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Ropinirole Is Effective in the Treatment of Restless Legs Syndrome. TREAT RLS 2: A 12-Week, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Study

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on behalf of the TREAT RLS 2 (Therapy with Ropinirole: Efficacy And Tolerability in RLS 2) Study Group

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Abstract: Restless legs syndrome (RLS) is a neurological condition with significant impact on sleep and quality of life (QoL). This double-blind, randomized, 12-week, multinational study compared the efficacy and safety of ropinirole and placebo in RLS. In total, 267 outpatients with moderate-to-severe RLS were randomly assigned to ropinirole (0.25–4.0 mg/day) or placebo, 1 to 3 hours before bedtime. The primary endpoint was the change in International Restless Legs Scale (IRLS) score at week 12. Key secondary endpoints were the percentage of patients showing significant improvement on the Clinical Global Impression-Improvement (CGI-I) scale at week 12 and changes in IRLS and CGI-I scale scores at week 1. Other measures included the Medical Outcomes Study sleep scale and Restless Legs Syndrome Quality of Life questionnaire. Improvements were significantly greater for ropinirole than placebo for change in IRLS score at week 12 (−11.2 [SE 0.76] vs. −8.7 [0.75], respectively; adjusted treatment difference −2.5 [95% confidence interval [CI], −4.6, −0.4], $P = 0.0197$); all key secondary endpoints; sleep and QoL parameters. Adverse events were typical for dopamine agonists; disease augmentation, although not directly assessed, was not reported during treatment. Ropinirole improves symptoms, associated sleep disturbance, and QoL of RLS patients and is generally well tolerated. © 2004 Movement Disorder Society

Key words: RLS; ropinirole; sleep; quality of life

Restless legs syndrome (RLS) is a neurological condition that is estimated to affect up to 10% of the general population, with varying degrees of severity.[1–3] It is characterized by sensory and motor symptoms that adversely affect sleep, as they lead to motor restlessness, delay or disruption of sleep onset, and multiple awakenings during the night.[4] Diagnosis is based on the presence of four cardinal features, first published in 1995[5] and recently updated in 2003.[6] With the updated criteria, motor restlessness has been clarified, and the importance of the urge to move emphasized. The key criteria comprise a desire to move the extremities, usually the legs, which is often associated with paresthesias deep within the legs, rather than superficially. Patients move to relieve those symptoms. Leg discomfort is worse or exclusively present at rest and is relieved, at least temporarily, by activity. Finally, symptoms show a circadian rhythm, as the movements are worse in the late evening, and less severe or absent during the day. In addition to these diagnostic symptoms of RLS, up to 80% of RLS patients may experience periodic limb movements during sleep (PLMs).[7] Some of these produce arousal (PLMA), either to waking or to a lighter stage of sleep, and PLMs may

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also occur when patients are awake. The symptoms of RLS, including the associated sleep disturbance (e.g., ability to fall asleep and to stay asleep), may have a large negative impact on patients' daytime functioning and quality of life (QoL).[8,9]

RLS may occur at any age. Patients whose symptoms occur earlier than 45 years of age more often have a family history of the disease, compared to those whose symptoms appear at a later age.[10] In addition, the idiopathic condition typically occurs at an earlier age than secondary RLS. Symptoms of RLS may fluctuate, and some patients experience symptom-free periods. However, with time, particularly in patients with an older age of onset, symptoms often progress: they may occur earlier in the day and become more intense at night.[10] Patients often seek treatment in middle or old age when symptoms become more pronounced.[11] Diagnosis is made on clinical grounds; physical examination is normal in the idiopathic form. Other conditions that can lead to secondary RLS symptoms include pregnancy, renal failure, iron deficiency, and neuropathy. The major differential diagnoses include medication-induced akathisia, peripheral neuropathy, and nocturnal leg cramps.

The etiology of RLS is unclear. However, there is now a general consensus that the origin of the disorder is in the central nervous system. There is evidence for the involvement of dopaminergic systems in this disorder, as RLS can be aggravated by dopamine antagonists[12,13] and relieved by dopamine agonists (see below). In addition, two positron-emission-tomography studies found small reductions in dopaminergic function, as measured by [^{18}F]fluorodopa uptake in the putamen (and caudate in one study).[14,15] A recent postmortem study of patients with RLS has also demonstrated markers of impaired iron transport into dopaminergic cells.[16] This local iron insufficiency may interfere with dopaminergic function in patients with RLS.

Levodopa improved RLS in several clinical trials.[17–19] However, disease augmentation, manifested by an earlier onset and increased intensity of RLS symptoms, often complicates L-dopa therapy.[20] Of the dopamine agonists, pergolide was, until recently, the most extensively tested in RLS. It has demonstrated good efficacy in several small clinical trials.[21–23] However, ergot-derived dopamine agonists such as pergolide carry the potential risk of fibrotic complications and may be associated with valvular heart disease.[24] As the dopamine agonists ropinirole and pramipexole are not ergot-derived, they are not typically associated with the risk of structurally related fibrotic complications. Both drugs have shown efficacy in small clinical trials of RLS.[25–27] However, the clinical trial reported here is part of a program of studies of ropinirole, which provides the largest investigation of any treatment conducted to date in RLS. The program includes two multicenter, double-blind, randomized, 12-week, parallel-group, flexible-dose trials designed to compare the efficacy and safety of ropinirole with those of placebo in the treatment of RLS. The results of one of these trials are presented here. The sister study was published recently. Results from both trials demonstrate consistent and significant benefits in favor of ropinirole on the symptoms of RLS, its effects on patients' sleep parameters and their QoL.[28]

PATIENTS AND METHODS

Patients

Male or female patients between 18 and 79 years of age, attending 46 centers in Australia, Europe, and North America, were included. All patients had a diagnosis of primary RLS, using the International RLS Study Group (IRLSSG) criteria published in 1995,[5] and a score at baseline of at least 15 on the International Restless Legs Scale (IRLS).[29] Severity criteria also required at least 15 nights of RLS symptoms during the previous month. Patients were required to discontinue any current RLS medications, or those affecting sleep, for 5 half-lives or 7 nights, whichever was longer, before baseline. For patients who were receiving treatment for RLS before washout, the clinician judged whether or not the patient would have experienced at least 15 nights of symptoms if they had not been treated.

Exclusion Criteria

Although patients with daytime RLS symptoms were eligible, they were excluded if they suffered from symptoms that required treatment during the day. Patients were also excluded if they suffered from augmentation or end-of-dose rebound with previous medication. Those suffering from known causes of secondary RLS (renal failure, iron-deficiency, pregnancy, or clinical peripheral neuropathy), other sleep disorders (e.g., narcolepsy, sleep terror disorder, sleepwalking disorder, breathing-related sleep disorder), other movement disorders, or from any medical conditions that would affect the assessment of RLS (e.g., rheumatoid arthritis, fibromyalgia syndrome) were excluded. In addition, patients taking any other medications known to affect sleep or RLS, those with a known intolerance to ropinirole, or those abusing substances were excluded.

Ethical Considerations and Informed Consent

The study was reviewed and approved by the national, regional, or investigational-center ethics committees or

institutional review boards. Written and dated informed consent was obtained from each patient at screening.

Interventions

At baseline, patients were randomly assigned in a 1:1 ratio to receive ropinirole or placebo. Doses were taken 1 to 3 hours before bedtime. The initial dose of ropinirole or matched placebo was 0.25 mg/day. The dose could be titrated after 2 days to 0.5 mg/day. From week 1 through week 7, the dose could be up-titrated by 0.5 mg/day in weekly increments up to 3 mg with a final increase from 3 to 4 mg/day. The flexible titration was guided by the results of the Clinical Global Impression (CGI) scale[30] and tolerability. No further drug titration was allowed after week 7. During the titration period, down-titration was allowed twice if patients experienced adverse events, provided the drug dose was at least 0.5 mg/day. A higher dose could be reinstated if the adverse event abated. Only two such dose reductions were allowed before week 8. From weeks 8 to 12, patients maintained a constant dose of ropinirole or placebo.

Randomization and Treatment Allocation

To maintain blinding, all study medication tablets and their packaging were identical in appearance. In addition, doses were referred to by their titration stage (levels 1–8). Each patient was registered and randomly assigned to one of the treatment arms by a centralized allocation system, the Registration And Medication Order System (RAMOS) provided by the study sponsor. To ensure balance in the number of patients assigned to each treatment group, the allocation schedule was generated in blocks. At patients' clinic visits, the investigator contacted RAMOS and was told the container number for the medication the patient was to receive.

Efficacy Assessments

The main efficacy measures were the IRLS and CGI Improvement (CGI-I) scale. The IRLS is a disease-specific 10-item scale (maximum severity score, 40) that reflects the frequency and intensity of sensorimotor features, associated sleep problems, and their impact on mood and activities of daily living.[29] The CGI-I is a seven-point scale ranging from 1 ("very much improved") to 7 ("very much worse").[30] A "response" on the CGI-I was defined as a report of very much improved (score of 1) or much improved (score of 2).

A primary inferential set of efficacy variables was prospectively defined for the study. The primary efficacy variable was the change from baseline in the IRLS score at week 12, using the last observation carried forward (LOCF). Analysis of the key secondary endpoints was conditional on the significance of the primary endpoint.

The three key secondary variables included in the primary inferential set were the percentage of patients showing a response, that is, very much improved (score of 1) or much improved (score of 2) on the CGI-I scale at week 12 LOCF; the change from baseline in the IRLS score at week 1, using observed cases (OC); and the percentage of patients with a score of 1 or 2 on the CGI-I scale at week 1 LOCF. Other secondary efficacy variables included the time to a response on the CGI-I scale; time to a response on the IRLS (a response was defined as a reduction of six points or more relative to the patient's score at baseline); mean change from baseline to week 12 LOCF in domains of the Medical Outcomes Study (MOS) sleep scale,[31] the RLS QoL questionnaire,[32] the MOS Short Form (SF)-36 Health Survey,[33] and the Work Productivity and Activity Impairment (WPAI) questionnaire.[34]

The MOS sleep scale is a comprehensive battery of questions that measures several aspects of sleep in patients that may have varying comorbidities, so it is appropriate for a medically diverse patient population. The RLSQoL questionnaire is a disease-specific instrument that assesses the impact of RLS on the daily life, emotional well-being, and social and work life of the sufferers. The SF-36 is a generic measure that assesses health concepts that represent basic human values relevant to everyone's functional status and well-being. The WPAI was developed to assess work and activity impairment in a range of different patient populations.

Clinic visits took place on day 2, weeks 1, 2, 3, 4, 5, 6, 7, 8, and 12, and at follow-up (1 week after the last dose of study medication, whether or not patients completed the study). At each visit, the investigator administered the IRLS and CGI scale. At baseline and for the weekly clinic visits, patients were asked to provide assessments for the IRLS based on the previous week; at day 2, week 1 and week 12, they were asked to provide an assessment of symptoms since their last study visit. The MOS sleep scale, RLSQoL questionnaire, and SF-36 were completed by the patient at baseline, at weeks 8 and 12, or at early withdrawal. The WPAI questionnaire was completed weekly by the patient.

Safety

Adverse events were assessed at each study visit by asking a nonleading question such as, "Have you felt different in any way since starting the new treatment/since the last visit?". Adverse events were categorized by intensity: a mild adverse event was easily tolerated by the patient, caused minimal discomfort, and did not in-

terfere with everyday activities; a moderate event was sufficiently discomforting to interfere with normal everyday activities; a severe event was one that prevented normal everyday activities. In addition, serious adverse events were those that were fatal, life-threatening, disabling or incapacitating, resulted in hospitalization of the patient, or were any other serious medical occurrence.

To assess any possible acute effects of treatment on patients' blood pressure or heart rate, at sites in the United States, vital signs were assessed before and immediately after ingestion of the study treatments, after the initial dose, and after each dose increase. On the days of these assessments, study medications were taken at 8:00 PM, between 2 and 4 hours before bedtime.

Statistics

A total of 116 patients were required in each treatment group to detect a difference of six points in the IRLS score between groups with 90% power. This value was based on a standard deviation of 14 and normally distributed errors with a two-sided significance level of 5%. Assuming an attrition rate of 20%, screening of 290 patients was planned. The primary analysis was conducted for the intention-to-treat population.

A hierarchical testing procedure was used to preserve the type-I error associated with the ordered group of endpoints in the primary inferential set (1 - the change from baseline in IRLS score at week 12 LOCF; 2 - the percentage of patients with a score of 1 or 2 on the CGI-I scale at week 12 LOCF; 3 - the change from baseline in the IRLS score at week 1 OC; 4 - the percentage of patients with a score of 1 or 2 on the CGI-I scale at week 1 LOCF). Following this procedure, ropinirole and placebo were compared for the primary endpoint. Provided the null hypothesis was rejected at the 5% level of statistical significance for that comparison, testing continued with the first key secondary endpoint in the primary inferential set. The hierarchical testing continued, provided the null hypothesis was rejected for each comparison. This testing procedure allowed inferences to be made on all of the endpoints in the primary inferential set, while preserving an overall type-I error rate of 0.05. There were no multiplicity adjustments made for the other secondary endpoints. The robustness of the LOCF analysis conducted for the IRLS was assessed by conducting an additional analysis for the week 12 OC data. The results supported those from the LOCF analysis.

Continuous variables, including the primary efficacy variable, were analyzed using parametric analyses of covariance, including terms for baseline score and treatment group, regardless of their significance. Binary variables were analyzed using logistic regression models, with treatment group as covariates. Survival variables were analyzed using Cox's regression models, with the covariates described above.

RESULTS

Patients

The study took place during 2002. A total of 267 patients were randomly assigned to receive treatment (131 to ropinirole and 136 to placebo, Fig. 1). The two treatment groups were well matched for demographic and disease characteristics (Table 1). All patients received at least one dose of study medication, although 1 patient in the placebo group had no post-dose efficacy assessments. The safety population, therefore, comprised 267 patients and the intention-to-treat population 266 patients. A similar number of patients taking ropinirole (102/131; 77.9%) and taking placebo (107/135; 79.3%) completed the study. Nine patients taking ropinirole (9/131, 6.9%) and 11 taking placebo (11/136, 8.1%) withdrew because of adverse events (see below for details).

Drug Treatments

Nearly half of the patients in each treatment group had received prior pharmacotherapy for RLS (ropinirole, 45.8%; placebo, 43.4%). The most frequently used therapies were antiparkinsonian drugs, analgesics, and benzodiazepines. Of the antiparkinsonian agents, L-dopa was the most commonly used: 19 patients (14.5%) in the ropinirole group and 19 patients (14.0%) in the placebo group. Additionally, 10 patients (7.6%) in the ropinirole group and 13 patients (9.6%) in the placebo group had taken dopamine agonists. Of the analgesics, acetaminophen was the most commonly used: 8 patients (6.1%) in the ropinirole group and 7 patients (5.1%) in the placebo group; narcotic drugs had been taken by 6 patients (4.6%) in the ropinirole group and 8 (5.9%) in the placebo group. Clonazepam was the most commonly used benzodiazepine: 7 patients (5.3%) in the ropinirole group and 13 patients (9.6%) in the placebo group. A total of 13 patients (9.9%) in the ropinirole group and 7 (5.1%) in the placebo group had been taking other benzodiazepines. At week 12, the median dose of ropinirole was 1.5 mg/day (LOCF) and the median dose of placebo was equivalent to 3.0 mg/day.

Primary Inferential Set of Efficacy Endpoints

The mean (SE) adjusted change in IRLS score between baseline and week 12 was significantly greater for ropinirole than placebo: −11.2 (0.76) vs. −8.7 (0.75), respectively. The adjusted treatment difference was −2.5 (95% CI, −4.6, −0.4), $P = 0.0197$ (F-statistic for the

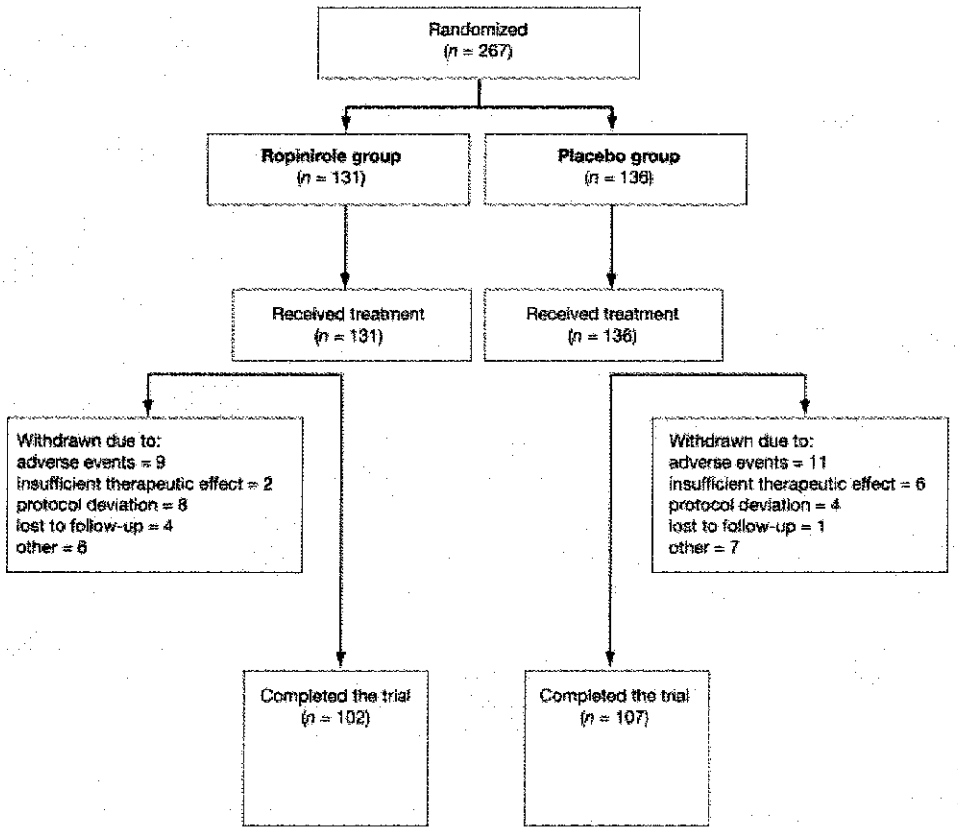

FIG. 1. The flow of participants through the study. Of the 267 patients randomly assigned to receive treatment, 43 were from Australia, 56 were from each of Canada and Germany, 15 from Norway, 34 from the United Kingdom and 63 from the United States. The number of patients receiving placebo and the number of patients receiving ropinirole were approximately equal for each country.

treatment difference = 5.50; effect size = −0.29). The ropinirole group showed consistently lower IRLS scores than the placebo group over the duration of the study (Fig. 2).

As the primary endpoint was statistically significant, the second endpoint in the primary inferential set was analyzed. At week 12, more patients in the ropinirole group (78/131, 59.5%) responded (much or very much improved) on the CGI-I scale compared to those in the placebo group (53/134, 39.6%), adjusted odds ratio 2.3 (95% CI, 1.4, 3.8), $P = 0.001$. As this endpoint was statistically significant, the third endpoint in the primary

TABLE 1. *Demographic and disease characteristics of patients in the intention-to-treat population*

Parameter	Ropinirole (n = 131)	Placebo (n = 135)
Age (yr)	54.9 (10.87)	56.0 (11.25)
Age range (yr)	29–77	29–79
Gender, F/M (%)	76/55 (58/42)	83/52 (61.5/38.5)
Age at onset of RLS (yr)	34.6 (17.15)	34.5 (17.49)
Disease duration (yr)	20.3 (14.82)	21.5 (16.36)
First-degree relation with RLS/PLMS (n)	62 (47.3%)	53 (39.3%)
Time symptoms mainly present, n (%)		
Nighttime only	19 (14.5)	27 (20.0)
Evening and nighttime	93 (71.0)	95 (70.4)
Daytime, evening and nighttime	19 (14.5)	13 (9.6)
Baseline IRLS score	23.6 (5.9)	24.8 (5.4)

Values are expressed as mean (SD), unless otherwise noted. IRLS, International Restless Legs Scale; PLMS, periodic limb movements in sleep.

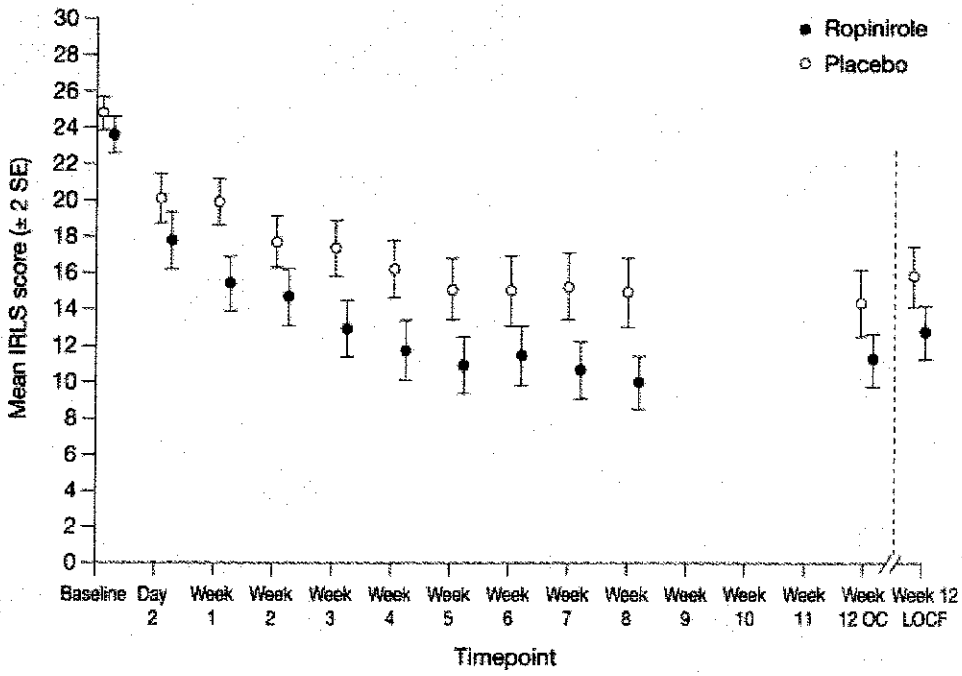

FIG. 2. Mean International Restless Legs Scale (IRLS) scores in the two treatment groups at each clinic visit during the study. (Data are for observed cases, except where stated.) IRLS, International Restless Legs Scale; LOCF, last observation carried forward; OC, observed cases.

inferential set was analyzed. The ropinirole group showed a greater change from baseline in the IRLS score at the end of week 1: mean (SE) was −8.4 (0.62), compared to −4.8 (0.62) in the placebo group; the adjusted treatment difference was −3.5 (95% CI, −5.3, −1.8), $P < 0.0001$. As this endpoint was statistically significant, the fourth endpoint in the primary inferential set was analyzed. At the end of week 1, more patients in the ropinirole group (48/131, 36.6%) than in the placebo group (22/134, 16.4%) were responders on the CGI-I scale; the adjusted odds ratio was 3.0 (95% CI, 1.7, 5.3), $P = 0.0003$. Thus, all the primary inferential set of endpoints showed a significant difference in favor of ropinirole.

Secondary Efficacy Endpoints

The median time to show a response on the CGI-I scale was 14 days for patients taking ropinirole and 22 days for those taking placebo. The hazard ratio was 1.66 (95% CI, 1.25, 2.20), $P = 0.0004$, a statistically significant difference in favor of ropinirole. The median time to a reduction of six points or more on the IRLS was 7 days in each treatment group. The hazard ratio for this comparison was 1.29 (95% CI, 0.99, 1.67), $P = 0.0588$, which did not quite reach statistical significance.

Patients in the ropinirole group showed improvements in all four domains of the MOS sleep scale at week 12 (Fig. 3). For somnolence, the adjusted treatment difference was −6.3; 95% CI, −10.5, −2.0; $P = 0.0043$. For sleep disturbance, the adjusted treatment difference was −13.4; 95% CI, −18.8, −8.1; $P < 0.0001$. For sleep adequacy, the adjusted treatment difference was 13.6; 95% CI, 7.2, 20.0; $P < 0.0001$. For sleep quantity, the adjusted treatment difference was 1.3 (hours), 95% CI, 0.3, 2.2; $P = 0.0097$. Likewise, at week 12, the overall life-impact score on the RLSQoL questionnaire (maximum score, 100) showed a significant difference in favor of ropinirole (17.4 [SE 1.42]) over placebo (12.9 [SE 1.40]). The adjusted treatment difference was 4.4 (95% CI, 0.5, 8.4), $P = 0.0263$. Three of the eight domains of the SF-36 Health Survey (score range, 0–100 points) showed a significant treatment difference in favor of ropinirole. For the mental-health domain, the change between baseline and week 12 was 6.9 (SE 1.28) for ropinirole and 1.7 (SE 1.26) for placebo; the adjusted treatment difference was 5.2 (95% CI, 1.7, 8.7), $P = 0.0041$. Corresponding values were for social functioning, 9.3 (SE 1.9) vs. 3.6 (SE 1.87); adjusted treatment difference 5.7 (95% CI, 0.5, 10.9), $P = 0.0331$, and for vitality, 12.5 (SE 1.58) vs. 6.3 (SE 1.56); adjusted treatment difference 6.3 (95% CI, 1.9, 10.6), $P = 0.0049$. Changes on the remaining domains were all also numerically in favor of ropinirole but did not achieve statistical

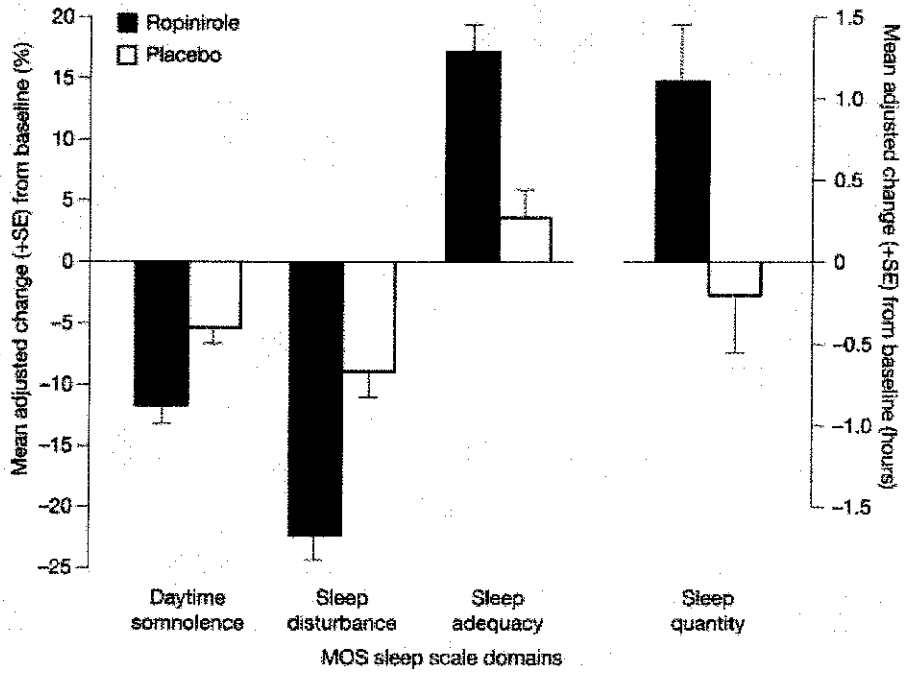

FIG. 3. Adjusted change from baseline in domains of the Medical Outcomes Study Sleep Scale at week 12, last observation carried forward. Positive changes in sleep quantity and sleep adequacy indicate a beneficial effect, whereas negative changes in sleep disturbance and somnolence indicate benefits. For somnolence, sleep disturbance, and sleep adequacy, the score range is 0 to 100; for sleep quantity, the score range is 0 to 24 hours ($P = 0.0097$).

significance. WPAI questionnaire scores were not significantly different between the two treatment groups.

Adverse Events

A total of 112 patients in the ropinirole group (112/131, 85.5%) and 102 patients in the placebo group (102/136, 75.0%) reported at least one adverse event during treatment. The most common adverse events, reported by at least 10% of patients in either group, are shown in Table 2. All of these events, except headache, occurred in a higher proportion of patients receiving ropinirole than those taking placebo.

Most of the adverse events were mild or moderate in severity; overall 32 patients (24.4%) in the ropinirole group and 24 patients (17.6%) in the placebo group experienced at least one adverse event that was categorized as severe. The only severe adverse events reported in more than 2% of patients were nausea (8 patients taking ropinirole, none taking placebo); headache (5 patients in each group); injury (ropinirole, 3 patients; placebo, 2 patients), dyspepsia (ropinirole, 3 patients; placebo, 1 patient), and insomnia (ropinirole, 2 patients; placebo, 4 patients). Adverse events led to the discontinuation of less than 10% of patients in each treatment group. The only events leading to the withdrawal of more than 1 patient were headache (3 patients in the ropinirole group, and no patients in the placebo group) and insomnia (no patients in the ropinirole group, 3 patients in the placebo group).

TABLE 2. *Common adverse events, experienced by at least 10% of patients in either treatment group during the trial (safety population)*

Event	Ropinirole (n = 131)	Placebo (n = 136)
Any adverse event	112 (85.5)	102 (75.0)
Nausea	52 (39.7)	11 (8.1)
Headache	29 (22.1)	35 (25.7)
Fatigue	20 (15.3)	9 (6.6)
Dizziness	20 (15.3)	6 (4.4)
Upper respiratory tract infection	18 (13.7)	11 (8.1)
Vomiting	16 (12.2)	3 (2.2)

Values are expressed as n (%).

A total of 2 patients in the ropinirole group and 5 in the placebo group reported a serious adverse event. Those in the ropinirole group were angina pectoris and a hospitalization after an unrelated injury. Neither of these was considered to be related to the study medication, and treatment was not stopped due to these events. In the placebo group, serious adverse events were atrioventricular block, angina pectoris, hypertension, and two reports of hospitalization following unrelated injuries. Again, none was considered to be related to study medication; treatment was stopped in 3 of the 5 patients (i.e., patients with atrioventricular block, hypertension, or hospitalization after unrelated injury). No deaths were reported during the study. Although augmentation was not sys-

tematically measured or directly assessed in this trial, there were no reports of augmentation during treatment in the study.

DISCUSSION

The results of this study, one of the largest placebo-controlled trials of a treatment for RLS conducted to date, demonstrate that ropinirole effectively treats the symptoms of moderate-to-severe RLS, as assessed by improvements in the IRLS and CGI-I scale. These improvements were seen as early as week 1 and continued through week 12, indicating that ropinirole produced rapid and sustained relief of symptoms. Ropinirole was generally well tolerated and withdrawal rates because of adverse events were comparable to those in the placebo group.

RLS may severely impact sleep[35–37] and impair QoL[38] to a similar degree to other chronic diseases (depression, arthritis, hypertension, and congestive heart failure).[8] Ropinirole significantly benefits subjective sleep, as demonstrated by improvements on all four domains of the patient-reported MOS sleep scale (sleep disturbance, sleep quality, sleep adequacy, and daytime somnolence). Thus, patients taking ropinirole slept more soundly (with less disturbance), for a longer time, perceived their sleep adequacy was improved and were less sleepy during the daytime than those taking placebo. As RLS is a major cause of chronic sleep problems, and such problems are one of the most distressing aspects of RLS to patients, these positive effects of ropinirole on sleep should prove beneficial in the management of this disorder. There were also improvements in patients' QoL, assessed using the disease-specific RLSQoL questionnaire and on subscales of the MOS SF-36 Health Survey. Changes in favor of ropinirole on the mental-health, social-functioning and vitality domains of the SF-36 Health Survey indicated that patients taking ropinirole experienced improvements in their mental well-being, in sociability, and had more energy and less tiredness than those taking placebo.

These results support those already published from the sister study comparing ropinirole with placebo.[28] Trenkwalder and colleagues demonstrated that ropinirole produced significant improvements in patients' IRLS and CGI-I scale scores after both 1 and 12 weeks. Moreover, ropinirole was associated with significant improvements in all four domains of the MOS sleep scale and in the RLSQoL questionnaire score. Results from these two trials are highly consistent. Together, these results indicate that ropinirole produces robust effects on subjective symptoms, sleep disturbances, and QoL in patients with RLS.

In addition, ropinirole was generally well tolerated by patients. Most adverse events were mild or moderate in severity, and less than 10% of patients in each group withdrew because of adverse events. There were also few serious adverse events, and none of these events were considered to be related to study medication. The adverse events were generally consistent with the class of dopamine agonists but were less severe than those experienced when using these drugs to treat Parkinson's disease. In particular, no patients receiving ropinirole experienced dyskinesias or hallucinations. This result is comparable to those from previous studies of dopaminergic drugs in RLS[21,26,27] and may be due to the lower doses of drugs used in RLS compared to Parkinson's disease or to the different disease pathologies. In addition, although not directly assessed, there were no reports of disease augmentation during treatment in this 12-week trial. This effect of therapy was first reported for L-dopa[20] and has been noted in trials of longer duration with dopamine agonists.[22,39] Longer studies of ropinirole will be needed to assess the prevalence of augmentation with this drug treatment in RLS.

A large placebo effect lessened the treatment difference in this study. Similar placebo responses are also common in patients being treated for conditions such as pain and depression who are assessed using subjective measures.[40] In this trial, the "dose" of placebo that patients were taking was greater than that of ropinirole, indicating that the dose had been increased in an attempt to produce better symptom relief. The results of this trial, therefore, underline the need to conduct parallel-group, placebo-controlled trials to ascertain the efficacy of new therapies in this indication.

An intrinsic weakness of any study of RLS is the subjective nature of the disease. The IRLS has been validated,[29] but its sensitivity to linear treatment effects remains unknown. Nevertheless, in the current study, improvements in other measures of efficacy corroborated those shown on the IRLS. Studies of ropinirole using both objective polysomnography measures and the IRLS are ongoing.

Comparison of scores with the baseline score may be confounded by the fact that patients who were taking other treatments before this trial were also undergoing treatment withdrawal during this baseline assessment period. (Patients underwent a 7-day washout period, and their baseline IRLS score was based on their assessment of symptoms in the previous 7 days.) However, any patients who experienced end-of-dose rebound at baseline were excluded, and the patients who had previously used other therapies to treat RLS were equally distributed in the ropinirole and placebo groups.

The single-dosing schedule, limited to 1–3 hours before bedtime, that was used in this trial may have lessened the relative treatment effects of ropinirole, particularly in more severely affected patients with symptom onset before dosing. These patients might have benefited from individualized earlier dosing, or multiple doses of the drug (e.g., one dose in the early evening and one at bedtime, based on the patient's pattern of symptom onset). This hypothesis could be evaluated in future trials.

Despite these potential limitations, the results presented indicate that ropinirole is an effective and generally well tolerated therapy for RLS, which is associated with no serious side-effects. These data, therefore, support the first-line use of ropinirole for patients with RLS.

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