverse effects.

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