ORIGINAL ARTICLE

Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

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ABSTRACT

BACKGROUND

Dopaminergic medications relieve symptoms of the restless legs syndrome (RLS) but have the potential to cause iatrogenic worsening (augmentation) of RLS with long-term treatment. Pregabalin may be an effective alternative.

METHODS

In this 52-week, randomized, double-blind trial, we assessed efficacy and augmentation in patients with RLS who were treated with pregabalin as compared with placebo and pramipexole. Patients were randomly assigned to receive 52 weeks of treatment with pregabalin at a dose of 300 mg per day or pramipexole at a dose of 0.25 mg or 0.5 mg per day or 12 weeks of placebo followed by 40 weeks of randomly assigned active treatment. The primary analyses involved a comparison of pregabalin and placebo over a period of 12 weeks with use of the International RLS (IRLS) Study Group Rating Scale (on which the score ranges from 0 to 40, with a higher score indicating more severe symptoms), the Clinical Global Impression of Improvement scale (which was used to assess the proportion of patients with symptoms that were "very much improved" or "much improved"), and a comparison of rates of augmentation with pregabalin and pramipexole over a period of 40 or 52 weeks of treatment.

RESULTS

A total of 719 participants received daily treatment, 182 with 300 mg of pregabalin, 178 with 0.25 mg of pramipexole, 180 with 0.5 mg of pramipexole, and 179 with placebo. Over a period of 12 weeks, the improvement (reduction) in mean scores on the IRLS scale was greater, by 4.5 points, among participants receiving pregabalin than among those receiving placebo ($P<0.001$), and the proportion of patients with symptoms that were very much improved or much improved was also greater with pregabalin than with placebo (71.4% vs. 46.8%, $P<0.001$). The rate of augmentation over a period of 40 or 52 weeks was significantly lower with pregabalin than with pramipexole at a dose of 0.5 mg (2.1% vs. 7.7%, $P=0.001$) but not at a dose of 0.25 mg (2.1% vs. 5.3%, $P=0.08$). There were six cases of suicidal ideation in the group receiving pregabalin, three in the group receiving 0.25 mg of pramipexole, and two in the group receiving 0.5 mg of pramipexole.

CONCLUSIONS

Pregabalin provided significantly improved treatment outcomes as compared with placebo, and augmentation rates were significantly lower with pregabalin than with 0.5 mg of pramipexole. (Funded by Pfizer; ClinicalTrials.gov number, NCT00806026.)

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Moderate-to-severe restless legs syndrome (RLS), now also known as Willis–Ekbom disease, with its predominantly nocturnal, rest-induced, distressing urge to move the legs, is a significant but poorly recognized and undertreated health problem.[1] Clinically significant RLS, which affects 2 to 3% of the European and American populations,[2,3] profoundly disrupts sleep, quality of life, and daytime productivity and often requires treatment for years, if not for life. Levodopa[4] and short-acting dopamine agonists (pramipexole and ropinirole)[5,6] relieve RLS symptoms.[7,8]

In patients treated with dopamine agonists, RLS can worsen over several years.[9] This worsening results in symptoms that are both more pervasive and more intense than they were before treatment.[10] It occurs in about one third of patients treated with the most commonly used dopaminergic treatment who are evaluated for up to 3 years[11,12] and is considered a primary factor in the reduction of the long-term efficacy of dopamine treatment.[13] The worsening of symptoms has been assumed to be iatrogenic, an "augmentation" of RLS severity that occurs with dopaminergic treatment rather than a natural progression of the disease.[10] This assumption has not been confirmed in a controlled clinical trial.

Two unblinded, retrospective studies have documented high rates of augmentation with dopamine agonists (including pramipexole and pergolide).[9,13] Both studies had a selection bias toward patients with more severe symptoms in whom the disease may have naturally progressed to very severe RLS symptoms. In contrast, the only two clinical trials with blinded, placebo-controlled evaluation of augmentation during treatment with dopamine agonists (pramipexole and ropinirole) lasted 6 months and showed very little augmentation.[14,15] In one of these clinical trials, the rate of augmentation with placebo reflected natural fluctuations in RLS symptoms and, if anything, was slightly higher than the rate with dopaminergic medication.[15] Thus, on the one hand, the discrepancy between the findings in short-term, controlled clinical trials and those in retrospective studies may indicate that augmentation is not iatrogenic but is rather a naturally occurring fluctuation in symptoms.[16] On the other hand, RLS augmentation may be an iatrogenic effect of dopaminergic treatment that is common in patients receiving treatment for 1 year or more, as suggested by uncontrolled studies, and the 6-month treatment period in the blinded, controlled studies may have been too short to observe the effect.

Augmentation, unlike loss of efficacy,[17] produces RLS symptoms that are worse than those occurring before treatment (e.g., symptoms start earlier in the day, are more intense, and extend to more areas of the body). Augmented symptoms often emerge first in the daytime, despite some continuing beneficial effects of nighttime treatment; this is particularly true for medications with evening-only dosing and half-lives that are too short to provide daytime treatment benefits. Dose increases appear to exacerbate augmentation. Augmentation differs from natural disease progression in that it is associated with pharmaceutical treatments and can cause extremely severe symptoms.

We sought to answer fundamental questions about the efficacy of an alternative drug type in patients with RLS and about the iatrogenic nature of RLS augmentation. In a 1-year, blinded evaluation of efficacy and augmentation, we compared a dopaminergic drug (pramipexole), administered at doses approved by the Food and Drug Administration for the treatment of RLS,[18] with a nondopaminergic drug (pregabalin), an $\alpha 2\delta$ ligand with analgesic and anticonvulsant activity[19] that is currently approved for the treatment of pain and epilepsy.[20] Pregabalin has recently been shown to be effective for the treatment of RLS.[21]

METHODS

PATIENTS

Adults (age ≥18 years) with moderate-to-severe primary RLS, diagnosed by study investigators on the basis of the International RLS (IRLS) Study Group criteria,[22] were screened for participation in the study.[23] The diagnosis was confirmed with the use of the clinical version of the Hopkins telephone diagnostic interview.[24] Eligibility criteria included symptoms that occurred predominantly at night, symptom onset at least 6 months before screening, and the presence of symptoms on 15 or more nights in the month before screening. In addition, the score on the IRLS Study Group Rating Scale[25] had to be 15 or higher at the beginning and end of a 1-week placebo run-in period. (The range of the IRLS scale is 0 to 40, with higher scores indicating more severe symptoms; score differences of more than

3 points are considered to be clinically significant.[26,27]) Patients with a prior clinical report of RLS augmentation were excluded. Written informed consent was obtained from all patients. Additional details on study participants are available in the protocol, available with the full text of this article at NEJM.org.

STUDY DESIGN AND OVERSIGHT

This randomized, active-comparator, placebo-controlled, double-blind trial was conducted at 102 sites in the United States and Europe between December 2008 and June 2011. The study was sponsored by Pfizer. All the authors were involved in the design and performance of the study, which was conducted according to the Declaration of Helsinki. The institutional review board at each site approved the study protocol and oversaw the process of obtaining informed consent. The fifth author was responsible for statistical analyses. The first author prepared the first draft of the manuscript. All the authors had full access to study data, edited drafts with the assistance of a medical writer paid by Pfizer, and made the final decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of this report to the study protocol.

STUDY TREATMENTS AND PROCEDURES

Patients were randomly assigned to receive placebo, 0.25 mg of pramipexole per day, 0.5 mg of pramipexole per day, or 300 mg of pregabalin per day for 12 weeks in capsules that were identical in appearance, after which patients receiving placebo were randomly assigned to one of the three active treatments for the remainder of the study (an additional 40 weeks) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Medication doses were increased over the first 2 weeks of the study to the final fixed dose. The pregabalin dose was based on the results of a prior dose-finding study.[21] Before randomization, patients discontinued all RLS medications for at least 1 week or five half-lives, whichever was longer. This period was followed by a 1-week single-blind placebo run-in. Thus, all study participants discontinued their RLS medications at least 2 weeks before starting the study medications. Medication was administered orally, 1 to 3 hours before bedtime. The use of concomitant RLS medications was not allowed.

Visits were scheduled at the start of treatment and at 2, 6, 10, 12, and 14 weeks after the start of treatment; thereafter (until the end of the study, 52 weeks from the start of treatment), visits were monthly. Patients also completed daily logs of symptoms during the week preceding each visit. At each visit, the patient, with an investigator, completed the IRLS severity scale,[25] the Augmentation Severity Rating Scale (ASRS) (which ranges from 0 to 24, with a score of 5 indicating mild augmentation and higher scores indicating more severe augmentation),[28] and the Structured Interview for the Diagnosis of Augmentation (SIDA) during RLS treatment,[29] a series of nested questions based on the NIH criteria for RLS augmentation[22] (for a list of the NIH criteria, see the Supplementary Appendix). The investigators evaluated participants with the use of the Clinical Global Impression of Improvement (CGI-I) scale; reports of symptoms that were "very much" or "much" improved were considered to indicate clinically significant improvement.[30,31] Identification of cases of possible augmentation was based on clinical judgment, a total ASRS score of 5 or higher, or a positive SIDA score. Cases were referred to an augmentation review board that consisted of three RLS augmentation experts (the first, third, and last authors). At the end of the study, the review board evaluated possible cases of augmentation by reviewing double-blind information consisting of entries from patients' logs and efficacy and augmentation data compiled by clinicians.[22] The determination of whether a case qualified as augmentation was based on unanimous agreement that established criteria had been met. This review was performed before the study-group assignments were revealed.

END POINTS

The study had three primary end points: for the comparison of pregabalin with placebo, the change from baseline to week 12 in the IRLS score and in the proportion of patients with a CGI-I evaluation of much improved or very much improved, and for the comparison of pregabalin with pramipexole, the change from baseline to week 40 or week 52 in the percentage of participants with augmentation (as defined above). Key secondary efficacy end points included a comparison of the efficacy of pregabalin and pramipexole over a period of 12 weeks (short-term comparison) and pramipexole over a period of 40 or 52 weeks (long-term comparison), as assessed with the use of the

IRLS scale. Patient-reported measures included limb pain as assessed on a visual-analogue scale, quality of life with RLS as assessed on a questionnaire,[32] and sleep as assessed on a subjective sleep questionnaire[33]; these factors were evaluated during the first 12 weeks of the study.

Safety was assessed by means of a review of reported adverse events and abnormal laboratory-test results. At each study visit, participants were asked to complete the Columbia Suicide Severity Rating Scale for suicidal ideation or behavior.

STATISTICAL ANALYSIS

We calculated that a sample of 750 patients would provide adequate power (at an alpha level of 0.05 in a two-sided t-test) for the proposed tests in this four-group study (99% power for a mean difference of 4.5 in the change in the IRLS score, 97% power for a difference of 20% in CGI-I evaluations, 85% for an absolute difference of 10 percentage points in augmentation rates with pregabalin as compared with 0.5 mg of pramipexole per day, and 84% for a 3-point noninferiority difference in the IRLS score). Changes from baseline to week 12 in the IRLS score were analyzed with a linear mixed model and the use of a spatial-power covariance structure. The CGI-I evaluation for the comparison of pregabalin with placebo at week 12, with the last observation carried forward, was analyzed with the use of the Cochran–Mantel–Haenszel test, stratified according to region (the United States or Europe). Augmentation rates were analyzed by means of a stratified log-rank test. The noninferiority of pregabalin with respect to each dose of pramipexole was assessed on the basis of 95% confidence intervals for the difference between pregabalin and pramipexole with the use of least-squares means derived from a mixed-effects model; the noninferiority margin was set at 3 points for the IRLS score. If noninferiority could be declared, a test of superiority was performed, with superiority declared if the upper limit of the confidence interval for the change from baseline in the IRLS score was less than 0. Analyses were conducted with data from the intention-to-treat population (patients who received ≥1 dose of the study drug and underwent ≥1 assessment after randomization).

The step-down testing order was selected to ensure a type I error rate of less than 0.05. The order, from first to last, was as follows: step 1, pregabalin versus placebo for the IRLS score over a period of 12 weeks; step 2, pregabalin versus placebo for the CGI-I evaluation over a period of 12 weeks; step 3, pregabalin versus 0.5 mg of pramipexole for augmentation over a period of 52 weeks; step 4, pregabalin versus 0.25 mg of pramipexole for noninferior efficacy (based on the IRLS score) over a period of 12 weeks; step 5, pregabalin versus 0.25 mg of pramipexole for noninferior efficacy over a period of 52 weeks; step 6, pregabalin versus 0.5 mg of pramipexole for noninferior efficacy over a period of 12 weeks; step 7, pregabalin versus 0.5 mg of pramipexole for noninferior efficacy over a period of 52 weeks; and step 8, pregabalin versus 0.25 mg of pramipexole for augmentation over a period of 52 weeks. Expecting a significant dose effect for augmentation, we ordered the step-down testing to test first for augmentation with pregabalin versus 0.5 mg of pramipexole, then for noninferior efficacy of pregabalin as compared with pramipexole, and then for augmentation with pregabalin as compared with 0.25 mg of pramipexole. Statistical significance was determined only for those analyses performed before the first nonsignificant result in the step-down testing, which occurred at step 8. Other statistical analyses for comparisons of potential interest did not test for statistical significance but are presented with P values for reference only.

RESULTS

STUDY PATIENTS

A total of 731 patients underwent randomization at 102 centers in the United States and Europe; 719 received one or more doses of the study drug. The characteristics of the patients at baseline and treatment-completion rates were similar across study groups (Table 1, and Table S1 and Fig. S1 in the Supplementary Appendix).

PRIMARY OUTCOMES

After 12 weeks, patients who received pregabalin, as compared with those who received placebo, had a significantly greater reduction (improvement) in the IRLS score, and a greater proportion of patients in the pregabalin group had symptoms that were reported as very much or much improved on the CGI-I evaluation (71.4% vs. 46.8%, P<0.001) (Table 2). As compared with placebo, the 0.5-mg dose of pramipexole, but not the 0.25-mg dose, was associated with a significant reduction

Table 1. Baseline Characteristics of the Patients.*

	Pregabalin, 300 mg Daily (N=182)	Pramipexole, 0.25 mg Daily (N=178)	Pramipexole, 0.5 mg Daily (N=180)	Placebo (N=179)†
Sex — no. (%)				
Female	123 (67.6)	108 (60.7)	99 (55.0)	111 (62.0)
Male	59 (32.4)	70 (39.3)	81 (45.0)	68 (38.0)
Age — yr				
Mean	54.3±13.0	56.5±12.8	54.2±13.5	53.5±13.3
Range	20–79	25–82	24–80	19–79
BMI				
Mean	28.0±5.0	28.6±5.2	28.2±5.2	28.4±5.3
Range	18.8–49.5	19.5–43.5	18.8–49.6	18.5–49.2
Interval since RLS onset — yr				
Mean	5.0	4.0	4.9	5.9
Range	0.0–52.5	0.0–35.1	0.0–47.9	0.0–35.1

* Plus–minus values are means ±SD. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), and RLS restless legs syndrome.
† The placebo group includes all patients who underwent randomization to receive placebo during the first 12 weeks of the study. For full details of participants' demographic and clinical characteristics according to study group at baseline, see Table S1 in the Supplementary Appendix. There were no significant differences among the study groups at baseline.

in the IRLS score and a significantly greater proportion of patients with improvement on the CGI-I evaluation (Table 2 and Fig. 1).

In a noninferiority assessment, a greater reduction in the IRLS score was seen with pregabalin than with pramipexole at a dose of either 0.25 mg or 0.5 mg (least-squares mean difference, −4.0 [upper limit of the 97.5% confidence interval {CI}, −2.8] and −1.7 [upper limit of the 97.5% CI, −0.5], respectively) over a period of 12 weeks and (−3.8 [upper limit of the 97.5% CI, −2.7] and −3.1 [upper limit of the 97.5% CI, −2.0], respectively) over a period of 52 weeks ($P<0.001$ for all comparisons). The upper boundary of the confidence interval for pregabalin versus pramipexole at either dose was less than 0, indicating the superiority of pregabalin for this outcome at both 12 and 52 weeks. In a post hoc analysis that was not specified in the protocol, the proportion of CGI-I responses showing symptom improvement after 12 weeks and 52 weeks (last observation carried forward for both time points) was greater with pregabalin than with pramipexole at a dose of 0.25 mg ($P<0.001$ for both comparisons), but not at a dose of 0.5 mg ($P=0.08$ for the comparison after 12 weeks and $P=0.36$ for the comparison after 52 weeks).

Among the 235 patients receiving pregabalin (for 40 or 52 weeks), 5 (2.1%) had augmentation, as compared with 12 of 225 patients receiving 0.25 mg of pramipexole (5.3%, $P=0.08$) and 18 of 235 patients receiving 0.5 mg per day (7.7%, $P=0.001$) (Table 3). (Patients initially assigned to placebo received active treatment for only 40 weeks, with the change in regimen occurring after receipt of placebo for 12 weeks.) Among patients receiving active treatment over the entire 52-week study period, augmentation occurred in 3 of 176 patients receiving pregabalin (1.7%), 11 of 167 receiving 0.25 mg of pramipexole (6.6%), and 16 of 178 receiving 0.5 mg of pramipexole (9.0%) (Table 3). During the first 6 months of treatment, none of the 176 patients receiving pregabalin had augmentation; 3 of the 167 patients receiving 0.25 mg of pramipexole (1.8%) and 2 of the 178 patients receiving 0.25 mg of pramipexole (1.1%) had augmentation during this period. During the initial 12 weeks of treatment, augmentation occurred in only 1 patient, who was receiving 0.25 mg of pramipexole.

SECONDARY OUTCOMES

Evaluations of secondary outcomes for active treatments as compared with placebo after 12 weeks were outside the step-down testing procedure. Statistical significance was therefore not assessed

for the following outcomes: limb pain, quality of life with RLS, and quality of sleep. Scores for limb pain and quality of life improved from baseline scores with pregabalin and with 0.5 mg of pramipexole (Table 2). In comparisons of the change from baseline with active treatment as compared with placebo, there was greater improvement in several measures of sleep with pregabalin than with either dose of pramipexole, including waking after sleep onset, quality of sleep, number of awakenings, and total sleep time. In contrast, a reduction in sleep latency (i.e., the time it took to fall asleep) was more pronounced with both doses of pramipexole versus placebo than with pregabalin versus placebo (Table 2).

ADVERSE EVENTS

The rate of study discontinuation due to adverse events was lower in the groups receiving pramipexole (18.5% for those receiving 0.25 mg and 23.9% for those receiving 0.5 mg) than for the group receiving pregabalin (27.5%) (Table 4). With pregabalin, the most common adverse events were dizziness, somnolence, fatigue, and headache, with pramipexole, the most common events were headache, nausea, and fatigue. For adverse events leading to study discontinuation, the most common events were somnolence and dizziness with pregabalin and nausea and headache with pramipexole. The majority of adverse events (94.0%) were mild or moderate in severity. A total of

Table 2. Primary and Secondary Efficacy End Points, According to Study Group.*

End Point	Pregabalin	Pramipexole, 0.25 mg Daily (N=178)	Pramipexole, 0.5 mg Daily (N=180)	Placebo
Primary efficacy end points				
IRLS score†				
Patients assessed — no.	177	169	178	172
Baseline	22.3±5.7	22.4±5.4	22.1±5.2	22.4±5.6
12 wk	10.9±7.3	14.6±7.3	12.0±7.5	15.5±7.1
Mean change from baseline vs. placebo (95% CI)	−4.5 (−5.9 to −3.2)	−0.6 (−2.0 to 0.7)	−3.2 (−4.5 to −1.9)	—
P value‡	<0.001	0.36	<0.001	—
CGI-I rating for symptom improvement (last observation carried forward)§				
Patients assessed — no.	175	168	177	173
Positive response to treatment — no. (%)	125 (71.4)	86 (51.2)	111 (62.7)	81 (46.8)
Little or no response to treatment — no. (%)	50 (28.6)	82 (48.8)	66 (37.3)	92 (53.2)
P value‡	<0.001	0.439	0.002	—
Secondary efficacy end points¶				
Limb pain, visual-analogue scale				
Baseline	4.2±2.7	4.3±2.6	4.0±2.5	4.1±2.5
12 wk	2.3±2.1	3.1±2.0	2.9±2.1	3.3±2.1
Mean change from baseline vs. placebo (95% CI)	−1.0 (−1.6 to −0.5)	−0.43 (−1.0 to 0.1)	−0.55 (−1.1 to 0.0)	—
Quality of life				
Baseline	67.7±13.8	65.8±15.9	66.4±14.6	67.2±15.4
12 wk	77.8±10.9	73.3±13.0	75.5±12.7	73.2±14.0
Mean change from baseline vs. placebo (95% CI)	3.9 (1.9 to 5.8)	0.5 (−1.5 to 2.4)	2.1 (0.1 to 4.1)	—
Sleep assessments				
Awake at night after onset of persistent sleep — min				
Baseline	90.6±76.1	100.2±85.9	83.9±77.4	79.5±69.9
12 wk	42.5±52.1	62.0±62.5	50.3±56.9	52.0±49.9
Mean change from baseline vs. placebo (95% CI)	−17.2 (−25.8 to −8.7)	−1.1 (−9.7 to 7.6)	−4.6 (−13.1 to 3.9)	—

Table 2. (Continued.)

End Point	Pregabalin	Pramipexole, 0.25 mg Daily (N=178)	Pramipexole, 0.5 mg Daily (N=180)	Placebo
Quality of sleep				
Baseline	44.1±20.6	44.3±18.9	45.5±20.0	46.9±18.2
12 wk	66.5±20.0	57.4±19.8	60.2±19.4	57.7±20.3
Mean change from baseline vs. placebo (95% CI)	10.6 (7.1 to 14.2)	1.2 (–2.4 to 4.7)	3.3 (–0.2 to 6.8)	—
Awakenings — no.				
Baseline	2.3±1.6	2.3±1.5	1.9±1.3	2.4±2.2
12 wk	1.1±1.1	1.7±1.2	1.5±1.1	1.8±2.1
Mean change from baseline vs. placebo (95% CI)	–0.6 (–0.8 to –0.4)	0.0 (–0.1 to 0.2)	0.0 (–0.2 to 0.2)	—
Total sleep time — hr				
Baseline	6.1±1.4	6.2±1.4	6.2±1.3	6.3±1.3
12 wk	7.0±1.1	6.7±1.2	6.8±1.1	6.7±1.2
Mean change from baseline vs. placebo (95% CI)	0.4 (0.3 to 0.6)	0.1 (–0.1 to 0.3)	0.2 (0.0 to 0.4)	—
Time to sleep onset — min				
Baseline	55.9±42.2	67.8±56.8	61.5±55.1	58.7±49.9
12 wk	41.6±35.8	43.1±35.8	35.9±33.1	47.7±44.9
Mean change from baseline vs. placebo (95% CI)	–5.5 (–11.4 to 0.5)	–8.2 (–14.3 to -2.2)	–13.1 (–19.0 to –7.2)	—

* Plus–minus values are means ±SD.
† The International Restless Legs Syndrome (IRLS) scale ranges from 0 to 40, with higher scores indicating more severe symptoms. Estimates and P values are from mixed models that included fixed effects for baseline value, region, treatment, and week. Values are the average over the first 12 weeks of treatment.
‡ P values were calculated for the comparison of pregabalin with placebo. Comparisons of pramipexole with placebo were not included in the step-down testing procedure; the P values shown for this comparison are for reference only.
§ Participants who reported that their symptoms were "very much improved" or "much improved" on the Clinical Global Impression of Improvement (CGI-I) scale were classified as having a positive response to treatment; all other participants were classified as having little or no response to treatment.
¶ Data for secondary efficacy end points were averaged over the first 12 weeks of treatment and were outside the step-down testing procedure (P values were not assessed). The visual-analogue scale for limb pain ranged from 0 to 10, with lower scores indicating less pain. Scores for quality of life with RLS ranged from 0 to 100, with higher scores indicating better quality of life. Scores for quality of sleep ranged from 0 to 100, with higher scores indicating better quality of sleep.

50 serious adverse events occurring during treatment were reported in 37 patients, with 11 events among those receiving pregabalin, 20 events among those receiving 0.25 mg of pramipexole, and 12 events among those receiving 0.5 mg of pramipexole; in addition, there were 5 events among patients who switched from placebo to pregabalin and 2 events among those who switched from placebo to pramipexole at a dose of 0.25 mg (see Table S2 in the Supplementary Appendix for further details). There were 11 cases of suicidal ideation: 6 in the group receiving pregabalin, 3 in the group receiving 0.25 mg of pramipexole, and 2 in the group receiving 0.5 mg of pramipexole. These included 1 case involving preparatory acts toward imminent suicidal behavior in a patient receiving pregabalin. One death was reported: a stroke in a 77-year-old woman receiving pregabalin.

DISCUSSION

Assessment of the study's primary end points showed that 300 mg of pregabalin per day, as compared with placebo, significantly improved RLS treatment outcomes after 12 weeks and was associated with significantly less augmentation than a dose of 0.5 mg of pramipexole per day, but not a dose of 0.25 mg per day, after 52 weeks. The study data also provide evidence of four important aspects of RLS augmentation.

First, our findings suggest that RLS augmentation is an iatrogenic worsening related to dopaminergic medication, not a naturally occurring

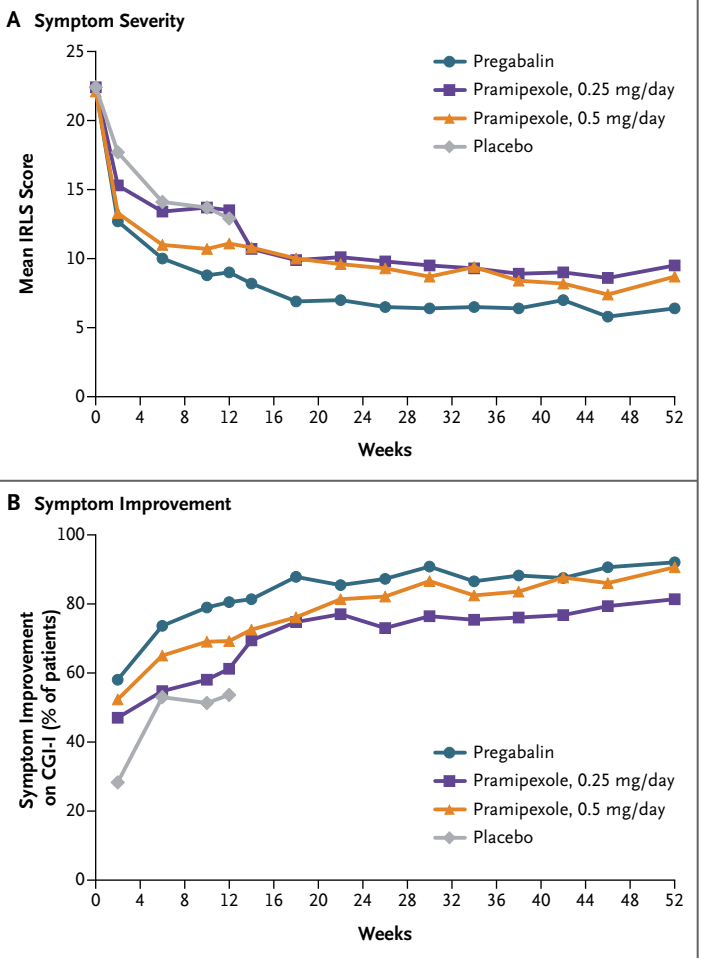

Figure 1. Mean Changes in Symptom Severity and Observed Proportion of Patients with Symptom Improvement, According to Study Group and Number of Weeks in the Study.

Changes in symptom severity were measured with the use of the International Restless Legs Syndrome (IRLS) Study Group Rating Scale, on which the score ranges from 1 to 40, with higher scores indicating more severe symptoms. Improvement in symptoms was measured with the use of the scale for Clinical Global Impression of Improvement (CGI-I), with symptoms reported as "very much" or "much" improved considered to reflect clinically significant improvement. The numbers of patients in each active-treatment group at baseline and at 12, 26, and 52 weeks were 177, 130, 148, and 126, respectively, for pregabalin; 169, 125, 138, and 112, respectively, for 0.25 mg of pramipexole; and 178, 135, 143, and 117, respectively, for 0.5 mg of pramipexole per day. Initially, 179 patients underwent randomization to the placebo group; after 12 weeks these patients were randomly assigned to one of the active-treatment groups. Panel A shows the observed mean IRLS score for each study group from baseline (0 weeks) until the end of the study. Panel B shows the participants with clinically significant symptom improvement as a proportion of the total participants observed at each visit. At 52 weeks, with the last observation carried forward, the proportions of patients with improved symptoms, according the CGI-I scale, were 72.2% with pregabalin, 57.1% with 0.25 mg of pramipexole, and 68.2% with 0.5 mg of pramipexole.

worsening or a worsening resulting from medical or behavioral factors. Symptom worsening from natural causes would presumably occur at the same frequency in all treatment groups, but the frequency was significantly greater with pramipexole than with pregabalin. Natural worsening might be blunted by a more effective treatment, but our findings suggest that whereas treatment efficacy was greater with 0.5 mg of pramipexole than with 0.25 mg of pramipexole, the higher dose was also associated with more, not less, augmentation. Conversely, augmentation would not be expected to result from an ineffective treatment, but our findings suggest that 300 mg of pregabalin was as effective as 0.5 mg of pramipexole and was associated with a lower rate of augmentation.

Second, our findings suggest that longer exposure to medication increases augmentation rates. For participants who received active therapy for the full 52 weeks of the study (not 40 weeks), augmentation rarely occurred until the second half of the study. The rates of augmentation with pramipexole during the first 6 months were low, at 1.8% with the 0.25-mg dose and 1.1% with the 0.5-mg dose. Estimates of augmentation rates based on a full year of treatment may be more accurate than estimates based on shorter periods of treatment. In this study, augmentation rates for treatment over the full 52 weeks were 6.6% with 0.25 mg of pramipexole, 9.0% with 0.5 mg of pramipexole, and 1.7% with pregabalin.

Third, the incidence of augmentation was greatest with the higher pramipexole dose. This dose effect has previously been documented for levodopa[34] but not for a dopamine agonist.

Finally, the 52-week rate of augmentation among patients receiving pramipexole in our study is similar to the rates in two long-term, uncontrolled, retrospective studies (7%[13] and 8%[9]), despite the use of different methods and different patient populations. Studies of longer-acting dopamine agonists have shown lower augmentation rates (e.g., a rate of approximately 3 to 4% per year among patients treated with the rotigotine patch[35,36]). Longer-acting agents may be less likely to cause augmentation, but their daytime treatment efficacy may complicate the detection of augmentation by masking the usual initial expression of augmented symptoms in the daytime that is seen with shorter-acting treatments.

Table 3. Rate of Augmentation after 40 and 52 Weeks of Treatment.*

Variable	Augmentation at 40 Wk	Augmentation at 52 Wk	Augmentation Overall	P Value
Pregabalin				
Patients assessed — no.	59	176	235	
Patients with augmentation — no. (%)	2 (3.4)	3 (1.7)	5 (2.1)	—
Pramipexole, 0.25 mg				
Patients assessed — no.	58	167	225	
Patients with augmentation — no. (%)	1 (1.7)	11 (6.6)	12 (5.3)	0.08
Pramipexole, 0.5 mg				
Patients assessed — no.	57	178	235	
Patients with augmentation — no. (%)	2 (3.5)	16 (9.0)	18 (7.7)	0.001

* P values, which are for overall augmentation rates in the pregabalin group as compared with each of the pramipexole groups, were calculated with the use of a stratified log-rank test according to block (40 or 52 weeks of active treatment). Data for patients without augmentation were censored at the time of discontinuation or completion of the study.

Table 4. Frequency of Adverse Events (All Causes) at 52 Weeks, According to Treatment Group.

Event	Pregabalin (N=182)	Pramipexole, 0.25 mg (N=178)	Pramipexole, 0.5 mg (N=180)	Switched from Placebo to Pregabalin (N=59)*	Switched from Placebo to Pramipexole, 0.25 mg (N=59)*	Switched from Placebo to Pramipexole, 0.5 mg (N=61)*
Serious adverse events — no.	11	20	12	5	2	0
Patients with serious adverse events — no. (%)	9 (4.9)	12 (6.7)	9 (5.0)	5 (8.5)	2 (3.4)	0
Patients with adverse events — no. (%)	155 (85.2)	142 (79.8)	140 (77.8)	52 (88.1)	46 (78.0)	48 (78.7)
Discontinuations due to adverse events — no. (%)	50 (27.5)	33 (18.5)	43 (23.9)	17 (28.8)	9 (15.3)	8 (13.1)
Common adverse events — no. (%)†						
Dizziness	39 (21.4)	15 (8.4)	17 (9.4)	10 (16.9)	6 (10.2)	3 (4.9)
Somnolence	32 (17.6)	12 (6.7)	14 (7.8)	7 (11.9)	4 (6.8)	5 (8.2)
Fatigue	23 (12.6)	19 (10.7)	22 (12.2)	7 (11.9)	5 (8.5)	8 (13.1)
Headache	22 (12.1)	30 (16.9)	35 (19.4)	9 (15.3)	6 (10.2)	12 (19.7)
Nasopharyngitis	19 (10.4)	20 (11.2)	17 (9.4)	3 (5.1)	3 (5.1)	9 (14.8)
Weight gain	16 (8.8)	12 (6.7)	12 (6.7)	2 (3.4)	7 (11.9)	4 (6.6)
Constipation	14 (7.7)	3 (1.7)	2 (1.1)	5 (8.5)	1 (1.7)	0
Nausea	11 (6.0)	18 (10.1)	26 (14.4)	3 (5.1)	3 (5.1)	4 (6.6)
Back pain	10 (5.5)	16 (9.0)	13 (7.2)	2 (3.4)	4 (6.8)	4 (6.6)
Influenza	9 (4.9)	13 (7.3)	3 (1.7)	4 (6.8)	8 (13.6)	7 (11.5)
Vomiting	3 (1.6)	4 (2.2)	10 (5.6)	3 (5.1)	2 (3.4)	5 (8.2)
Diarrhea	7 (3.8)	9 (5.1)	10 (5.6)	2 (3.4)	5 (8.5)	5 (8.2)

* Participants who received placebo at the beginning of the study were randomly assigned to one of the three treatment groups at 12 weeks.
† Common adverse events were defined as those occurring in 8% or more of the patients in any treatment group.

The preference for dopaminergic treatment of RLS has been partly based on the assumption that RLS is due primarily to dopamine abnormalities.[8] Our finding that pregabalin, which has no direct effect on dopaminergic systems,[37] is effective in the treatment of RLS casts doubt on this basic rationale.

We also found that IRLS scores for patients receiving pregabalin were significantly higher than the scores for patients receiving 0.25 mg of pramipexole (with a clinically significant difference defined as a difference in improvement of 3 points or more[26]); however, in this regard, treatment with pregabalin was not superior to treatment with 0.5 mg of pramipexole. Pregabalin was associated with lower rates of nausea, vomiting, and headache than pramipexole but with higher rates of suicidal ideation, dizziness, somnolence, and weight gain, factors that may limit its long-term use.

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