Original Article

Long-term use of pramipexole in the management of restless legs syndrome

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A R T I C L E  I N F O

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A B S T R A C T

Objective: Few studies have examined the long-term use of dopamine agonists for restless legs syndrome (RLS). We report a cohort study of 50 patients initially prescribed pramipexole between 1998 and 2002. The objective was to determine duration of treatment, long-term efficacy, development of side effects and augmentation over an extended period.

Methods: We performed a long-term analysis on a previously reported group of patients initially followed for a mean of 27.2 months. Data were collected using retrospective chart reviews, written surveys and systematic telephone interviews.

Results: Pramipexole was used for a mean of 8 years (range 0.6–12 years). Nine (18%) discontinued pramipexole because of poor efficacy (four), impulse control disorders (ICD) (two), augmentation (one) and resolved symptoms (two). Pramipexole was reported completely effective in 40% (compared to 67% at the end of the initial study), partially effective in 58% and ineffective in 2%. The median daily dose increased from 0.38 mg after initial stabilization to 1.0 mg at the end of the study. As many as 74% of patients experienced side effects. A total of 56% reported daytime sleepiness including 10% reporting sleep attacks while driving and 10% developed ICDs. Augmentation developed in 42% of patients, after a mean of 16.5 months, and no later than 4.1 years after commencing treatment. A total of 28% needed additional non-dopaminergic medications.

Conclusion: The efficacy of pramipexole dropped with time, with increase in dose and addition of other agents, although the majority of patients remained on the drug. Problems included the development of augmentation within the first 4 years of therapy and side effects such as sleepiness increasing with time and the development of ICDs. The study highlights the need for further research into alternative non-dopaminergic treatments for RLS.

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1. Introduction

Restless legs syndrome (RLS) (Willis–Ekbom disease) is characterized by an urge to move the legs, usually associated with uncomfortable sensations. RLS symptoms manifest during rest, are relieved with movement and are typically most severe in the evening or night [1,2]. RLS is associated with insomnia in 50–85% of cases, affecting both sleep onset and sleep maintenance [3]. At least 80% of patients with RLS have periodic limb movements of sleep, which may lead to sleep disruption [4]. RLS is a common disorder affecting between 5% and 15% of the general population, and prevalence has been observed to rise with age [4–10]. The prevalence of symptomatic primary RLS in the United States and Europe is estimated to be 2.4–4.4%, and 1.5–2.7% experience symptoms at least twice a week, resulting in moderate to severe distress [5–12].

Pharmacologic treatment options for RLS include dopamine agonists, opioids, benzodiazepines and anticonvulsants.

Dopamine agonists, including pramipexole, are the mainstay of treatment for daily RLS (defined as symptoms frequent and troublesome enough to require daily therapy) [13]. Multiple controlled studies have demonstrated their efficacy; however, long-term use in clinical practice is constrained by the development of side effects and augmentation in many patients [3]. Although the mechanism of dopamine agonists in treating RLS is uncertain, it likely involves stimulation of dopamine receptors in the striatum. Pramipexole, a non-ergot agonist, is primarily metabolized through the kidneys and has a half-life of 8–12 h [14].

We have previously reported a study of 60 RLS patients initiated on pramipexole and followed for a mean of 27 months [2]. We now report an extended study on a cohort of 50 of these patients followed for a mean of 8 years. The goals of our study were to determine over an extended period the duration of therapy in this patient cohort, dosing parameters, long-term efficacy, side-effect profile and development of augmentation.

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2. Methods

Fifty of the original 60 adult patients were recruited from the previous study [2]. The other 10 patients had discontinued pramipexole within 4 months of initiation of therapy due to either side effects or lack of efficacy. Each patient was diagnosed with RLS in the Mayo Clinic Center for Sleep Medicine. Patients were initiated on pramipexole therapy between 1 January 1998 and 31 December 1999.

Our study used data obtained from a retrospective chart review (n = 50), a written survey (n = 22) (Appendix 1) and telephone interviews (n = 9). Twenty-six patients were followed by a single physician (M.H.S). The remainder were diagnosed and followed by eight other board-certified sleep specialists who work collaboratively in an academic group practice. While subtle variations in practice could be present, no striking inconsistencies between the approaches of different physicians were detected during the review process. Survey or phone interview data were only used if a signed authorization to use and disclose protected health information was received from the patient. Six patients did not return this authorization; in these cases only chart review data were used. This study was approved by the Mayo Clinic Institutional Review Board.

We compared data from the original study in 2002 (in which patients had used pramipexole for a mean of 27 months) to our current results (after patients had continued to use pramipexole for a mean of 8 years).

2.1. Definition of terms

For the purposes of this study, augmentation was defined as earlier onset, increased severity, duration or new anatomic distribution of RLS symptoms during treatment [2]. A decision to consider augmentation present was made jointly by the authors if any of these phenomena were clearly documented in the notes. We also attempted to calculate the augmentation rate using the more rigorous World Association of Sleep Medicine—International RLS Study Group (WASM–IRLSSG) criteria for augmentation but were limited by the frequent absence of documentation of the precise number of hours that RLS symptoms advanced [15]. Impulse control disorders (ICDs) were defined as symptoms of pathologic gambling, hypersexuality, compulsive shopping or compulsive eating attributed to pramipexole therapy [16,17]. Efficacy was judged from charts and survey/interview data by the reviewing investigators and was graded as completely effective (no residual RLS symptoms), partially effective (improvement in RLS symptoms) or ineffective (no improvement in RLS symptoms). These are the same criteria used in the 2002 study to facilitate comparison. Daytime sleepiness attributed to pramipexole therapy was defined by patient or physician report of this symptom. Epworth sleepiness scale (ESS) scores were obtained on 26/28 patients reporting daytime sleepiness [18]. For any reported symptoms of ICDs or sleep attacks while driving, which had not been addressed in previous clinical visits, patients were offered a visit to the Mayo Center for Sleep Medicine or encouraged to discuss the issue with their local provider.

2.2. Statistics

Given the variables of interest and sample size, primarily descriptive statistics were used. The spreadsheet application Microsoft Excel was used for data comparisons and generating percentages, median values, interquartile ranges (IQRs) and mean calculations. The Kaplan–Meier survival curves were produced using the R statistical computing survival library package.

3. Results

3.1. Demographic information

Fifty patients were identified and studied. Forty-six patients (92%) resided in Minnesota, Iowa or Wisconsin. Thirty-one were females (62%); 19 were males (38%). The mean age at onset of RLS symptoms was 42 years. The mean age at time pramipexole therapy was initiated was 60 years. Co-existing medical, sleep and psychiatric conditions included peripheral neuropathy (two patients), parkinsonism (one patient), obstructive sleep apnea (eight patients), central sleep apnea (one patient) and narcolepsy (two patients). Nine patients were diagnosed with depression and one with anxiety disorder; all were taking antidepressants. No other patient was on medication that might induce or exacerbate RLS. Iron status was assessed in 44 patients (88%) with low serum ferritin levels in 11 (22%). At the time of last follow-up, 31 patients had normal iron indices and 13 serum ferritin levels below 50 µg l⁻¹, of whom 11 were taking iron supplementation.

3.2. Treatment initiation

Forty-seven patients had received prior dopaminergic medications (levodopa or pergolide) for 1 week to greater than 4 years. Pramipexole was substituted because of augmentation, other side effects or an inadequate therapeutic response. All patients had daily RLS with resultant impaired quality of life. In all patients, pramipexole was initiated as a single evening dose of 0.125 or 0.25 mg. Dosing was increased in 0.125 or 0.25 mg increments every 2–3 days until relief was obtained. All patients were treated with pramipexole as monotherapy, and any previous medications were either immediately discontinued or tapered off within 1 week.

3.3. Follow-up data

Treatment duration varied from 0.6 to 12 years, with a mean duration of treatment of 7.96 ± 3.73 years; and median duration 9.68 years (IQR 4.10, 11.02). For 28 patients (56%), data from chart review, survey or interview were available within 1 year from the time of data analysis. For 35 patients (70%), data were available within the past 5 years. For 15 patients (30%), the time of last contact was more than 5 years from the time of data analysis. Analysis includes chart review data from five (10%) patients who were deceased between the conclusion of the 2002 study and the end of the current study.

3.4. Dosing parameters

The median initial effective dose (after a stabilization period) was 0.38 mg (range 0.125–2.0 mg). The median dose at the end of the 2002 study was 0.63 mg (range 0.25–4.5 mg). The median dose at the end of our study was 1.0 mg (range 0.125–3.75 mg). Forty-four patients (88%) required increased dosage over time. Eighteen of these patients required earlier dosing (before 6 p.m.), 16 between noon and 5:59 p.m. and 10 between 6 a.m. and noon. Dose adjustments were judged due to augmentation in 21 patients (42%), 13 of whom took additional doses before 6 p.m. In the other 23 patients (46%), doses were increased over time to gain better control of pre-existing symptoms, without documentation of increasing severity or earlier onset of symptoms. In all cases, the decision to increase the dose, change the time of dosing or add earlier doses was made when the residual or new symptoms were sufficiently severe to interfere with quality of life.
Forty-one patients (82%) were still using pramipexole at date of last contact. Nine patients (18%) discontinued pramipexole during the study, 14 patients (28%) were using one or more adjunct therapies. Reasons for discontinuation included poor efficacy (five), ICD symptoms (two), augmentation (one) and resolution of RLS symptomatology, or later after more than 8 years of treatment did so because of poor efficacy or development of ICD symptoms.

### 3.6. Efficacy

At date of last contact, pramipexole was found to be completely effective in controlling RLS symptoms in 20 patients (40%); 29 patients (58%) received partial benefit from therapy and one patient (2%) found pramipexole ineffective. Five patients (10%) discontinued pramipexole due to poor efficacy; these patients stopped taking pramipexole after an average of 9.72 ± 2.63 years. By the end of the study, 14 patients (28%) were using one or more adjunct treatments for RLS, including calcium channel ligands (n = 6, gabapentin and pregabalin), benzodiazepines (n = 4, clonazepam and temazepam) and opioids (n = 9, tramadol, codeine, oxycodone, hydrocodeine and propoxyphene). These were added because of augmentation in eight patients and due to persistence of RLS symptomatology despite pramipexole use in six patients.

### 3.7. Side effects

Side effects attributed to pramipexole were reported by 37 patients (74%) at time of last contact (Table 1). The most common side effect was daytime sleepiness, which was reported by 28 patients (56%). The mean pramipexole dose in patients reporting daytime sleepiness was 1.05 ± 0.73 mg versus 1.03 ± 0.74 mg in the 22 patients without daytime sleepiness. ESS scores were available for 26 of the 28 patients with daytime sleepiness. The median score was 10 (range 2–22). Seventeen of these patients had ESS scores ≥ 10. Five patients (10%) reported having at least one sleep attack while driving, which they attributed to pramipexole therapy.

Symptoms suggestive of ICD were reported by five patients (10%), after an average of 8.6 years of treatment (Table 2). Symptoms included: compulsive eating, hypersexuality, pathologic gambling and compulsive shopping. ICDs were treated by the discontinuation of pramipexole therapy (n = 1), or dose reduction (n = 4). The average dose of pramipexole at the time ICD symptoms first reported was 1.33 ± 0.39 mg.

Augmentation, as defined in the Section 2, developed in 21 patients (42%) after a mean of 16.5 ± 12.1 months. Four of these patients had serum ferritin levels below 50 µg l⁻¹ at the time of last follow-up. (Only 12 of these patients met the WASM–IRLSSG criteria, but this was judged a falsely low number because the frequent absence of information regarding the number of hours by which RLS symptoms advanced precluded us from including many patients with otherwise clear-cut augmentation [15]). The earliest development of augmentation was 3 months after treatment onset and no cases of augmentation commenced more than 4.1 years after starting therapy (Fig. 2). Augmentation was treated using additional doses of pramipexole earlier in the day. One patient (2%) discontinued pramipexole due to augmentation, after 2.9 years of therapy.

### 4. Discussion

The results of our study suggest that pramipexole decreases in efficacy over time, dose increases are required and patients frequently need adjunct therapies. Data previously gathered on this cohort over a mean follow-up time of 27 months demonstrated that pramipexole was completely effective in 67% of patients [2]. In our study, after a mean follow-up period of 8 years, pramipexole was found to be completely effective in only 40% of patients. Despite this decrease in efficacy, 82% of our patients remained on pramipexole therapy at the date of last contact. By contrast, in a Johns Hopkins University study of 164 patients on pramipexole for RLS, only 58% remained on the drug for more than 5 years [23]. All of our patients initiated the study on pramipexole as monotherapy for RLS. However, 28% of patients were using one or more additional non-dopaminergic treatments for RLS by the date of last contact. Most patients on pramipexole therapy required increased amounts of the medication over time. At the end of our study, 88% of patients had increased pramipexole from their initial therapeutic dose. The median initial effective dose was 0.38 mg whereas the median dose at the date of last contact was 1.0 mg. Dose increases over time were judged due to augmentation in 42% and attempts to adequately control initial symptoms in the other 46% of patients.

Side effects were reported by 74% of patients at the end of our study, compared to 40% of patients reporting side effects in the initial 2002 study [2]. The most common side effect was daytime
sleepiness, which was reported by 56% of patients, compared to only 5% reporting daytime sleepiness in 2002. Ten percent experienced sleep attacks while driving, which were attributed to pramipexole. No sleep attacks were reported by this cohort in 2002. The cause of the increase in daytime sleepiness is unclear. Mean pramipexole doses were similar in patients with and without daytime sleepiness and therefore, this side effect cannot be explained as simply a dose-related effect. The relationship between daytime sleepiness and pramipexole may be complex, involving a possible combination of dose effect, change in dopaminergic response with time and decreased efficacy of the medication causing daytime sleepiness from suboptimally treated RLS. Short-term studies have demonstrated no significant change or even reductions in daytime sleepiness when treating RLS with pramipexole [19,20]. However, there is little information regarding the development of daytime sleepiness in the long-term use of dopaminergic agonist therapies in RLS patients. The computer-assisted learning method (CALM) Cohort study provides information on extended follow-up in Parkinson's disease patients. Patients were randomized into groups initially treated with pramipexole or carbidopa–levodopa. After a mean of 6 years of follow-up, mean ESS scores were significantly higher in the group initially treated with pramipexole compared to the carbidopa–levodopa group (11.3 compared to 8.6) [21]. These results suggest that prolonged use of dopaminergic agents may independently lead to excessive daytime sleepiness.

ICDs developed in 10% of patients during pramipexole treatment, and were generally associated with higher doses of pramipexole. An observational study [22] of 89 patients using pramipexole for RLS demonstrated ICDs in 8.6%, whereas a prospective case-control study [23] demonstrated ICD symptoms in 17% of RLS patients using dopaminergic medications. In these studies, the mean dose at the time of ICD symptom onset was 1.3 and 1.25 mg, respectively. This is similar to the mean dose in our study of 1.33 mg. Thus, ICDs tend to emerge at dosages in the upper range of those used for RLS, but considerable variation is present, with some cases starting at much lower doses. Although symptoms were reported after an average of 8.6 years of treatment, the actual onset of ICDs was difficult to determine, as some patients described symptoms dating back an unspecified time. Our study highlights the importance of regularly querying all patients on pramipexole therapy regarding ICD symptomatology.

Augmentation occurred in 42% of patients, commencing after a mean of 16.5 months treatment. This is a slight increase from the initial 2002 study, where augmentation was reported in 33% of patients, after a mean of 14 months treatment. No new cases of augmentation developed after 4.1 years. This finding differs from the Hopkins study in which augmentation severe enough to require discontinuation of the medication continued at about a rate of 7% per year over 10 years follow-up [24]. Our data for rates of augmentation are similar to those of previously published short-term treatment studies of pramipexole. Of 59 patients followed for a mean of 21.2 months, 32% developed augmentation [25]. Augmentation occurred in 22.4% of 195 patients followed for a mean of 30.5 months [20]. In a questionnaire study of 266 patients treated with dopaminergic agents by primary care physicians or neurologists, 20% were felt to have definite or highly suggestive symptoms of augmentation [26]. In a study of 83 subjects treated with dopamine agonists (predominantly pramipexole) followed for a mean of 39.2 months, 48.2% reported mild augmentation and 21.7% developed augmentation severe enough to require additional doses of medication [27]. In our study, augmentation was generally well-tolerated with additional doses of pramipexole earlier in the day, resulting in higher total daily doses of the drug.

Some of our results differ from those described in the Johns Hopkins study, the only other long-term report of pramipexole therapy for RLS [24]. In particular, the discontinuation rate was lower in our cohort, especially due to augmentation, and augmentation was confined to the first 4 years of treatment, rather than continuing to appear at a constant rate over 10 years. The vast majority (92%) of our patients were from Minnesota or adjacent states, suggesting that these patients may have used Mayo Clinic for routine specialist care. Thus, it is possible that our patients had less severe RLS than those seen in the Johns Hopkins tertiary referral sleep medicine practice [24] and may represent a somewhat more community-based cohort. Alternatively, the difference may be due to variations in practice approaches between the two clinics with Mayo physicians persevering longer with using dopaminergic agonists in the setting of early augmentation.

The strengths of our study are the length of follow-up and the well-defined cohort of patients. However, the study has certain limitations: follow-up was not complete for all patients and retrospective chart review results in less accurate data than a prospectively recorded database. However, data were also obtained from written surveys and telephone communications. Quantitative instruments were not used to assess efficacy or augmentation. Augmentation rates may have been underestimated as it is possible that some of the patients requiring increased doses of pramipexole may have had augmentation despite no documentation of increasing RLS severity or earlier onset of symptoms.

In summary, the ability of pramipexole alone to treat RLS over many years of therapy decreased, with higher doses and additional medications being required in many patients. Limitations associated with long-term pramipexole therapy included the development of augmentation in the first 4 years of treatment, reduced efficacy with time and the development of serious side effects, especially ICDs and hypersomnia. Nevertheless, the majority of patients were still taking the drug many years later. Our study highlights the need for further research into alternative non-dopaminergic treatments for RLS.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2012.08.004.
Appendix 1. Written Questionnaire

Instructions

Please answer the following questions to the best of your ability. It is okay if you cannot answer all of the questions.

Once you have completed this questionnaire, please return it along with the enclosed Authorization to Use and Disclose Protected Health Information form. Also, if you give permission to be called by a physician to ask a few follow-up questions, please fill out your contact information below. Thank you very much for your time.

Your name: _________________________________________
Telephone number: (_______) ________-____________________
Best time to call: □ Morning □ Afternoon □ Evening
Best day(s) to call:______________________________

Questions

1. Are you experiencing symptoms of restless legs syndrome? (Symptoms include an urge to move the legs when you are resting, you may also have uncomfortable sensations in the legs that go away when you move your legs.)
   □ Yes □ No □ Not sure

2. Are you currently using pramipexole (also called Mirapex) to treat your restless legs symptoms?
   □ Yes □ No □ Not sure
   - What dose are you taking? ____________ How often?______________
   - When did you stop taking this medication? ____________________

3. If you stopped using pramipexole (also called Mirapex), why did you stop this medicine?
   □ This medicine helped at first, then it stopped helping
   □ This medication worsened my restless legs
   □ I had side effects from this medication. Please describe all of the side effects that you had below:
   □ I stopped the medication for a different reason. Please describe below:

4. While you were taking pramipexole (also called Mirapex), did you feel sleepy during the day?
   □ Yes □ No □ Not sure

5. While you were taking pramipexole (also called Mirapex), did you ever experience difficulty in controlling impulses which led you to do things that could be harmful? (Some examples are: having trouble controlling money spent on shopping or gambling, increased sexual desire, or not being able to stop eating.)
   □ Yes – Please describe:
   □ No
   □ Not sure

6. While you were taking pramipexole (also called Mirapex) did you start experiencing new or worse restless legs symptoms earlier and earlier in the day?
   □ Yes – How was this treated?
   □ No
   □ Not sure

7. Apart from pramipexole (Mirapex), what other medications are you taking for restless legs?
   Name_______________ Dose_______ At what times?__________________
References


