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Efficacy of Pramipexole in Restless Legs Syndrome: A Six-Week, Multicenter, Randomized, Double-Blind Study (Effect-RLS Study)

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Abstract: We evaluated the efficacy of pramipexole versus placebo in restless legs syndrome (RLS) for 6 weeks. Overall, 345 patients were randomly assigned in a 1:2 ratio to receive either placebo (n = 115) or pramipexole (n = 230) with a starting dose of 0.125 mg/day. The dose was individually optimized according to the Patient Global Impression (PGI) assessment, up to a maximum of 0.75 mg/day. The primary endpoint consisted of two assessments: the change from baseline in the International RLS Study Group Rating Scale (IRLS) and the proportion of patients with Clinical Global Impressions-Improvement (CGI-I) assessments of "much/very much improved" (CGI-I responders) at week 6. Secondary endpoints included PGI and IRLS responder rates. Patient demographics and baseline characteristics were comparable between treatment groups. At baseline, mean IRLS scores were 24.9 (placebo) and 24.7 (pramipexole), representing severely affected patients. After 6 weeks, adjusted mean reductions (±SE) in IRLS score were 5.7 (±0.9) for placebo (median dose 0.47 mg/day) and 12.3 (±0.6) for pramipexole (median dose 0.35 mg/day; $P < 0.0001$). CGI-I responder rates were 32.5% (placebo) and 62.9% (pramipexole) ($P < 0.0001$). For all secondary endpoints, pramipexole showed superior results. Pramipexole was well tolerated throughout the study. © 2006 Movement Disorder Society

Key words: pramipexole; restless legs syndrome; clinical trial; dopamine agonist

Restless legs syndrome (RLS) is characterized by an urge to move the limbs and is usually associated with unpleasant sensations, such as paresthesias. The symptoms occur at rest and typically worsen in the evening and during the night. In more severe forms of RLS, patients experience symptoms every day and frequently suffer from sleep disturbances and impaired quality of life.[1,2] RLS is relatively common, with a prevalence ranging from 2.5% to 10% in the general population.[3,4] The pathophysiology of this disease is not yet fully understood; however, based on medication efficiency, dopaminergic pathways are thought to be involved.

Pramipexole, a nonergoline dopamine agonist, has been shown to be successful in the treatment of RLS in a small double-blind study.[5] Doses of 0.375 to 1.5 mg/day led to a significant reduction of 84% in subjective leg restlessness and of 97.7% in nocturnal periodic limb movements (PLM) after 4 weeks of treatment. Long-term efficacy of pramipexole treatment was demonstrated for up to 27.2 months of treatment.[6] The current study is the largest double-blind, placebo-controlled trial for the evaluation of pramipexole in the treatment of

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RLS to date. The study's aim was to show the efficacy and safety of pramipexole in the treatment of RLS.

PATIENTS AND METHODS

Patients

Male and female patients, 18 to 80 years of age, from 37 centers in 5 European countries (Austria, Germany, Norway, Sweden, and the Netherlands) were included in the study. All patients had a diagnosis of primary RLS, according to International RLS Study Group criteria,[1,2] and moderate to severe symptoms, as indicated by a baseline score on the International RLS Study Group Rating Scale (IRLS) of >15. Their RLS symptoms had to be present for at least 2 to 3 days per week in the 3 months before study entry. All pharmacologic treatment for RLS was discontinued within 14 days before the study's start. Patients were barred from study entry if they were pregnant or breastfeeding women; were not using adequate contraception; were diabetic; or had significant renal, hepatic, gastrointestinal, pulmonary, or endocrine disorders. Also, patients with any other neurologic disease were excluded. Patients with sleep disorders unrelated to RLS, psychotic disorders, or mental disorders were excluded. In addition, patients with a history of substance abuse and those working on a shift schedule were not allowed to participate.

Ethical Considerations and Informed Consent

The study protocol was reviewed and approved by the institutional review board/ethics committee of each participating center and by the relevant local, regional, or national regulatory authorities. Each patient was informed verbally and in writing about the study and provided written, dated, informed consent.

Randomization, Blinding, and Treatments

The study was performed with a double-blind design; at baseline, patients were randomly assigned in a 1:2 ratio to either placebo or pramipexole. Doses were taken once daily in the evening 2 to 3 hours before bedtime. The starting dose of pramipexole was 0.125 mg/day or matched placebo. During the first 4 weeks, the daily dose could be increased by the treating physician in weekly intervals to 0.25, 0.50, or 0.75 mg/day, according to the Patient Global Impression scale (PGI) rating and overall tolerability of the drug. In the case of adverse events (AEs), the dose could be reduced to the previous dose step. During weeks 5 and 6, the dose was kept constant.

Efficacy Assessments

The primary endpoint consisted of two assessments: the change from baseline in the IRLS score and the proportion of patients with Clinical Global Impressions-Improvement scale (CGI-I) assessments of "much improved" and "very much improved" at week 6. The IRLS is a 10-item, patient self-rating instrument that assesses the severity of RLS symptoms in 5 degrees, ranging from 4 ("very severe") to 0 ("none"); the maximum total score is 40.[7,8] The Clinical Global Impressions scale (CGI) is widely used for investigators' risk-benefit evaluation of drug treatment. For the primary endpoint, the subscale of global improvement (CGI-I) was used. The global improvement subscale assesses the patient's condition using 7 degrees, ranging from "very much improved" to "very much worse"; side effects of treatments are assessed by 4 degrees, ranging from "none" to "outweighs therapeutic effect."[9]

Several secondary efficacy parameters were also specified in the study protocol. These parameters included two responder criteria: namely, IRLS responders, defined as patients with an at least 50% reduction of their baseline IRLS score; and PGI responders, defined as the proportion of patients who assessed their condition at week 6 as either "much better" or "very much better" compared with baseline. In addition, the PGI responder rate at week 1 was calculated. Visual analogue scales (VASs) were used to measure the severity of RLS symptoms during the previous week on 3 occasions: (1) while getting to sleep, (2) in the course of the night, and (3) in the course of the day. Patients marked their condition on a continuous 10-cm line, with the left-most position, 0, representing "not present," and the right-most position, 100, indicating "severe." For their satisfaction with sleep, the left-most position, 0, represented "very satisfied," and the right-most position, 100, indicated "very dissatisfied."[10]

Including the screening visit, there were eight study visits during the 6-week treatment period (screening, baseline [day 0], weeks 1, 2, 3, 4, 5, and 6). Patients completed the IRLS at screening, baseline, and week 6; the CGI and VAS were completed at baseline and week 6; the PGI was completed weekly.

Safety

Safety was assessed by monitoring for adverse events (AEs), recording the patient's medical history including the use of concomitant medications, performing a physical examination, and conducting clinical laboratory tests and an electrocardiogram. AEs were assessed at each study visit and categorized by the investigator according to intensity and relationship to study drug. Serious adverse events (SAEs) were recorded and reported expediently to the regulatory authorities. At each visit, patients were specifically asked whether they had experienced any sleep attacks since the last visit.

Statistical Issues

To include patients with moderate to very severe RLS in the study, the IRLS score at baseline was chosen to be >15, and the standardized effect size (delta/common standard deviation) was expected to be 0.4, based on previous placebo-controlled studies.[11] With alpha = 0.05 (two-sided) and beta = 0.20, sample-size estimation for a 1:2 randomization required 85 patients for the placebo arm and 169 patients for the pramipexole arm. Thus in total 254 randomized patients were required. To account for early dropouts, at least 300 patients were to be screened. The primary endpoint and secondary endpoints were analyzed using the intent-to-treat (ITT) population (the full-analysis set) that consisted of all patients who had received at least 1 dose of study drug, had a baseline IRLS score, and a postbaseline assessment (N = 338).

To establish treatment superiority, both parts of the primary endpoint assessment had to be significantly improved in the pramipexole group versus placebo. Because the final IRLS score was assumed to correlate with the baseline score, an analysis of covariance model was selected for the change in IRLS from baseline with factors "treatment," "pooled center," and the covariates "age" and "baseline IRLS score." For the statistical analysis of the CGI-I assessments, the seven-item response was collated into two categories, namely, "much improved" and "very much improved" (two best categories; CGI responder) vs. "minimally improved" to "very much worse" (five remaining categories), and a Cochran–Mantel–Haenszel test with pooled center stratification was performed. Because both assessments had to show significance in favor of pramipexole to establish superiority, no alpha-adjustment was necessary, and the test of each hypothesis was performed at the 5% level. Similarly to the CGI-I, IRLS, PGI responders and the VAS were analyzed by the Cochran–Mantel–Haenszel test, with stratification by country. In some instances, nonparametric tests were performed.

The safety analysis was based on the safety population, which comprised all patients who received at least 1 dose of study medication (N = 345). AEs were coded centrally according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) V7.0 codes. The baseline value was the last value before initial study drug intake.

RESULTS

Patients

The study was conducted in 2004. A total of 345 patients were randomly (1:2) assigned to receive either placebo (n = 115) or pramipexole (n = 230). In the course of the study, 7.0% of placebo-treated and 5.2% of pramipexole-treated patients discontinued prematurely (Fig. 1). The most frequent reason for premature withdrawal was the occurrence of AEs in 4.3% (placebo) and 2.6% (pramipexole) of patients. The safety population comprised 345 patients; 7 patients did not have a postbaseline IRLS assessment; thus the ITT population consisted of 338 patients (placebo, 114; pramipexole, 224). Demographic and baseline characteristics of the treatment groups are listed in Table 1.

Drug Treatments

At baseline, approximately two thirds of the patients had never received any RLS medication (Table 1). Of the previously taken RLS medications, which were discontinued before study start, levodopa was the most frequent at 14.8% (placebo group) and 13.9% (pramipexole group). Few patients had previously received benzodiazepine (3.5% and 3.5%) or other dopamine agonists (2.6% and 1.3%) for the placebo and pramipexole groups, respectively.

The study was conducted using an individually optimized dose design. At week 6, 14.8% of the pramipexole-treated patients received 0.125 mg/day, 26.5% received 0.25 mg/day, 28.7% received 0.50 mg/day, and 30.0% received 0.75 mg/day. The median daily dose was 0.35 mg in the pramipexole group and 0.47 mg in the placebo group.

Primary Efficacy Variables

At baseline, the mean IRLS scores (±SD) was 24.9 (±5.4) in the placebo group and 24.7 (±5.2) in the pramipexole group. After 6 weeks of treatment, the IRLS

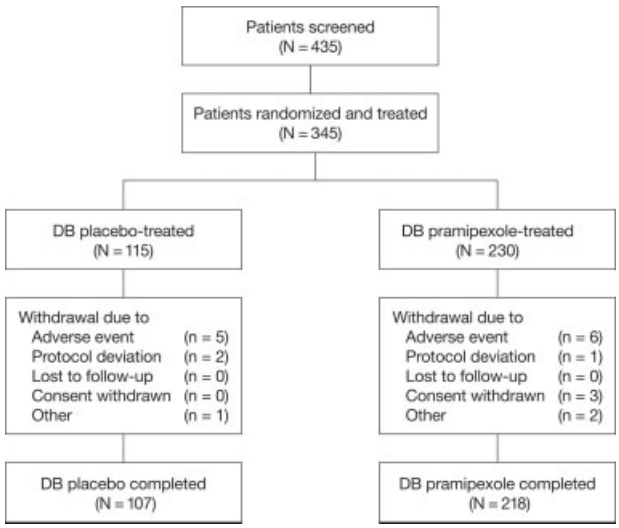

FIG. 1. Patient flow through the study. Of the 345 patients randomized, the breakdown by country of origin is as follows: 136 Sweden, 77 Germany, 71 the Netherlands, 36 Norway, and 25 Austria. DB, double-blind.

TABLE 1. *Demographic and baseline characteristics: ITT population*

	Placebo	Pramipexole
No. of patients (%)	114 (100.0)	224 (100.0)
Race, n (%)		
Caucasian	113 (99.1)	221 (98.7)
Asian	1 (0.9)	3 (1.3)
Sex, n (%)		
Male	36 (31.6)	80 (35.7)
Female	78 (68.4)	144 (64.3)
Age, yrs: mean (±SD)	55.8 (10.9)	55.4 (11.6)
RLS treatment status, n (%)		
Pretreated	36 (31.6)	68 (30.4)
De novo	78 (68.4)	156 (69.6)
Time since clinical diagnosis of RLS, yrs: mean (±SD)	5.63 (9.06)	4.95 (9.21)
IRLS score (maximum 40): mean (±SD)	24.9 (5.4)	24.7 (5.2)
CGI severity at baseline, n (%)		
Not at all ill	5 (4.4)	3 (1.3)
Borderline ill	4 (3.5)	12 (5.4)
Mildly ill	16 (14.0)	29 (12.9)
Moderately ill	33 (28.9)	65 (29.0)
Markedly ill	42 (36.8)	75 (33.5)
Severely ill	11 (9.6)	35 (15.6)
Most extremely ill	3 (2.6)	5 (2.2)

ITT, intent-to-treat; SD, standard deviation; RLS, restless legs syndrome; IRLS, International RLS Study Group Rating Scale; CGI, Clinical Global Impressions scale.

score was reduced by an adjusted mean (±SE) of 5.7 (±0.9) in the placebo group and 12.3 (±0.6) in the pramipexole group; the adjusted mean difference (±SE) in favor of pramipexole was −6.6 (±1.1), with a 95% confidence interval of −8.6 to −4.5 ($P < 0.0001$; Table 2). At week 6, in the analysis of the CGI-I, 32.5% of patients in the placebo group and 62.9% of those in the pramipexole group were assessed as either "much improved" or "very much improved" compared with baseline ($P < 0.0001$; Table 3).

TABLE 2. *IRLS score at baseline and after 6 weeks of treatment: ITT population*

	Placebo	Pramipexole
No. of patients (%)	114	224
Baseline, mean (±SD)	24.9 (5.4)	24.7 (5.2)
Week 6, mean (±SD)	18.8 (10.0)	12.3 (9.3)
Change from baseline		
Mean[a] (±SE)	−5.7 (0.9)	−12.3 (0.6)
Difference from placebo		
Mean[a] (±SE)	–	−6.6 (1.1)
95% CI	–	[−8.6, −4.5]
P value	–	< 0.0001

[a]Adjusted, ANCOVA with factors treatment and pooled center and covariates baseline and age.

IRLS, International RLS Study Group Rating Scale; ITT, intent-to-treat; SD, standard deviation; SE, standard error; CI, confidence interval; ANCOVA, analysis of covariance.

Secondary Endpoints

At week 6, 28.9% (placebo) and 52.2% (pramipexole) of patients had a reduction of their baseline IRLS score of ≥ 50% (IRLS responder, $P < 0.0001$; Table 4). The proportions of PGI responders were 31.6% (placebo) and 61.6% (pramipexole), $P < 0.0001$. After 1 week of treatment, the PGI responder rates were 7% (placebo) and 30.6% (pramipexole). Approximately 20% of patients were responders at the 0.125-mg dose of pramipexole, and more than 85% of patients were IRLS responders and CGI-I responders with doses of ≤ 0.50 mg/day (Fig. 2).

The VAS assessments at week 6 showed that symptom severity was slightly reduced with placebo treatment but substantially lowered with pramipexole (Table 5). Increase in daytime symptoms, referred to as "augmentation," was neither specifically assessed nor spontaneously reported by patients in either group.

Effects on Sleep

The effects of the treatment on sleep were evaluated using Item 4 ("Overall, how severe is your sleep disturbance due to your RLS symptoms?") and Item 5 ("How severe is your tiredness or sleepiness during the day due to your RLS symptoms?") of the IRLS, and Question 4 of the VAS: "How satisfied have you been with your sleep in the past week?" At baseline, the mean score (±SD) for sleep disturbance (IRLS Item 4) was 2.7 (±1.0) in both the placebo and pramipexole groups. At study end, mean changes (±SD) from baseline were −0.8 (±1.3) for placebo and −1.7 (±1.4) for pramipexole ($P < 0.0001$). For tiredness or sleepiness (IRLS Item 5), both treatment groups had the same mean score (±SD) at baseline with 1.9 (±1.1). At study end, the mean changes (±SD) from baseline were −0.5 (±1.2) for placebo and −1.1 (±1.3) for pramipexole ($P < 0.0001$). Using the VAS, patients in both treatment groups expressed a large dissatisfaction with sleep at baseline. This finding was indicated by mean (SD) VAS values of 60.4 (±27.5) in the placebo group and 63.0

TABLE 3. *CGI-I after 6 weeks of treatment: ITT population*

	Placebo N (%)	Pramipexole N (%)
No. of patients	114 (100.0)	224 (100.0)
"Much/very much improved"	37 (32.5)	141 (62.9)
All other CGI-I assessments from "minimally improved" to "very much worse"	77 (67.5)	83 (37.1)
P value	–	< 0.0001

CGI-I, Clinical Global Impressions-Improvement scale; ITT, intent-to-treat.

TABLE 4. *Responder analysis at week 6: ITT population*

	Placebo n (%)	Pramipexole n (%)
No. of patients	114 (100.0)	224 (100.0)
IRLS responder[a]	33 (28.9)	117 (52.2)
P value	–	< 0.0001
PGI responder[b]	36 (31.6)	138 (61.6)
P value	–	< 0.0001

[a]Patients were classified as IRLS responders if they had an at least 50% reduction in their baseline IRLS score at week 6.

[b]PGI responders were patients who assessed their condition at week 6 as "much better" or "very much better" compared with baseline.

ITT, intent-to-treat; IRLS, International RLS Study Group Rating Scale; PGI, Patient Global Impression scale.

(±28.1) in the pramipexole group. After 6 weeks of treatment, the mean values had decreased to 48.1 (±32.7) with placebo and 33.1 (±32.4) with pramipexole. The adjusted mean change from baseline (±SE) in the placebo group was −13.8 (±3.0) compared with −29.9 (±2.2) in the pramipexole group ($P < 0.0001$).

Safety

Overall, 47.8% of patients in the placebo group and 65.2% of those in the pramipexole group reported AEs while receiving treatment. The majority of AEs were of mild intensity in both treatment groups, affecting 32.2% in the placebo group and 51.7% in the pramipexole group. AEs with severe intensity were more frequent in the placebo group, reported by 7.8%, compared with 3.5% in the pramipexole group. Two patients in the placebo group reported SAEs (fall/radius fracture and transient ischemic attack) versus no patients in the pramipexole group. Of the more common AEs (overall frequency > 5%) seen in the placebo and pramipexole groups, respectively, headache (9.6% vs. 13.0%), nausea (6.1% vs. 12.2%), and fatigue (6.1% vs. 9.1%) were more frequent in the pramipexole group, whereas in the placebo group, nasopharyngitis (7.8% vs. 4.3%) and dizziness (5.2% vs. 3.5%) were more frequent.

AEs that were considered by the investigator to be related to the study drug were experienced by 21.7% of placebo-treated patients and 36.5% of pramipexole-treated patients. The most frequent drug-related AEs were nausea (5.2% vs. 9.6%), fatigue (4.3% vs. 9.1%), headache (6.1% vs. 7.0%), and dizziness (3.5% vs. 3.5%) in the placebo and pramipexole groups, respectively.

In total, 11 patients discontinued the study prematurely because of AEs: 5 patients (4.3%) in the placebo group and 6 patients (2.6%) in the pramipexole group. The only AE that led to the withdrawal of more than 1 patient was headache, which was reported in 2 placebo-treated patients. Blood pressure and heart rate did not change in either treatment group. Orthostatic hypotension was reported by 1 patient in the placebo group, and hypotension was reported by 1 patient in the pramipexole group; both events were of mild intensity. Somnolence was reported in 2.6% of patients in the placebo group and 2.6% of patients in the pramipexole group. No patients experienced sudden onset of sleep. Analysis of the CGI side effects subscale revealed that the vast majority of patients in both treatment groups (97.4% with placebo vs. 93.3% with pramipexole) were not impaired by side effects.

DISCUSSION

In this large multinational study, 345 patients with moderate to very severe RLS were included. The primary endpoint included both the IRLS, a validated, disease-specific scale for the evaluation of RLS,[1,2] and the CGI-I. Both assessments demonstrated significant improvement in RLS severity in pramipexole-treated patients compared with patients who had received placebo.

The treatment effect of pramipexole was substantiated by the analysis of responder rates. The proportion of patients with a ≥ 50% reduction of their baseline IRLS score was significantly higher in those treated with pramipexole than with placebo. Likewise, the proportion of patients who rated their condition on the PGI as "much better" and "very much better" at week 6 was significantly higher in the pramipexole group. The effect of pramipexole occurred rapidly and at the lowest dose. After 1 week of treatment, 30.6% of patients in the pramipexole group assessed their condition as "much/very much better" (PGI responders) compared with 7.0% in the placebo group. Because pramipexole was titrated in weekly intervals, all patients were receiving 0.125 mg/day at the end of week 1.

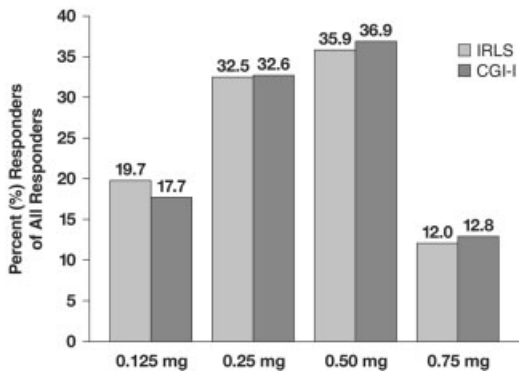

FIG. 2. Incremental efficacy of different pramipexole doses. Contribution of each dose group (at week 6) to overall responder rates for IRLS (44.4%) and CGI-I (52.7%) is depicted. More than 85% of patients were IRLS/CGI-I responders at doses of ≤ 0.50 mg/day. IRLS, International RLS Study Group Rating Scale; CGI-I, Clinical Global Impressions-Improvement scale.

TABLE 5. *Analysis of VASs for the severity of RLS symptoms after 6 weeks of double-blind treatment*

	Placebo		Pramipexole		
RLS Severity	Mean (±SD) at baseline	Adjusted mean change from baseline (±SE)[a]	Mean (±SD) at baseline	Adjusted mean change from baseline (±SE)[a]	*P* value
While getting to sleep	52.6 (30.9)	−13.8 (2.7)	56.8 (29.7)	−30.6 (1.9)	<0.0001
In the course of the night	60.7 (28.8)	−12.4 (2.7)	57.2 (29.7)	−32.3 (2.0)	<0.0001
In the course of the day	32.5 (26.9)	−1.5 (2.1)	32.1 (26.8)	−12.1 (1.5)	<0.0001

[a]Adjusted, ANCOVA with factors treatment and pooled center and covariates baseline and age.
VASs, Visual Analogue Scales; RLS, restless legs syndrome; SD, standard deviation; SE, standard error.

According to VAS assessments, pramipexole reduced the severity of RLS symptoms both during the night and during the day. The greatest reductions were observed while patients were going to sleep and during the night, the times when RLS symptoms were most distressing. This amelioration of RLS symptoms led to major improvements in sleep satisfaction and resulted in reduced daytime tiredness and sleepiness.

Our results confirm the findings of Montplaisir and colleagues, who conducted the first randomized, double-blind study with pramipexole in RLS.[5,6] The investigators used doses between 0.375 and 1.5 mg/day, while the current study demonstrated the efficacy of pramipexole in a dose range of 0.25 to 0.75 mg/day. With a median daily dose of 0.35 mg pramipexole, the IRLS score was reduced by 12.3 points, compared with 5.7 points in the placebo group. The greatest reduction of 16.1 points was seen in the 0.25-mg/day dose group, the second-lowest dose used in the study. Decreases in IRLS scores of a similar magnitude were found in the highest-dose groups of double-blind, placebo-controlled trials with other dopamine agonists, such as cabergoline (2.0 mg/day cabergoline: reduction of 15.7 points vs. 3.3 points placebo),[12] ropinirole (1.9 mg/day ropinirole: reduction of 11.0 points vs. 8.0 points placebo),[13] and rotigotine (4.5 mg/day rotigotine: reduction of 15.7 points vs. 8.0 points placebo).[14]

During the entire study period, pramipexole was well tolerated. The proportion of patients who discontinued because of AEs was higher with placebo than with pramipexole; no SAE was reported with pramipexole, and AEs were predominantly mild in nature. Nausea and fatigue were slightly more frequent with pramipexole than with placebo. The low incidence of AEs observed with pramipexole is most likely related to the low doses needed to achieve efficacy in patients with RLS, compared with the dose range used in the treatment of Parkinson's disease of up to 4.5 mg/day. The study design used an individually optimized titration, thus allowing an adequate evaluation of the effective dose range. All patients randomly assigned to pramipexole started with a dose of 0.125 mg, and, at the end of week 6, a considerable proportion of patients (26.5%) were still receiving this dose. The majority of patients (58.7%) had a daily dose of 0.25 mg or 0.50 mg at week 6, and approximately one third of patients (30.0%) achieved treatment satisfaction with 0.75 mg/day; thus the entire dose range was effective.

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