

# Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries

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*J Neurol Neurosurg Psychiatry* 2004;75:92-97

**Objective:** To assess the efficacy, safety, and tolerability of ropinirole in the treatment of patients with restless legs syndrome.

**Methods:** A 12 week, prospective, double blind, randomised comparison involving 284 patients from 10 European countries. All participants had a score of  $\geq 15$  on the international restless legs scale (IRLS). Patients were randomised (1:1) to receive either ropinirole 0.25-4.0 mg once daily or placebo. The primary efficacy end point was mean change from baseline to week 12 in total IRLS score. Global improvements (clinical global impression (CGI) scale) and improvements in sleep, health related quality of life (QoL; using generic and disease specific measures), work, and other activities were also assessed.

**Results:** 112/146 patients (76.7%) taking ropinirole and 109/138 (79.0%) taking placebo completed the study. Improvement in IRLS at week 12 with ropinirole (mean (SD) dose, 1.90 (1.13) mg/day) was greater than with placebo (mean (SE):  $-11.04$  (0.719) v  $-8.03$  (0.738) points; adjusted difference =  $-3.01$  (95% confidence interval (CI),  $-5.03$  to  $-0.99$ );  $p=0.0036$ ). More patients in the ropinirole group (53.4%) showed improvement on the CGI scale at week 12 than in the placebo group (40.9%; adjusted odds ratio = 1.7 (1.02 to 2.69);  $p=0.0416$ ). Significant differences on both IRLS and CGI scales favouring ropinirole were apparent by week 1. Ropinirole was also associated with significantly greater improvements in sleep and QoL end points. The most common adverse events were nausea and headache.

**Conclusions:** Ropinirole improves restless legs syndrome compared with placebo, with benefits apparent by week 1. It is generally well tolerated.

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Restless legs syndrome is a distressing sensorimotor disorder characterised by an urge to move the legs, and accompanied by sensations deep in the limbs that are variously described as twitching, pulling, and sometimes painful. These symptoms present at rest, particularly in the evening and at night, and are alleviated by movement. Sufferers commonly report considerable difficulty in getting to sleep and staying asleep as a result of these sensations. Additional distress, however, is often caused by periodic leg movements, the primary motor symptoms of restless legs syndrome. Periodic leg movements are described as rhythmic extensions of the big toe and foot, sometimes with flexions of the knee or hip. These can also cause sufferers to waken during the night and have difficulty returning to sleep. The profound sleep disturbance resulting from restless legs syndrome symptoms may contribute to the impaired cognitive functioning and quality of life (QoL) reported in these patients compared with population norms.<sup>1,2</sup>

Current estimates suggest that 5-10% of the adult population suffer from restless legs syndrome.<sup>3-5</sup> However, it seems that a smaller proportion, essentially those with moderate to severe symptoms, seeks medical treatment. As the condition is not commonly recognised or is misdiagnosed, patients receive either no treatment or drugs to alleviate the secondary symptoms, particularly those relating to sleep.

Where the disorder is correctly diagnosed, benzodiazepines and other sedative drugs have often been used in the past, but these have now been largely superseded by dopaminergic agents as the treatment of choice. The latter are very effective in restless legs syndrome, which suggests a central role for the dopaminergic system in the pathophysiology of the disorder.

Among the dopaminergic agents, the efficacy of L-dopa (with a peripheral decarboxylase inhibitor) has been established<sup>6,7</sup> but it is associated with a high incidence of long term side effects involving increased symptom severity (that is, augmentation).<sup>8</sup> Preliminary data suggest that the dopamine agonists offer an important alternative in this regard, as augmentation rates are reported to be substantially lower.<sup>9-11</sup> To date, the most rigorous assessment of dopamine agonists has been with pergolide. However, while this particular agent alleviates symptoms,<sup>12,13</sup> there are important safety and tolerability concerns associated with ergot derived dopamine agonists generally, even at the low doses employed for the treatment of restless legs syndrome.<sup>14</sup> Small or open label studies with two non-ergoline agonists, ropinirole and

**Abbreviations:** CGI, clinical global impression; CGI-I, clinical global impression-global improvement scale; IRLS, international restless legs scale; IRLSSG, International Restless Legs Syndrome Study Group; ITT, intention to treat; MOS, medical outcomes study; QoL, quality of life; RLS, restless legs syndrome; SF-36, 36 item short form health survey; WPAI, work productivity and activity impairment

\* A full list of the members of the TREAT RLS 1 Study Group is given in the appendix.

pramipexole, have yielded promising results<sup>15–18</sup> and large, double blind, controlled trials are now needed to confirm these preliminary findings.

The present study is the first large, international, randomised, double blind, placebo controlled trial to examine the efficacy, safety, tolerability, and patient reported outcomes of ropinirole in the treatment of restless legs syndrome. Additional work, focusing specifically on periodic leg movements, will be reported separately.

## METHODS

### Participants

Men and women aged 18 to 79 years and diagnosed as having restless legs syndrome (using the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria<sup>19</sup>) were included in the study. Patients had a score of at least 15 on the international restless legs scale (IRLS)<sup>20</sup> and had either experienced at least 15 nights with symptoms of restless legs syndrome in the previous month or, if receiving treatment, reported they had had symptoms of this frequency before treatment.

Patients were excluded if they were suffering from other movement or primary sleep disorders, if they required treatment for restless legs syndrome during the daytime (defined as 10.00 to 18.00 hours), if they were experiencing augmentation or end of dose rebound, or if they had restless legs syndrome associated with end stage renal disease, iron deficiency anaemia, or pregnancy. Patients were also excluded if they had a history of alcohol or drug abuse, had previous intolerance to dopamine agonists, or were suffering from other clinically relevant conditions affecting assessments.

Patients gave written, informed consent before entering the study, which was done according to the principles of the 1996 amendment of the Declaration of Helsinki and approved by local ethics committees.

### Study design

This was a double blind, randomised, placebo controlled trial of 12 weeks' duration. It was conducted in 43 hospitals, sleep centres, and neurology clinics in 10 European countries (Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the United Kingdom).

Patients receiving treatment known to affect restless legs syndrome or sleep, or to cause drowsiness, entered a washout phase equal to either five half lives of the drug or seven consecutive nights, whichever was the greater. A small proportion of patients may have had a washout period shorter than seven days before the implementation of the protocol amendment.

Patients were randomly assigned in a 1:1 ratio to receive ropinirole or placebo for 12 weeks. To ensure balance in the number of patients assigned to each treatment group, the allocation schedule was generated in blocks using the sponsor's coding memo system. Investigators phoned into the randomisation and medication ordering system (RAMOS) to register and randomise each patient. Investigators, patients, and study monitors were blinded to the treatment status of the patients at all times. Investigators and the study sponsor held sealed envelopes containing patient code breaks (comprising the container number and the treatment allocation). In an emergency, an investigator could have scratched the disclosure panel with a coin to reveal details of a patient's treatment. All envelopes were returned unopened to the sponsor at the end of the study.

### Interventions

Ropinirole and matched placebo tablets were used to maintain study blinding. Patients received treatment once

daily between one and three hours before bedtime and started ropinirole treatment at 0.25 mg/day. The dose was then titrated upwards during weeks 1 to 7, through seven predetermined dose levels, until patients were receiving the maximum dose (4.0 mg/day) or they were judged to have reached their optimal dose. A maximum of two dose reductions because of adverse events (by one dose level in each case) was permitted during the titration period. The dose could be increased again if adverse events ameliorated. Dose changes were not permitted after week 7.

### Assessments and outcome measures

Patients visited the clinic at baseline, on day 2, weekly for the first two months, and then at week 12.

The primary end point was the mean change from baseline to week 12 in the IRLS total score. This scale was developed and validated by the IRLSSG<sup>20</sup> and comprises 10 questions about restless legs syndrome symptoms and their impact on daily activities and mood. All the responses are graded in the range 0 to 4 (0 = absence of a problem, 4 = very severe problem), giving a maximum score of 40 (table 1).

The clinical global impression–global improvement (CGI-I) scale was used to assess general improvements. Changes in the proportions of patients with scores of “much improved” or “very much improved” on this scale at weeks 1 and 12, and the mean change in the IRLS total score between baseline and week 1, were identified as the three key secondary end points.

Other secondary end points, concerning the impact of treatment on sleep (sleep adequacy, quantity, disturbance, and daytime somnolence), health related quality of life, work, and other activities, were measured using four patient reported questionnaires: the medical outcomes study (MOS) sleep scale, the MOS 36 item short form health survey (SF-36), the RLS QoL questionnaire, and the work productivity and activity impairment (WPAI) questionnaire.

Safety was assessed by collecting information on adverse events, vital signs, and laboratory parameters.

### Statistical analyses

The intention to treat (ITT) dataset was used for all efficacy analyses; this comprised all patients who received at least one dose of double blind drug treatment and had at least one valid post-baseline efficacy assessment. Safety and tolerability data were reported for all patients who received at least one dose of the study drug. For this study, the ITT and safety populations were identical. For all end points, when data were missing, the value from the previous visit was carried forwards (except for the IRLS total score at day 2, which represented an inadequate recall period from baseline and was not carried forward to estimate week 1 or week 12 results).

Continuous efficacy variables were assessed using analyses of covariance, dichotomous variables using logistic regression, and “time to event” data with Cox's regression model. Baseline score (with the exception of CGI-I), country group, and treatment were fitted as terms in the model. Statistical modelling assumptions were assessed and not found to be violated.

For the primary end point, a sample size of 116 patients per group was necessary to ensure 90% power to detect a difference of six points between groups with an SD of 14 ( $\alpha = 0.05$ , two tailed test).

## RESULTS

### Patient characteristics and flow through the study

The study was carried out between 8 November 2001 and 19 August 2002. In all, 286 patients were randomised and 284

**Table 1** The international restless legs scale for severity developed and validated by the International Restless Legs Syndrome Study Group<sup>20</sup>

- Overall, how would you rate the RLS discomfort in your legs or arms?
- Overall, how would you rate the need to move around because of your RLS symptoms?
- Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?
- Overall, how severe is your sleep disturbance from your RLS symptoms?
- How severe is your tiredness or sleepiness from your RLS symptoms?
- Overall, how severe is your RLS as a whole?
- How often do you get RLS symptoms?
- When you have RLS symptoms how severe are they on an average day?
- Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school, or work life?
- How severe is your mood disturbance from your RLS symptoms—for example, angry, depressed, sad, anxious, or irritable?

RLS, restless legs syndrome.

received treatment (146 ropinirole, 138 placebo; the ITT population). Similar numbers of patients completed the study in the two groups (fig 1). Patient characteristics at entry were also similar in the two groups (table 2).

**Treatment**

The mean (SD) daily dose of ropinirole at 12 weeks was 1.90 (1.13) mg. The corresponding placebo “dose” was 2.80 (1.25) mg.

**Efficacy results**

**Primary end point**

The mean (SD) IRLS total score at week 12 was lower in the ropinirole group (13.5 (9.3) points) than with the placebo group (17.1 (9.4) points). The adjusted mean (SE) improvement in the IRLS total score at week 12 was significantly greater for ropinirole (−11.04 (0.719) points) than for placebo (−8.03 (0.738) points; adjusted treatment difference = −3.01 (95% confidence interval (CI), −5.03 to −0.99)) (p = 0.0036).

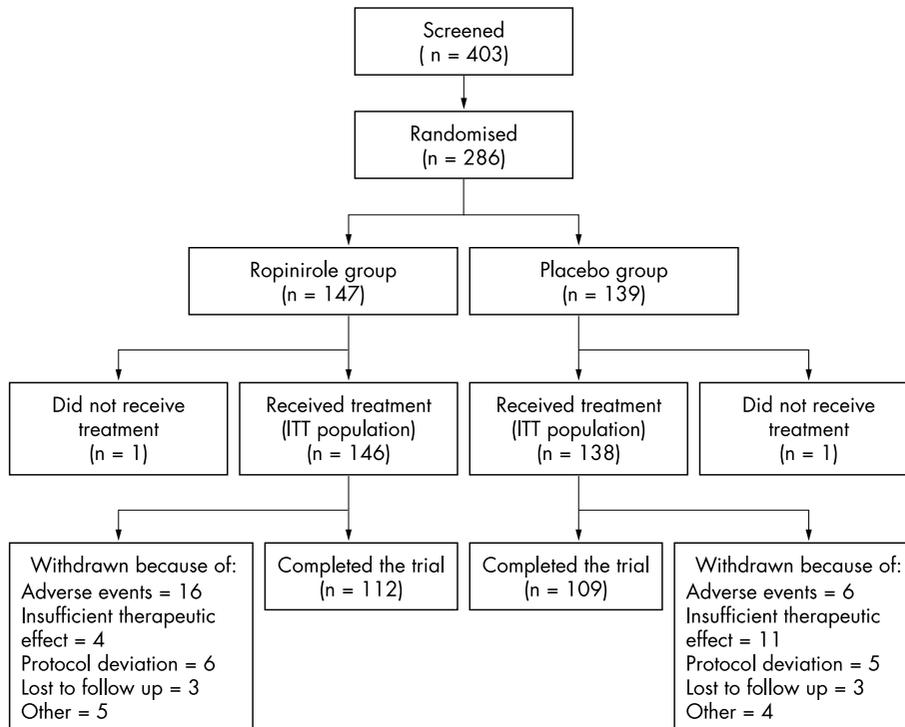
**Key secondary endpoints**

Significantly more patients in the ropinirole group (53.4%, 78/146) showed a “much improved” or “very much improved” score on the CGI-I scale at week 12 compared with the placebo group (40.9%, 56/137; adjusted odds ratio = 1.7 (1.02 to 2.69)) (p = 0.0416).

Treatment differences in favour of ropinirole were apparent by the first assessment—that is, at week 1. The mean (SE) reduction in the IRLS total score from baseline was significantly greater for ropinirole (−8.19 (0.59) points) than for placebo at week 1 (−5.14 (0.62) points; adjusted treatment difference = −3.05 (−4.72 to −1.38)) (p = 0.0004). Similarly, significantly more patients in the ropinirole group (34.2%; 50/146) had a score of “much improved” or “very much improved” on the CGI-I scale compared with the placebo group at week 1 (13.1%; 18/137; adjusted odds ratio = 3.7 (2.02 to 6.94)) (p < 0.0001).

**Other secondary end points**

There were significant differences in favour of ropinirole for the median time taken to show a decrease of at least six



**Figure 1** The flow of participants through the study.

**Table 2** Patient characteristics at entry to the study

Characteristic	Ropinirole (n = 146)	Placebo (n = 138)
Age (years)	54.0 (11.1)	56.2 (11.2)
Range (years)	30 to 78	28 to 77
Women (n (%))	88 (60.3)	91 (65.9)
Age at onset of symptoms (years)	37.6 (17.1)	38.9 (16.4)
Range (years)	5 to 73	4 to 72
Duration of symptoms (years)	16.4 (14.1)	17.3 (14.9)
Range (years)	<1 to 60	<1 to 61
Time of day when symptoms are mainly present (n (%)):		
Night-time only	22 (15.1)	18 (13.0)
Evening and night-time	109 (74.7)	108 (78.3)
Daytime, evening and night-time	15 (10.3)	12 (8.7)
IRLS total score at baseline	24.4 (5.75)	25.2 (5.63)
Range	14* to 40	15 to 40
CGI "severity of illness" score of $\geq 4$ † (n (%))	126 (86.3)	123 (89.1)

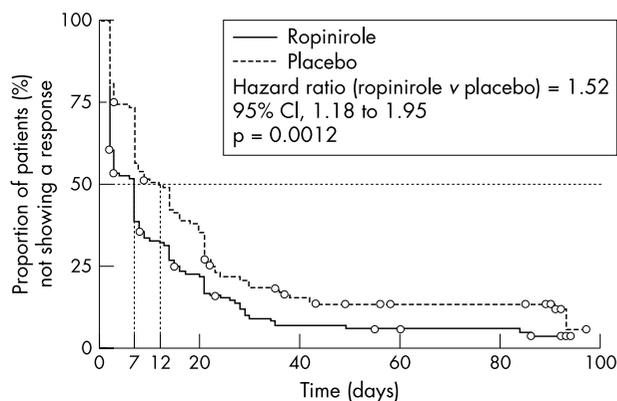
Values are mean (SD) unless stated otherwise.  
 \*One patient had a baseline IRLS total score of 14 despite an entry criterion of  $\geq 15$ .  
 †Patients with a score of  $\geq 4$  on the CGI "severity of illness" scale are considered to be moderately ill or worse.  
 CGI, clinical global impression; IRLS, international restless legs scale.

points on the IRLS total score and the median time taken to report a score of "much improved" or "very much improved" on the CGI-I scale (figs 2 and 3).

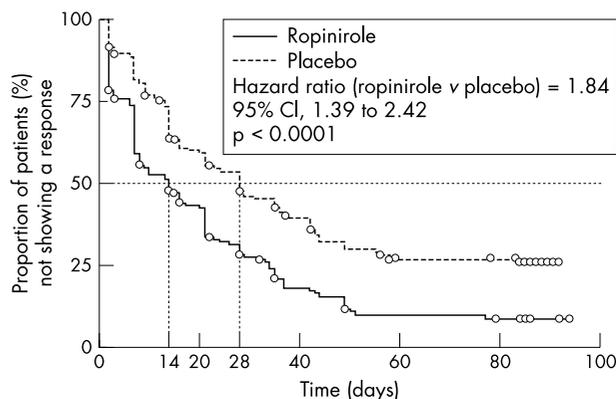
The ropinirole group experienced significantly greater mean improvements in sleep adequacy and quantity ( $p = 0.0015$  and  $p = 0.0331$ , respectively), and greater mean reductions in daytime somnolence and sleep disturbance ( $p = 0.0064$  and  $p = 0.0245$ ) compared with the placebo group (fig 4). Furthermore, ropinirole was also associated with a greater mean improvement in quality of life as assessed with the disease specific measure, the RLS QoL questionnaire (17.1 v 12.6, respectively) ( $p = 0.0314$ ). There were no differences between groups, however, in the changes on the generic measures, the SF-36 and the WPAI questionnaire.

**Safety results**

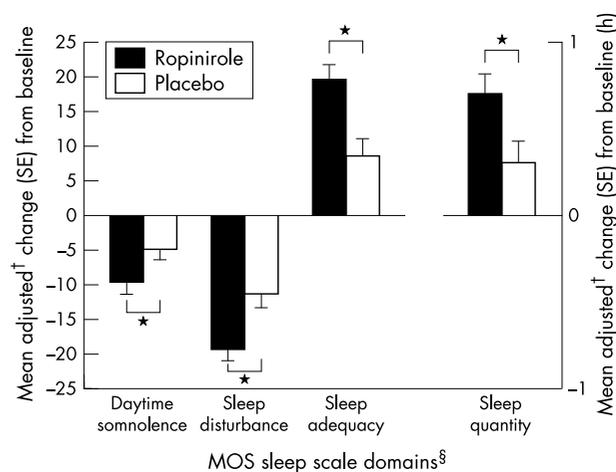
The most commonly reported adverse events were nausea and headache; nausea was more common with ropinirole than with placebo (table 3). Most events were mild to moderate in intensity (table 3). The frequency of adverse events declined over time in both groups: after day 70, only 9.6% (14 patients) in the ropinirole group and 5.8% (eight patients) in the placebo group reported new adverse events. There were no reports of augmentation.



**Figure 2** Kaplan-Meier plot of median time to show a decrease of at least six points on the international restless legs scale.



**Figure 3** Kaplan-Meier plot of median time to report a score of "much improved" or "very much improved" on the clinical global impression global improvement scale.



**Figure 4** Mean adjusted changes (SE) from baseline in medical outcomes study sleep scale domains. \* $p < 0.05$ ; 95% CI: daytime somnolence, -9.36 to -0.65; sleep disturbance, -13.29 to -2.20; sleep adequacy, 4.19 to 17.58; sleep quantity, 0.03 to 0.73. †Adjusted for country and baseline scores. §Scale 0-100, except for sleep quantity; decreases in daytime somnolence and sleep disturbance, and increases in sleep adequacy and quantity represent improvements. MOS, medical outcomes study.

Few patients withdrew because of adverse events (16 with ropinirole v 6 with placebo). Nausea led to most withdrawals in the ropinirole group (6, v 0 with placebo), and restless legs symptoms in the placebo group (3, v 0 with ropinirole). Serious adverse events were also unusual (3 with ropinirole v 4 with placebo) and none led to withdrawal or was judged to be related to the study drug (menstrual disorder; injury; gastrointestinal disorder; urinary tract infection; fever, syncope and pharyngitis; fever; abdominal pain).

**DISCUSSION**

Ropinirole, at single doses of up to 4.0 mg/day, was significantly more effective than placebo in alleviating symptoms of restless legs syndrome, improving sleep quantity and adequacy, reducing sleep disturbance and daytime somnolence, and improving health related quality of life. Importantly, the superiority of ropinirole was apparent as early as week 1. Furthermore, ropinirole was generally well tolerated and there were no reports of augmentation or sudden onset of sleep.

**Table 3** Adverse events reported by at least 10% of patients in either group

Symptom	Ropinirole (n = 146)	Placebo (n = 138)
Nausea	55 (37.7)	9 (6.5)
Headache	29 (19.9)	23 (16.7)
Vomiting	19 (13.0)	2 (1.4)
Abdominal pain	18 (12.3)	12 (8.7)
Somnolence*	18 (12.3)	10 (7.2)
Upper respiratory tract infection	14 (9.6)	15 (10.9)
Patients reporting at least one adverse event	120 (82.2)	103 (74.6)
Patients reporting at least one severe adverse event†	34 (23.3)	21 (15.2)

Values are n (%).

\*Despite reports of somnolence as an adverse event, the overall level of daytime somnolence measured by the medical outcomes study sleep scale showed significant improvement related to ropinirole treatment over the duration of the trial.

†Severe adverse events were defined as those that prevented normal everyday activities. Only nausea occurred in more than five patients in either group (ropinirole 7; placebo 0).

This is the largest controlled trial in restless legs syndrome conducted to date and it employs a validated scale,<sup>20</sup> the IRLS, to determine the impact of treatment on the severity of the condition. As there has been limited experience with the IRLS as a tool for monitoring treatment response, the CGI-I was also employed, and these data confirm the clinical relevance of the IRLS results. Furthermore, in the key area of sleep disruption, which is troublesome to a very large proportion of patients with restless legs syndrome, ropinirole was significantly superior to placebo on all of the variables tested. The reduction in daytime somnolence has particular importance as it indicates that ropinirole is not acting as a sedative. This is further supported by the fact that similar proportions of patients in each group reported somnolence (not necessarily daytime somnolence) as an adverse event (12% of patients in the ropinirole arm and 7% in the placebo arm).

The positive results in this trial are consistent with the efficacy findings from small short term studies in which ropinirole doses of up to 6.0 mg/day were associated with significant improvements in symptoms<sup>15-17</sup> and benefits were apparent within one day.<sup>18-21</sup> An early onset of action is clearly an important factor influencing the choice of treatment.

The adverse event profile of ropinirole in the present study is typical of those associated with dopaminergic treatment generally. The rates of withdrawal because of nausea and vomiting were, however, rather low (5%).

Ropinirole was effective despite the presence of a placebo effect that was larger than expected. Such effects are common in trials in other disease areas in which subjective tools are used to assess efficacy (for example, migraine and depression). Furthermore, restless legs syndrome is generally poorly recognised,<sup>22</sup> and the receipt of a long awaited diagnosis, coupled with individual attention from physicians, may have enhanced the patients' expectations of treatment. In support of this, patients receiving placebo experienced a greater number of dose increments, with 45% reaching the maximum "dose" compared with 16% in the ropinirole group.

Ropinirole is an effective and well tolerated treatment for restless legs syndrome. Follow up studies are required, however, to confirm that efficacy and the lack of augmentation are maintained in the longer term and to explore whether improved sleep among patients treated with ropinirole will be associated with improved cognitive functioning. Data from additional work examining the

efficacy of ropinirole on periodic leg movements and further sleep measures are expected soon.

## ACKNOWLEDGEMENT

The study was supported by GlaxoSmithKline Research and Development.

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Competing interests: PT has received sponsorship from GSK and other pharmaceutical companies marketing dopamine agonists to attend international meetings, and has been an investigator in clinical trials of dopamine agonists in Parkinson's disease. CT has received honoraria for educational lectures and consultancy fees from GSK, Eli Lilly, and Boehringer Ingelheim. No other authors have any disclosures to make.

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## REFERENCES

- Allen R, Kirsch J, Abetz L, et al. The impact of restless legs syndrome (RLS) on sleep and cognitive functioning [abstract]. *Eur J Neurol* 2002;9(suppl 2):50.
- Kirsch J, Abetz L, Allen R, et al. The impact of restless legs syndrome (RLS) on quality of life (QoL) [abstract]. *Eur J Neurol* 2002;9(suppl 2):201.
- Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. *Arch Intern Med* 2000;160:2137-41.
- Rothdach AJ, Trenkwalder C, Haberkost J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. *Neurology* 2000;54:1064-8.
- Ulfberg J, Nystrom B, Carter N, et al. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord* 2001;16:1159-63.
- Brodeur C, Montplaisir J, Godbout R, et al. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. *Neurology* 1988;38:1845-8.
- Trenkwalder C, Stiasny K, Pollmächer T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep* 1995;18:681-8.
- Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep* 1996;19:205-13.
- Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology* 1998;51:1599-602.
- Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. *Sleep Med* 2002;3:S23-5.

- 11 **Staedt J**, Hunerjager H, Ruther E, *et al*. Pergolide: treatment of choice in restless legs syndrome and nocturnal myoclonus syndrome. Long-term follow-up on pergolide. *J Neural Transm* 1998;**105**:265–8.
- 12 **Wetter TC**, Stiasny K, Winkelmann J, *et al*. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 1999;**52**:944–50.
- 13 **Stiasny K**, Wetter TC, Winkelmann J, *et al*. Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 2001;**56**:1399–402.
- 14 **Danoff SK**, Grasso ME, Terry PB, *et al*. Pleuropulmonary disease due to pergolide use for restless legs syndrome. *Chest* 2001;**120**:313–16.
- 15 **Freeman A**, Rye DB, Bliwise D, *et al*. Ropinirole for restless legs syndrome (RLS): an open-label and double-blind placebo-controlled study [abstract]. *Neurology* 2001;**56**(suppl 3):A5.
- 16 **Montplaisir J**, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol* 2000;**7**(suppl 1):27–31.
- 17 **Ondo W**. Ropinirole for restless legs syndrome. *Mov Disord* 1999;**14**:138–40.
- 18 **Saletu M**, Anderer P, Saletu B, *et al*. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals and respiratory variables. *Neuropsychobiology* 2000;**41**:190–9.
- 19 **Walters AS**, The International Restless Legs Syndrome Study Group. Toward a better definition of the restless legs syndrome. *Mov Disord* 1995;**10**:634–42.
- 20 **The International Restless Legs Syndrome Study Group**. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003;**4**:121–32.
- 21 **Saletu B**, Gruber G, Saletu M, *et al*. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. *Neuropsychobiology* 2000;**41**:181–9.
- 22 **Allen R**, Hening W, Montplaisir J, *et al*. Restless legs syndrome (RLS) is a common disorder rarely diagnosed in Europe or USA: the REST (RLS epidemiology, symptoms and treatment) study in primary care. *Mov Disord* 2002;**17**(suppl 5):S240–1.



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