The aim of the present study was to look at the long-term efficacy and side effects profiles of pramipexole in a large cohort of drug naïve patients with regard to dopaminergic medications. In all, 195 consecutive restless legs syndrome (RLS) patients who were prescribed pramipexole more than 1 year previously, agreed to undergo a telephone interview to assess both the efficacy and side effects of pramipexole. Forty-three patients had discontinued pramipexole: Twenty because of side effects, six because of a lack of efficacy, six for both and eleven for other reasons. Patients who continued pramipexole for more than 1 year (n = 152) reported a mean decrease in RLS symptoms severity of 80.9% (SD = 19.6%). At the onset of treatment, the most common side effects were nausea (30%), tiredness (9%), dizziness (8%), headache (4%), insomnia (3%), dry mouth (2%), difficulty to concentrate (1.3%) and sleepiness (0.7%). At 30 months, most patients (n = 124/152; 81.6%) reported an absence of side effects of pramipexole. None of the adverse effects occurred in more than 5% of patients at follow-up. The present study confirms, in a large cohort of unselected patients, that pramipexole is effective and safe in the long-term treatment of RLS.

Introduction

The restless legs syndrome (RLS) is characterized by an urge to move the legs usually associated with unpleasant leg sensations.1 Typically symptoms worsen at rest2 and they are at least temporarily relieved by activity. They also worsen in the evening and during the night due, in great part, to a circadian rhythm of RLS symptom severity.3–5 RLS is often familial and more than 50% of RLS patients have at least one first-degree relative affected with RLS.6–8 A majority of RLS patients have periodic leg movements during sleep (PLMS).6,9 These movements are characterized by a dorsiflexion of the big toe and the foot and occur approximately every 20–40 s.

Dopaminergic (DA) agents are presently the treatment of choice for RLS.10,11 Levodopa was the first medication of this class of drugs to be used for treating RLS. Since 1982, several open clinical trials and placebo-controlled studies have demonstrated the short-term efficacy of levodopa.12–16 However, increased symptom severity in the morning (morning rebound) was reported with administration of levodopa at bed-time.13,17 Allen and Earley18 also observed an increased severity of RLS symptoms in the afternoon or early evening in patients treated for several months with levodopa, a phenomenon they called augmentation of RLS symptoms. These authors found that augmentation occurred in 82% of 30 RLS patients treated with levodopa. Because of the morning rebound and daytime augmentation of symptoms with levodopa, DA agonists progressively replaced levodopa as the first choice treatment for RLS.10,11 Several DA agonists have been identified so far for the treatment of RLS. Bromocriptine, pergolide, cabergoline, rotigotine, ropinirole and pramipexole were all found to be superior to placebo in alleviating symptoms of RLS in double-blind placebo-controlled short-term efficacy studies.19–24 Follow-up studies of 6 months or longer were published for pergolide and pramipexole only. Regarding pergolide, several studies have demonstrated its long-term efficacy.25–27 However, these authors stated that side effects, in particular nausea, were very common amongst patients treated with pergolide. Slow titration and concomitant administration of domperidone were required in a majority of patients, at least in the early treatment phase, to prevent gastrointestinal side effects. Recent studies have also showed that pergolide may cause severe pulmonary fibrosis and valvular heart disease.28,29

Two long-term follow-up studies were published where pramipexole was administered for more than 1 year. The first study was based on a retrospective review of the record of 60 RLS patients treated with pramipexole. Eleven patients (18%) discontinued pramipexole after less than 4 months, the remainder were followed for a mean of 27.2 months. Forty percent of these patients experienced mild side effects such as insomnia, nausea, dyspepsia or dizziness. Augmentation developed in 33% of patients, mostly in the first year. In the second study, Winkelman and Johnston31 specifically studied side effects in 59 patients treated with pramipexole for a mean of 21.2 months. They noted augmentation in 32% of patients and tolerance in 46%. However, these complications were generally manageable by earlier dosing or small dose increases and rarely required medication discontinuation.

Methods

For the present study, our sleep disorders clinic records were reviewed and all patients who fulfilled the following inclusion and exclusion criteria were identified: a diagnosis of primary RLS; treatment with pramipexole initiated at least 12 months...
before; no history of previous treatment with DA medication (either levodopa or DA agonists); no other conditions known to be associated with RLS.

The diagnosis of primary RLS was based on the presence of the four standard criteria necessary for the clinical diagnosis of this condition. None of the patients had clinical or laboratory evidence of anemia, renal insufficiency, peripheral neuropathy or rheumatoid arthritis. These conditions were excluded on the basis of the clinical examination and appropriate laboratory tests. All patients had a ferritin level >20 µg/l. None of the patients was taking any other medication known to trigger or aggravate RLS or PLMS such as tricyclics, specific serotonin reuptake inhibitor antidepressants or neuroleptics. In addition, none of the patients had never been treated with DA agents (neither levodopa nor DA agonists).

One hundred and ninety-six patients who fulfilled these criteria were identified and asked to participate in a telephone interview. All patients except one (n = 195) accepted the invitation. This interview included questions about the duration of treatment, past and current dosage of pramipexole and for those who had stopped taking pramipexole, the reasons for discontinuing medication. The questionnaire also included a set of questions inquiring about the percentage of subjective improvement in symptom severity and about side effects including augmentation defined as de novo occurrence or worsening of symptoms in the afternoon as well as the impact of pramipexole on sleep and daytime vigilance.

This patient population was made of 85 males and 110 females with a mean age of 55.1 ± 12.1 years (range: 25.8–88.8 years). The mean age at onset of symptoms was 31.5 ± 16.7 years (range: 2–75 years). The family history was available for 191 patients and 121 (63%) reported that at least one of their first-degree relative was affected with RLS. One hundred and fifty-two (152) patients were still taking the medication at the time of the telephone interview. For these patients, the mean duration of pramipexole treatment was 30.5 ± 10.5 months (range: 11.6–61.9 months). Nocturnal polygraphic data were available for 192 of these patients at baseline including the recording of right and left anterior tibialis muscles for the detection of PLMS. PLMS were scored by the standard method:32 only movements lasting 0.5–5 s and occurring in series of at least four consecutive movements separated by intervals of 4–90 s were included. An amplitude criterion was also used: movements had to be at least 25% of the amplitude of EMG potentials recorded at the time of voluntary dorsolateral flexion of the foot performed during calibration prior to nocturnal sleep recording. Of the entire patient population (n = 195), 154 patients (80.2%) had a PLMS index >5 and 137 patients (71.4%) had a PLMS index >10.

Comparison of demographic and clinical data obtained in patients who discontinued pramipexole and those who were still taking this medication was performed by using Students t-test, chi-square and Mann–Whitney U-tests, depending on the nature and distribution of the data.

Results

Patients who Discontinued Pramipexole

Forty-three patients (16 men and 27 women; mean age = 54.5 ± 13.1 years; range: 31.0–87.1 years) discontinued pramipexole: 20 because of side effects, six because of a lack of efficacy, six for both and 11 for reasons other than side effects of treatment such as fear of taking an antiparkinsonian drug for an extended period of time, need to take other medications for other conditions and fear of potential drugs interaction and for economical reason. The main side effects responsible for treatment cessation were dizziness (n = 7), nausea (n = 5), sleepiness (n = 5), and insomnia (n = 3). Two patients complained of sleepiness at the wheel but no sudden onset of sleep occurred. None of the patients reported car accidents because of sleepiness. Table 1 shows the demographic, clinical and polygraphic characteristics of patients who continued and those who had stopped pramipexole at the time of the interview. There was no statistical difference between these two patient populations except for the PLMS index. The PLMS index and the percentage of patients with a PLMS index >5 or >10 were significantly lower amongst those who discontinued medication (Table 1).

Patients who Continued Pramipexole

Dosage of Pramipexole

Figure 1(a) shows the distribution of treatment duration (mean = 30.5 ± 10.5 months) for the 152 patients still taking pramipexole at follow-up, and Fig. 1(b) shows the distribution of pramipexole dosage at the time of the telephone interview. The mean dose of pramipexole was 0.59 ± 0.31 mg and the range was 0.125–2.25 mg; 88 patients (58%) were taking 0.5 mg or less and four patients (2.6%) were taking a dose exceeding 1 mg. A significant correlation was found between the PLMS index at baseline and dosage of pramipexole at follow-up (Pearson’s correlation coefficient: r = 0.20; P = 0.02). However, no correlation was found between dosage of pramipexole and duration of treatment (Pearson’s correlation coefficient: r = 0.04; P = 0.65), suggesting that there is no tendency to progressively increase the dose with time at least after the first year of treatment.

Efficacy of Pramipexole

Two questions inquired separately about the effects of pramipexole on RLS symptom frequency and severity. The answers to these two questions were identical for all but one patient (151/152 or 99.3%). To avoid redundancy, only severity data will be presented here as a measure of efficacy. Overall,
patients who continued pramipexole for more than 1 year, reported a mean decrease in RLS symptom severity of $80.0 \pm 20.8\% \ (n = 152)$ and 144 of 152 patients (94.7\%) reported a decrease in severity of 50\% or more at follow-up compared with baseline (Fig. 2).

**Effects on Sleep**

Another indication of treatment efficacy is the decrease in the percentage of patients complaining of difficulty in falling asleep or reporting RLS symptoms upon awakening in the middle of the night compared with the baseline condition. Before treatment, 82\% patients (40 = 107/130) reported difficulties in falling asleep and 75\% (40 = 97/130) reported nocturnal awakenings associated with RLS symptoms. After treatment with pramipexole, these percentages decreased to 13.1\% (40 = 17/130) and 14.6\% (40 = 19/130), respectively. Pre-and post-treatment comparisons were significant (McNemar chi-square test: $\chi^2(1) = 82.5, P < 0.0001$; and $\chi^2(1) = 74.1, P < 0.0001$; respectively). Patients also answered a general question on the effect of pramipexole on their nocturnal sleep. A large majority of patients (40 = 139/152; 91.4\%) reported that their nocturnal sleep improved either moderately or markedly after treatment with pramipexole.

**Adverse Effects of Pramipexole**

The interviewer specifically asked about the presence of the following side effects: tiredness, nausea or vomiting, dizziness, daytime sleepiness, insomnia, headaches and hallucinations. Patients were also asked to report any other side effect. In addition, patients were asked to retrospectively assess the presence of adverse effects both during the first month of treatment and at the time of the interview. Only side effects reported by more than 1\% of patients are listed in Table 2.

At the onset of treatment (Table 2), the most common side effects were nausea (29.6\%), tiredness (8.6\%), dizziness (7.9\%), headache (3.9\%), insomnia (3.3\%), dry mouth (2.0\%), difficulty to concentrate (1.3\%) and sleepiness (0.7\%). None of the patients reported hallucinations. The severity of nausea was generally mild and only 5\% of the patients were prescribed domperidone. At 30 months, a majority of patients (40 = 124/152; 81.6\%) reported an absence of side effects of pramipexole. None of the adverse effects occurred in more than 5\% of the patients at follow-up. A significant decrease in the prevalence of nausea and dizziness was found during long-term treatment with pramipexole compared with the early treatment phase (29.6\% vs. 2.6\%; $P = 0.00001$).

Patients were also asked about morning rebound and afternoon augmentation: 21 patients (13.8\%) reported a worsening of symptoms in the morning under long-term treatment with pramipexole long-term while 34 patients (22.4\%) reported that symptoms either worsened or de novo occurred in the afternoon. Those patients presenting an earlier onset of symptoms were not taking higher doses of pramipexole (0.59 mg vs. 0.60 mg; ns). In the majority of patients, symptoms were controlled by an earlier administration of pramipexole but eight patients were taking pramipexole twice a day (afternoon and evening).

**Discussion**

Overall, these results show that pramipexole administered at a mean dosage of 0.5 mg is an effective long-term treatment of RLS and only 2\% of patients required a dose exceeding 1 mg.

Eighty-two percent of patients who were prescribed pramipexole were still taking pramipexole 1 year later and 96\% of those who continued pramipexole for more than 1 year reported sustained efficacy after a mean of 30 months of treatment. These results confirm those of a previous study showing a long-term efficacy in more than 80\% of patients who were given pramipexole as a replacement treatment for other DA agents. This percentage is higher than those obtained with levodopa or
onset of sleep. Stiasny et al. looked specifically at sleepiness associated with a sudden onsets of sleep. Nevertheless, patients should be informed of the possibility of experiencing sleepiness as part of their disease or as a consequence of treatment.

Approximately one-third of patients reported augmentation defined as earlier onset of symptoms during long-term administration of pramipexole (main feature of augmentation). However, the interview did not include questions on shorter latency to symptoms at rest, increase in severity with dosage increase or progression to other body parts (considered as the secondary features of augmentation). Previous studies of pramipexole reported prevalence of augmentation from 8.8% to 32%. These differences may be because of different methods of assessing augmentation. The prevalence of augmentation seen in the present study was elevated although lower than with levodopa. As in the study of Winkelmann and Johnston, augmentation was easily manageable by an earlier administration of pramipexole or twice per day dosing.

In conclusion, the present study confirms, in a large cohort of DA drug-naive patients, that pramipexole is effective and safe in the long-term treatment of RLS. This study was restricted to patients with primary RLS with or without a positive family history. Therefore, these conclusions should be restricted to patients with primary RLS. Other studies will be needed to assess the long-term efficacy and side effects of pramipexole in patients with RLS associated with uremia, neuropathies or anemia. Moreover, long-term studies of other DA agonists, shown to be effective in the short-term treatment of RLS, especially nonergoline derivatives such as ropinirole and rotigotine, should be undertaken in order to compare different treatments with more accuracy.

Acknowledgements
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References

Table 2. Side Effects at the Onset of Treatment with Pramipexole and at Follow-up

<table>
<thead>
<tr>
<th></th>
<th>At Onset of Treatment (% Cases)</th>
<th>At Follow-up (% Cases)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>29.6</td>
<td>2.6</td>
<td>0.00001</td>
</tr>
<tr>
<td>Tiredness</td>
<td>8.6</td>
<td>3.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.9</td>
<td>0.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Headache</td>
<td>3.9</td>
<td>2.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3.3</td>
<td>2.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>2.6</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.0</td>
<td>2.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Confusion/difficulty</td>
<td>1.3</td>
<td>2.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>0.7</td>
<td>1.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s., not significant; *McNemar significance of change test (comparison between disappearance and new cases).

pergolide. However, any comparison may be misleading as different instruments have been used to measure efficacy and as no study has directly compared the efficacy of these drugs.

Results also showed that pramipexole improves nocturnal sleep. It decreased the occurrence of symptoms at bedtime and during the night. Two shorter term placebo-controlled studies showed that pramipexole markedly decreased PLMS at night. No PSG data were collected during long-term follow-up studies but it is possible that pramipexole continues to suppress PLMS during long-term treatment and this may contribute to the improvement of sleep noted in the present study.

Side Effects

Nausea was the most frequently reported side effect during the early phase of treatment. Nausea has been reported during treatment with all DA agents, especially during the first few weeks of treatment. However, nausea is generally worse in patients treated with DA agonists which are ergoline derivatives, such as bromocriptine, pergolide or cabergoline, than in patients treated with non-ergoline derivatives, such as pramipexole or ropinirole. Because of gastrointestinal side effects, the titration of pergolide required several weeks to reach the therapeutic dose. In studies of pergolide, domperidone in dosage up to 60 mg has been administered to limit the severity of nausea. In the present study, nausea was generally mild and only 10 patients were prescribed 10–20 mg of domperidone, 1 h prior to the administration of pramipexole. Several cases of sleepiness, including some resulting in car accidents, have been reported in patients with Parkinson’s disease treated with levodopa or various DA agonists including pramipexole. Sleepiness is generally considered a class effect of DA agents. In the present study, 0.7% patients reported sleepiness at the time of the follow-up interview but five had discontinued treatment because of sleepiness. In none of these patients was sleepiness associated with a sudden onset of sleep. Stiasny et al. looked specifically at sleepiness in patients treated with pramipexole and found that 5 of 24 patients reported daytime sleepiness but none complained of sudden onsets of sleep. Nevertheless, patients should be informed of the possibility of experiencing sleepiness as part of their disease or as a consequence of treatment.

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