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Controlled Withdrawal of Pramipexole After 6 Months of Open-Label Treatment in Patients With Restless Legs Syndrome

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Abstract: Although dopamine agonists are becoming first-line therapy for restless legs syndrome (RLS), few reports describe treatment periods exceeding 12 weeks. Here, 150 RLS patients who had responded to pramipexole during a 6-month run-in period (mean dose, 0.50 mg) were randomly assigned to receive placebo or continue receiving pramipexole at an individually optimized dose of 0.125 to 0.75 mg/day for a further 3 months. Patients switched to placebo reached the primary endpoint (a predefined worsening on both the Clinical Global Impressions-Global Improvement scale and the International RLS Study Group Rating Scale) significantly more often than patients who continued to receive pramipexole (85.5% vs. 20.5%; $P < 0.0001$). They also reached the primary endpoint faster, in 5 versus 42 days to a Kaplan–Meier survival estimate of 0.85 and 7 versus > 84 days to an estimate of 0.5. Over the total 9 months, clinician and patient ratings of symptoms, sleep, and quality of life identified no decline in pramipexole's benefit or tolerability. The great majority of adverse events (AEs) were mild or moderate, and of expected types. Augmentation was considered an AE, but in this population of responders it did not occur. © 2006 Movement Disorder Society

Key words: restless legs syndrome (RLS); pramipexole; therapy; nonergot dopamine agonists; sleep

In treating restless legs syndrome (RLS), the long-term outcome of pharmacologic intervention remains an important and difficult issue. Dopamine (DA) agonists have been reported to offer amelioration of symptoms, with less risk of augmentation than levodopa has shown,[1,2] and are now considered first-line therapy for patients with frequent RLS symptoms,[3,4] yet few large studies describe treatment periods exceeding 12 weeks,[5–7] and the most extensive longitudinal data pertain to an ergot derivative, pergolide.[8]

Pramipexole is a nonergoline DA agonist with good selectivity for the D_3 subtype of the DA receptor family.[9] In the United States and Europe, the drug has been approved for treating signs and symptoms of idiopathic Parkinson's disease (PD). In preliminary studies[10,11] and in a 10-week placebo-controlled crossover study[12] with a mean 7.8 months of open-label follow-up,[13] pramipexole has also been found to address the symptoms of RLS. The present study was designed to evaluate its sustained efficacy against RLS during 3 months of placebo-controlled, double-blind treatment of patients who had responded to a 6-month open-label trial. Hence, the results represent a 9-month treatment period. The results explore pramipexole's effects on symptom severity and improvement, withdrawal phenomena, subjective sleep parameters, and quality of life, and also the agent's safety and tolerability.

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PATIENTS AND METHODS

Study Design

The trial was a Phase 3 randomized, double-blind, parallel-group, placebo-controlled, multicenter pramipexole withdrawal study of 3 months' duration. During a preceding 6-month period (Period 1), open-label pramipexole was up-titrated to individually optimized dosage (0.125, 0.25, 0.50, or 0.75 mg once daily). All patients were instructed to take their medication 2 to 3 hours before anticipated bedtime. At the end of this run-in phase, patients with a Clinical Global Impressions-Global Improvement (CGI-I) rating of "very much improved" or "much improved" and an International RLS Study Group Rating Scale (IRLS) total score ≤ 15 were randomly assigned to receive 3 months of either placebo or the optimized dosage of pramipexole (Period 2).

Randomization and Treatment Allocation

In all, 150 patients were randomly assigned to active treatment or placebo, in a 1:1 ratio. On completing Period 1, each patient received a treatment number in ascending numerical order and was randomized.

Inclusion Criteria

For Period 1, patients 18 to 80 years of age were recruited from 13 sites in Germany. All patients met diagnostic criteria for idiopathic RLS,[14,15] with symptoms at least 2 to 3 days per week for the previous 3 months, and at baseline (the start of Period 1) had an IRLS score > 15. (Among patients who later entered Period 2, the mean was 28.4.) To enter Period 2, they were required to have responded to pramipexole (see above), with $\geq 80\%$ compliance and no dose adjustments during the final 12 weeks of Period 1. The study was approved by ethics committees of the participating centers, and all patients gave written, informed consent in accordance with the Declaration of Helsinki (1996 version).

Exclusion Criteria

Patients were excluded for use of L-dopa (the preceding week) or other drugs known to influence RLS (the preceding 2 weeks); for medical conditions that might affect assessment of RLS; for any specific sleep disorder; for failure of prior pramipexole treatment; and (among fertile females) for pregnancy or inadequate contraception.

Sample Size Determination

The proportion of patients experiencing the Period 2 target event (see below) within 3 months was predicted to be 70% to 75% for placebo and 40% for pramipexole. By log-rank test for a survival difference $\geq 30\%$ between 2 groups followed for a fixed time with constant hazard ratio (nQuery Advisor, release 4.0), 120 patients would be required, or 180 to offset a predicted 20% to 30% ineligibility for Period 2.

Outcome Measures

For Period 2, the primary outcome was the time to a target event representing insufficient response, as defined by concurrence of two independently rated parameters: a CGI-I score[16] of "minimally," "much," or "very much" worse (compared with the score at the start of Period 2), and an increase of the IRLS[17] to a score > 15.

Secondary outcome measures were the CGI-I rating; other CGI subscales; the Patient Global Impression scale (PGI)[16]; the Johns Hopkins Restless Legs Syndrome Quality of Life questionnaire (RLS-QOL)[18]; the 10-cm visual analogue scales (VAS) for RLS severity while getting to sleep, during the night, and during the day, and for satisfaction with sleep the previous week (modified RLS-6 scale[19]); and the Epworth Sleepiness Scale (ESS) of daytime somnolence.[20]

For Period 2, the safety-analysis population comprised all patients who received at least 1 dose of trial drug during Period 2 ($n = 150$), and the final-analysis (efficacy) population consisted of all such patients who yielded data for the final visit of Period 1, underwent at least 1 postrandomization assessment of CGI-I/IRLS, and took at least 2 doses of randomized study medication on consecutive days ($n = 147$). Visits were scheduled for the end of weeks 1, 2, 6, and 12.

Statistical Analyses

For the primary outcome measure, differences in time to event were presented as Kaplan–Meier estimates, and were tested using the log-rank test. Among secondary outcome measures, discontinuous variables were analyzed by χ^2 or Mantel–Haenszel tests and continuous variables by analysis of covariance (ANCOVA for change from baseline) or parametric methods. For missing data, "last observation carried forward" (LOCF) methodology was implemented.

RESULTS

Patient Disposition

Among 183 Period 1 completers (Fig. 1), 82% entered Period 2. Completion of Period 2 was much greater in the pramipexole group, at 91% (71 of 78), than in the pla-

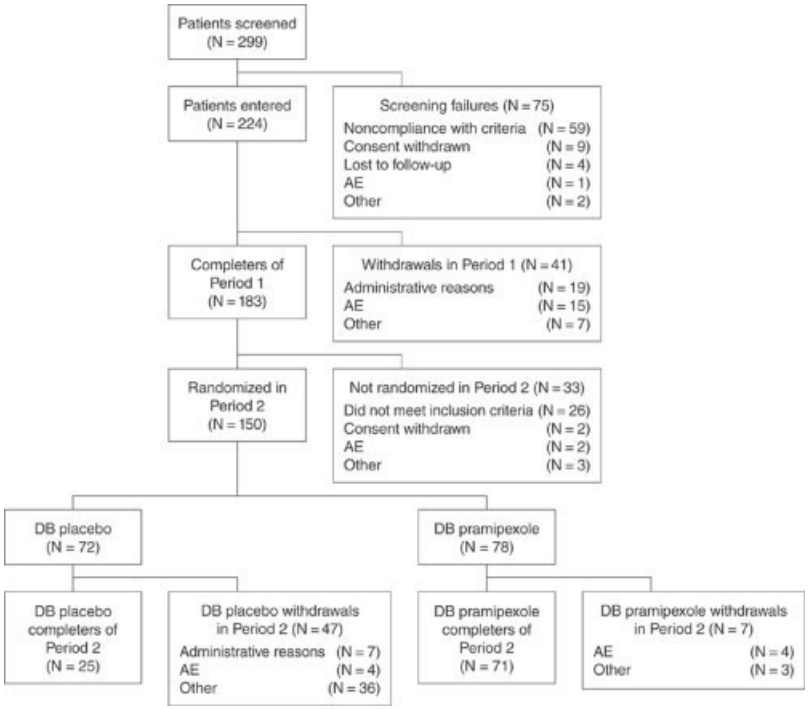

FIG. 1. Disposition of patients. AE, adverse event; DB, double-blind.

cebo group, at 35% (25 of 72). Baseline characteristics of the final-analysis population are shown in Table 1.

Efficacy: Primary Endpoint

By Kaplan–Meier analysis (Fig. 2) and log-rank test, the time to a survival estimate of 0.85 was 5 days for placebo, and the time to an estimate of 0.50 was 7 days. For pramipexole, the corresponding times were 42 days and $>$ 84 days ($P < 0.0001$). Because less than 50% of pramipexole recipients reached the target event, the exact duration of the latter interval could not be calculated.

Efficacy: Secondary Endpoints

Number of Target Events

In the placebo group, 85.5% of patients reached the target event, compared with 20.5% of patients in the pramipexole group ($P < 0.0001$).

TABLE 1. *Baseline characteristics of the Period 2 final-analysis population*

	Placebo	Pramipexole	Total
Patients, n	69	78	147
Caucasian, %	100	100	100
Female, %	72.5	73.1	72.8
Age, yrs, mean (SD)	58.9 (10.7)	60.2 (10.0)	59.6 (10.3)
RLS duration, yrs, mean (SD)	6.14 (10.11)	5.03 (8.40)	5.55 (9.23)
IRLS score, mean (SD)[a]	29.1 (5.2)	27.8 (5.9)	28.4 (5.6)
Previous RLS treatment, %	60.9	56.4	58.5
CGI-Severity, %[a]			
Not at all ill	0.0	0.0	0.0
Borderline ill	1.4	0.0	0.7
Mildly ill	4.3	10.3	7.5
Moderately ill	18.8	16.7	17.7
Markedly ill	34.8	41.0	38.1
Severely ill	34.8	26.9	30.6
Most extremely ill	5.8	5.1	5.4

[a]Before inception of pramipexole therapy in Period 1.

RLS, restless legs syndrome; IRLS, International RLS Study Group Rating Scale; CGI, Clinical Global Impressions scale.

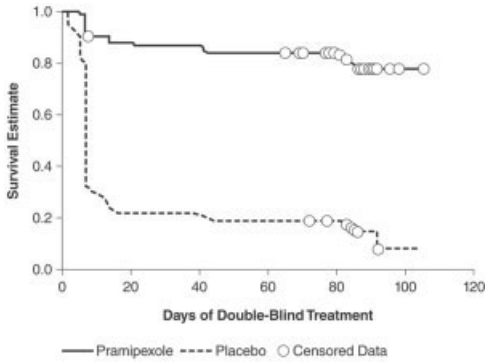

FIG. 2. Kaplan–Meier analysis of time to target event.

IRLS

At the end of Period 2, the mean IRLS total score (± SD) was 24.6 ± 11.1 in the placebo group, compared with 11.0 ± 9.1 in the pramipexole group. The adjusted mean change from baseline (start of Period 2) was +14.9 for placebo and +2.0 for pramipexole ($P < 0.0001$). The groups' divergence was evident after 1 week of treatment.

CGI-I

At the end of Period 2, 75.4% of placebo recipients had a CGI-I rating of "worse" (see Table 2). Another 17.4% had not changed, and 7.2% had improved. By contrast, 16.7% of pramipexole recipients had worsened, 60.3% had not changed, and 23.1% had improved ($P < 0.0001$). Worsening on CGI-I was evident in the placebo group after 1 week.

CGI-Severity of Illness

At the beginning of Period 2, a time point when all patients had been using pramipexole, almost all were no worse than "mildly ill." By the end of Period 2 (Table 2), 62.5% of placebo recipients but only 12.8% of continuing pramipexole users ($P < 0.0001$) had worsened by more than 1 severity category.

CGI-Therapeutic Effect

At the beginning of Period 2, almost all patients exhibited a "marked" or "moderate" therapeutic effect. By the end of Period 2 (Table 2), the proportion was 85.9% for pramipexole and 27.5% for placebo ($P < 0.0001$).

CGI-Side Effects

At the beginning of Period 2, all but 1 patient reported either no side effects or none that interfered significantly with their life. At the end of Period 2 (Table 2), no patient reported significant side effects.

TABLE 2. *CGI and PGI ratings at the end of Period 2*

	Placebo	Pramipexole	*P* value*
CGI-Global Improvement, n (%)			< 0.0001
Improved[a]	5 (7.2)	18 (23.1)	
Unchanged	12 (17.4)	47 (60.3)	
Worse[b]	52 (75.4)	13 (16.7)	
CGI-Severity of illness, n (%)			< 0.0001
Improved[c]	1 (1.4)	3 (3.8)	
Essentially unchanged[d]	25 (36.2)	65 (83.3)	
Worse[c]	43 (62.3)	10 (12.8)	
CGI-Therapeutic effect, n (%)			< 0.0001
Sufficiently improved[e]	19 (27.5)	67 (85.9)	
Insufficiently improved[f]	50 (72.5)	11 (14.1)	
CGI-Side effects, n (%)			
None, no significant interference	69 (100)	78 (100)	
Significant interference	0 (0)	0 (0)	
PGI, n (%)			< 0.0001
Improved[g]	4 (5.8)	15 (19.2)	
Essentially unchanged[h]	21 (30.4)	55 (70.5)	
Worse[i]	44 (63.8)	8 (10.3)	

*Mantel–Haenszel test.
[a]Combines "very much," "much," and "minimally" improved.
[b]Combines "minimally," "much," and "very much" worse.
[c]Change of > 1 severity category.
[d]Change of 0 or 1 severity category.
[e]Combines "marked" and "moderate" therapeutic effect.
[f]"Minimal" or no therapeutic effect.
[g]Combines "very much" and "much" better.
[h]Combines "a little better," "no change," and "a little worse."
[i]Combines "much" and "very much" worse.
CGI, Clinical Global Impressions scale; PGI, Patient Global Impression scale.

PGI

At the end of Period 2 (Table 2), 70.5% of pramipexole recipients judged themselves essentially unchanged, and 10.3% judged themselves to be worse. In the placebo group, 30.4% were unchanged and 63.8% were worse ($P < 0.0001$).

RLS-QOL

Patients' responses to items 1 to 5, 7 to 10, and 13 were summed and inverted to yield a score of 0 to 100, with higher scores indicating better health status. At the start of Period 2, the median was 85 for placebo and 90 for pramipexole. At the end of Period 2, the pramipexole group was unchanged, whereas the placebo group showed a decrease, for a median final difference of 12.5 points ($P < 0.0001$).

Modified RLS-6

At the start of Period 2, the median scores on all scales were < 10 mm for the RLS-severity scales and < 15 mm for satisfaction with sleep, indicating low severity of RLS and high satisfaction with sleep. In the pramipexole group, these ratings remained virtually unchanged. By contrast, the placebo group exhibited a median 48-mm increase in RLS severity while getting to sleep ($P < 0.0001$), a median 47-mm increase in severity during the night ($P < 0.0001$), a median 9-mm increase in severity during the day ($P = 0.0056$), and a median 41-mm loss in satisfaction with sleep ($P < 0.0001$).

ESS

At the start of Period 2, the mean score was 6.44 in the placebo group and 5.31 in the pramipexole group. No significant changes ensued ($P = 0.3464$, ANCOVA for treatment-group difference).

Safety

Overall, 32.0% of patients experienced adverse events (AEs) during Period 2 and the 48 hours after final intake of study drug. The incidence was lower for placebo (23.6%) than for pramipexole (39.7%). But because a high proportion of placebo recipients left Period 2 prematurely, and such departures were especially numerous early in Period 2, placebo recipients had a median 13 days of participation, compared with a median 84 days for pramipexole recipients.

Five types of AEs had overall frequencies ≥ 2%: worsening RLS (5.5% for placebo vs. 6.4% for pramipexole), nasopharyngitis (1.4% vs. 3.8%), diarrhea (1.4% vs. 3.8%), vomiting (2.8% vs. 2.6%), and upper abdominal pain (0% vs. 3.8%). Among pramipexole recipients, AEs showed no dose dependency and no associations with clinically relevant changes on laboratory parameters, vital signs, physical examination, or electrocardiogram.

Overall, the great majority of AEs were mild or moderate in intensity. Only 5 patients (3.3%) had AEs classified as severe: 3 in the placebo group (all worsening of RLS) and 2 in the pramipexole group (1 forearm fracture and 1 worsening of RLS). Two patients experienced a serious AE (defined as fatal, life-threatening, or significantly disabling): a 0.50-mg pramipexole recipient was hospitalized for coronary artery disease during Period 2, and a 0.50-mg recipient experienced positional vertigo more than 2 months after withdrawing from Period 2 (due to worsened RLS). Other significant AEs (defined as leading to discontinuation or reduction of study drug) occurred in the pramipexole and placebo groups with similar frequency—and overall in 8 patients (5.3%). Queried explicitly about sudden onset of sleep (SOOS), patients reported no such episodes. Among pramipexole recipients, the frequency of AEs was substantially lower in Period 2 (39.7%) than in Period 1 (75.0%).

Among 71 pramipexole recipients and another 25 patients who completed the study on placebo, none was classified as presenting with augmentation at the end of the trial, as rated by experienced investigators. The Augmentation Severity Rating Scale[15] was used, but because this tool is an experimental instrument still being validated,[21] a final method to calculate its results has not yet been determined.

DISCUSSION

The present study documents a sustained capacity of pramipexole, at evening doses of 0.125 to 0.75 mg, to address RLS symptoms, as rated by both patients (IRLS) and clinicians (CGI-I), with corresponding improvements in sleep and quality of life (QOL). Additionally, the results prove that pramipexole is safe and well tolerated up to 9 months.

The results also show the dramatic effect of a withdrawal design. Patients switched to placebo reached the study's primary endpoint (representing insufficient therapeutic response) faster and more often than patients who continued to receive pramipexole, as shown by a time of only 5 days (vs. 42 days) to reach a survival estimate of 0.85. The survival difference was significant after only 2 days. In a trial of once-a-day bedtime L-dopa (averaging 159 mg), full efficacy was likewise attained in the first few days and disappeared soon after the treatment was discontinued.[22] The rapid efficacy of a variety of dopaminergic therapies suggests a shared mode of action.

In randomized, placebo-controlled trials, L-dopa,[23–25] pergolide,[26] rotigotine,[27] cabergoline,[7] ropinirole,[28–30] and pramipexole[12] have all shown substantial benefit.

Sleep-related symptoms are illustrative. In the present study, tools including a modified RLS-6 VAS linked pramipexole to significant improvement in sleep quality. Perhaps at least partly in consequence, patients who continued to be treated with pramipexole reported a significantly better QOL than those treated with placebo, as measured with an RLS-specific instrument.[18] The findings resemble those of a recent 47-week open-label extension of a double-blind dose-finding trial of cabergoline,[7] in which nighttime RLS severity, as reported on a VAS, was the primary endpoint, and severity at bedtime and during the day were among the secondary measures. The findings also resemble those of a recent 12-week, double-blind, randomized, placebo-controlled trial of ropinirole,[28] in which the Medical Outcomes Study (MOS) sleep scale identified significant improvements in subjective sleep quality.

In the present trial, spanning 9 months, pramipexole was safe and well tolerated, with AEs of expected types, and generally of mild to moderate intensity. A risk of all dopaminergic RLS treatment appears to be augmentation: characteristically an onset of symptoms progressively earlier in the day, but sometimes an expansion of symptoms from the legs to the arms or trunk, or even the entire body.[31] So far, augmentation appears to be markedly less frequent for DA agonists than for L-dopa, reportedly affecting roughly 20% to 30% of patients receiving an agonist,[1] contrasted with observations of up to 60% to 80% of patients receiving L-dopa.[31] In one report, a retrospective analysis of 59 patients treated with pramipexole for a mean of 21.2 months, augmentation occurred in 32%.[32] The augmentation was statistically predicted by prior augmentation or tolerance involving L-dopa. However, all available data have been retrospective, impeding identification of augmentation risk factors in, for example, a patient's baseline comorbidities or laboratory findings. Additionally, the trials' dose regimens have not included controls and have not followed predefined rules, as in controlled trials. For these reasons, the reported augmentation data are not commensurable with those from prospective trials.

The present prospective trial found no cases of augmentation. It should be noted that all patients randomized for double-blind treatment were pramipexole responders, none of whom exhibited augmentation during the trial's initial, dose-finding phase. Conceivably, augmentation and lack of efficacy may be closely related. It should also be noted that persons accustomed to using pramipexole may sense a shift to placebo, perhaps creating a bias toward withdrawal from a randomized trial. Nevertheless, the 9-month results show no decline in either the efficacy or safety of pramipexole for RLS. It may be concluded, therefore, that patients who respond well to pramipexole within the first weeks are good candidates for a long-term response.

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