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Original article

Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS)

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Abstract

Background: Dopaminergic agents have become first-line treatments for restless legs syndrome (RLS). The most common serious complications of L-Dopa treatment of RLS are 'augmentation', in which RLS symptoms appear earlier during the day, and tolerance, in which medication effectiveness wanes over time. The aims of this study were to assess rates of augmentation and tolerance, and their interrelationship, with pramipexole treatment of RLS.

Patients and methods: Retrospective assessment of all patients ($N = 59$) treated for RLS with pramipexole for at least 6 months (mean duration = 21.2 ± 11.4 months) by the senior author. Pramipexole dosing and clinical follow-up were performed in a standardized fashion. L-Dopa was discontinued and other medications for RLS were tapered as tolerated. Rates of augmentation (need for earlier administration of the same dose of pramipexole) and tolerance (need for an increase in pramipexole dose) were determined.

Results: Augmentation developed in 32% (19/59), and tolerance occurred in 46% (27/59), of patients. These two complications were statistically related ($P < 0.05$). The only clinical predictors of these complications were previous augmentation or tolerance to L-Dopa.

Conclusions: Augmentation and tolerance are more common with extended pramipexole treatment of RLS than has been previously reported in preliminary studies. However, these complications are generally manageable by earlier dosing or small dose increases of this agent, and only rarely require medication discontinuation.

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Keywords: Pramipexole; Restless legs syndrome; Augmentation; Tolerance; Sleep disorders; Periodic leg movements of sleep

1. Introduction

Restless legs syndrome (RLS) is a sensory-motor disorder consisting of dysesthesia and an abnormal urge to move the legs, predominantly during the evening and night time. It interferes with activities requiring immobility, most prominently, sleep. Dopaminergic precursors (e.g. L-Dopa) and agonists (e.g. pramipexole, ropinirole, pergolide) have become first-line treatments for RLS over the past 10 years due to their extraordinary effectiveness in reducing these primary symptoms as well as periodic leg movements during sleep [1]. However, due to concerns regarding complications of L-Dopa, the longer acting dopaminergic

agonists have superseded this agent as the primary treatment for RLS.

The most common serious complication of L-Dopa treatment of RLS is 'augmentation', in which RLS symptoms appear earlier during the day, or less commonly, extend beyond the originally affected limbs [2]. Augmentation occurs in nearly 70% of those given L-Dopa for RLS [3] and can at times be quite severe, with patients' increasing the number and strength of L-Dopa doses and ending up with increasingly severe symptoms throughout the day. Previous reports suggest that the dopaminergic agonist pergolide less commonly produces augmentation than L-Dopa in the treatment of RLS [3–6].

The rate of augmentation with the newer dopaminergic agonists, ropinirole and pramipexole, is not well defined, though preliminary reports are available. Montplaisir [7] followed seven patients on pramipexole (mean dose = 0.5 mg) for a mean of 7.8 months and found continued benefit of this agent, without augmentation. Similarly, Ferini-Strambi [8]

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found that only 9 of 102 patients (9%) with RLS, followed for at least 6 months, had augmentation with pramipexole (mean dose = 0.4 mg). In both patient populations, pramipexole was given as a single dose at bedtime. On the other hand, Silber [9] described 50 patients treated with pramipexole for RLS who were followed for a mean of 13.1 months, nearly all of whom had failed previous dopaminergic treatment. Augmentation occurred in 18% of these patients at a mean duration of 8.5 months (range 2–16 months). Nearly two-thirds of those with augmentation to pramipexole had developed this complication with either L-Dopa or pergolide. In general, augmentation was easily managed by earlier medication dosing.

Another potential complication of long-term medication treatment is the need for larger doses of medication to maintain the original effect (tolerance). Earley and Allen [3] documented an increase in L-Dopa dose in 59% of patients with RLS followed for an average of 21 months. However, it is unclear from their data whether the L-Dopa dose was increased due to the development of augmentation or due to tolerance. It is unknown whether tolerance to the direct dopaminergic agonists develops or whether this process is related to that of augmentation for these agents. Defining the frequency of tolerance, and its relationship to augmentation, for dopaminergic treatments in RLS may be of value in understanding the physiology of therapeutic action of these agents. In addition, tolerance is a frequent concern of patients and physicians.

The aims of this study were to assess the long-term effects of pramipexole in the treatment of RLS. In particular, we were interested in the rates of augmentation and tolerance, and their interrelationship, with this agent.

2. Methods

Charts were reviewed for 72 consecutive patients begun on pramipexole treatment for RLS by the senior author. An RLS diagnosis was confirmed if the following criteria, established by the International Restless Legs Syndrome Study Group [10], were met: an urge to move the limbs, particularly the legs, usually associated with dysesthesia; motor restlessness; symptoms are worse with immobility and improve with movement; symptoms initially appear or worsen in the evening or at night. In addition, sleep disruption at least 3 nights per week as a result of RLS was required for this diagnosis.

Patients who were maintained on pramipexole for at least 6 months with regular clinical contact were eligible for entry into this retrospective naturalistic study. Those who had been on pramipexole less than 6 months at the time of this chart review ($N = 5$), or who discontinued pramipexole before 6 months of treatment due to side-effects or ineffectiveness ($N = 6$), or did not maintain regular contact ($N = 2$), were excluded from further analysis.

All patients had physical examinations and medical, psychiatric and sleep histories performed by the senior

author and filled out a standardized questionnaire regarding their sleep and medical histories. Polysomnography was performed in 66% (39/59) of these patients. Ferritin determinations were performed on all patients, and pramipexole dose was not considered stable until a ferritin level above 40 was achieved. Family history of RLS was determined by interview with the patient but was not corroborated by interviews with family members.

Demographic information, primary or secondary RLS, previous history of RLS treatment (including previous augmentation and/or tolerance), and concomitant prescription of other sleep or RLS medications were elicited from each patient. Baseline stable dose and timing of pramipexole administration was defined when adequate control of RLS symptoms was reported, which usually occurred on the first visit following initial pramipexole administration (most commonly 8 weeks after medication initiation). The course of RLS symptoms, any changes in pramipexole timing and/or dose, intercurrent medical or psychiatric symptoms, and sleep timing and quality were established on the basis of information from follow-up visits or telephone consultation, which generally occurred every 3 months after pramipexole was begun. Physician clinical global impression of initial response to pramipexole was graded as 1 (<50% response of RLS symptoms), 2 (50–75% response to pramipexole), 3 (75–99% response to pramipexole) and 4 (complete elimination of RLS symptoms with pramipexole), where RLS symptoms included sensory, motor and sleep symptoms.

Pramipexole dosing was performed in a standard fashion for all patients. Pramipexole was initiated at 0.125–0.25 mg, 2 h before symptom onset. L-Dopa was discontinued once pramipexole was initiated. Other medications (for RLS or for sleep) were tapered as tolerated over the first 2 months of dopaminergic agonist use. Pramipexole dose was increased by 0.125–0.25 mg every 4–7 days at the patient's discretion until symptoms were eliminated or nearly completely relieved. If, by patient report, symptoms returned, pramipexole dose was increased by 0.125–0.25 mg at the same time of administration (if symptoms occurred after medication dosing); or, if symptoms consistently (three or more times per week) began earlier than the time of dosing, the same dose was administered 1–2 h before symptom onset. A number of options were available if symptoms reappeared during nocturnal awakenings: (1) if pramipexole administration was before 6 pm, a second dose was added; (2) if the medication was administered at 6 pm or later, the evening dose of pramipexole was increased; or, (3) if these failed, additional medication (e.g. gabapentin, trazodone, benzodiazepine, opioid) was added to supplement the effects of pramipexole and/or assist with sleep maintenance.

Augmentation was defined as the need for earlier (by at least 2 h) administration of the same dose of pramipexole, due to an earlier appearance of RLS symptoms (at least 5 times per week), or a need to increase pramipexole dose due

to an extension of RLS symptoms beyond the originally affected area (e.g. from legs to arms) [12]. *Tolerance* was defined as the need for an increase in pramipexole dose due to the reappearance of RLS symptoms *after* medication administration.

For continuous variables, Student's *t*-test was used for normally distributed data; the Mann–Whitney rank sum test was employed for continuous variables without a normal distribution. The χ^2 test was used for categorical variables, and the Fisher exact test was used if the 2×2 table had very unequal or low values. An α of $P < 0.05$ was accepted as significant.

3. Results

Fifty-nine patients met inclusion criteria (see Table 1). Mean age was 60.8 years (± 14.4 ; range 31–91); 34 were female (58%), 25 were male (42%), 58 were Caucasian and 1 was Asian. Thirteen of the patients (22%) had secondary RLS (8 neuropathy, 2 end-stage renal disease, 1 Parkinson's, 1 anemia, 1 multiple sclerosis). Twenty percent (12/59) had a family history of RLS in a first-degree relative. The mean PLMS index was 46.6 (± 40.0) and the mean PLM arousal index was 14.7 (± 17.6).

Stable baseline doses were as follows: 18 patients (31%) were taking 0.125–0.25 mg of pramipexole daily, 29 (49%) were taking 0.375–0.5 mg, 9 (15%) were taking 0.625–0.75 mg, and 3 (5%) were using 1.0 mg or more per day. Seventy-six percent (44/58, with one unknown) of the patients had received previous L-Dopa treatment for their RLS. At the baseline visit, roughly 7% (4/59) were taking their first daily dose of pramipexole before noon (morning dose), 10% (6/59)

were taking it after noon and before 6 pm (evening dose) and 83% (49/59) were taking it at 6 pm or later (evening dose). Twenty percent (12/59), once stabilized, were taking pramipexole at least twice per day.

Pramipexole treatment was remarkably effective in alleviating RLS symptoms in this group of heterogeneous RLS patients. Average initial clinical response was 2.97 (± 0.83), indicating just under 75% reduction in RLS symptoms. Initial (baseline) response to pramipexole was not predicted by age or gender.

RLS patients in this sample took pramipexole continuously for an average of 21.2 (± 11.4) months (range 6–60 months). Augmentation requiring earlier time of medication administration developed in 32% of patients (19/59). Six patients changed their initial daily dose from an evening dose to an afternoon dose, two changed from an evening dose to a morning dose, two changed from an afternoon dose to a morning dose and seven patients changed their dose within the evening dosing period. Only one patient who required earlier dosing of pramipexole described extension of RLS symptoms to other limbs. Two patients who described only extension of symptoms to other limbs (i.e. without earlier appearance of symptoms) did not require a change in pramipexole dose or timing, and thus were not considered as cases of augmentation for the purposes of this study. At the last evaluation visit, 39% (23/59) of the sample were taking pramipexole at least twice per day, nearly double the number at baseline. In these patients, once augmentation developed and pramipexole was administered earlier, a second (evening) dose was required to maintain effectiveness throughout the evening and sleep period. However, the total daily dose was stable in all of these patients (except for one), as the same total dose

Table 1
Characteristics and response of patients taking pramipexole long-term for RLS

	Total sample	Augmentation with pramipexole		Tolerance with pramipexole	
		Yes	No	Yes	No
Number	59	19	40	27	32
Age (years)	60.8 (± 14.4)	62.5 (± 13.2)	60.0 (± 14.9)	63.0 (± 15.8)	58.9 (± 12.9)
Gender (% male)	25 (42)	9 (47)	17 (43)	10 (37)	15 (47)
Family history (%)	12 (20)	5 (26)	7 (18)	7 (26)	5 (16)
Diagnosis (primary RLS) (%)	46 (78)	15 (79)	31 (78)	20 (74)	26 (81)
Previous L-Dopa use (%)	44 (75)	12 (63)	32 (80)	21 (78)	23 (72)
Dose at baseline (mg/day)	0.47 (± 0.22)	0.47 (± 0.24)	0.46 (± 0.21)	0.43 (± 0.19)	0.49 (± 0.23)
Supplemental medications at baseline (%)	30 (51)	9 (47)	21 (53)	15 (56)	15 (47)
Initial response (1–4)	2.97 (± 0.83)	3.00 (± 0.94)	2.95 (± 0.78)	2.93 (± 0.91)	3.00 (± 0.76)
Duration of treatment (months)	21.2 (± 11.4)	24.4 (± 14.5)	19.7 (± 9.6)	24.5 (± 13.7) ^a	18.4 (± 8.2)
Extension of symptoms to arms (%)	3 (5)	1 (5)	2 (5)	1 (4)	2 (6)
Awakenings with RLS symptoms (%)	6 (10)	4 (21) ^b	2 (5)	5 (19) ^b	1 (3)
Supplemental medications at final visit (%)	35 (59)	11 (58)	24 (60)	15 (56)	20 (63)
Dose at final visit (mg/day)	0.66 (± 0.35)	0.82 (± 0.42) ^c	0.59 (± 0.30)	0.82 (± 0.38) ^d	0.52 (± 0.25)

^a $t = 2.1$, $P < 0.05$; ^b $\chi^2 = 4.53$, $P < 0.05$.

^b Fisher exact, $P = 0.08$.

^c $t = 690.5$, $P < 0.05$.

^d $t = 979.5$, $P < 0.01$.

Table 2
Augmentation and tolerance with pramipexole based on previous L-Dopa use

		Augmentation with pramipexole			Tolerance with pramipexole		
		Yes	No	Total	Yes	No	Total
Previous augmentation with L-Dopa ^a (<i>N</i> = 38)	Yes	9	15	24	14	10	24
	No	1	13	14	2	12	14
Previous tolerance with L-Dopa ^b (<i>N</i> = 34)	Yes	7	9	16	11	5	16
	No	1	17	18	2	16	18

Previous augmentation with L-Dopa (*N* = 38) increased the probability of both augmentation (Fisher exact, *P* = 0.06) and tolerance to pramipexole ($\chi^2 = 5.4$, *P* < 0.05). Previous tolerance with L-Dopa (*N* = 34) increased the probability of both augmentation (Fisher exact, *P* = 0.01) and tolerance to pramipexole ($\chi^2 = 9.6$, *P* < 0.05).

^a 6 unknown.

^b 10 unknown.

of medication was redistributed throughout the evening dosing period rather than requiring a dosage increase.

The mean time to the first episode of augmentation was 8.8 months (± 6.5). For two patients this occurred after 1–3 months on pramipexole, for six it occurred after 4–6 months, for eight it occurred after 7–12 months, and for two it occurred after greater than 12 months (for one patient this information could not be accurately determined). In five patients, augmentation continued to evolve over time, with a need to administer pramipexole earlier and earlier. Two additional patients taking pramipexole at 6 pm were also taking an early afternoon dose PRN (roughly every 2 weeks). Only one patient discontinued pramipexole due to the development of augmentation.

The only clinical variables assessed at baseline that were of statistical significance in predicting the eventual presence of augmentation to pramipexole were previous augmentation to L-Dopa (Fisher exact, *P* = 0.06) and previous tolerance to L-Dopa (Fisher exact, *P* = 0.01) (see Table 2).

Tolerance to pramipexole developed in 46% (27/59) of RLS patients. In these patients, mean total daily dose increased from 0.43 (± 0.19) mg to 0.82 (± 0.38) mg over the period of treatment. Duration of treatment was longer in the group with tolerance than that without tolerance (*t* = 2.1, *P* = 0.04), although there was no significant correlation between duration of pramipexole treatment and change in pramipexole dose.

The only clinical variables assessed at baseline that were of statistical significance in predicting the eventual development of tolerance were previous tolerance to L-Dopa ($\chi^2 = 9.6$, *P* = 0.002) and previous augmentation ($\chi^2 = 5.35$, *P* = 0.02) to L-Dopa (Table 2).

Augmentation and tolerance processes were statistically related, in that each of these complications was more common in individuals who developed the other one ($\chi^2 = 4.53$, *P* = 0.03; Table 3). For example, nearly one-half of those who developed tolerance to pramipexole also developed augmentation, whereas less than one in five who did not develop tolerance showed augmentation.

New onset of morning symptoms ('rebound') was not reported by those on long-term pramipexole treatment.

On the other hand, 10% of patients had persistent symptoms of RLS after sleep onset, with this being more common in those with augmentation (4/19) compared to those without augmentation (2/40) (Fisher exact, *P* = 0.08), and in those with tolerance (5/27) compared to those without tolerance (1/32) (Fisher exact, *P* = 0.08).

Most (35/59 or 59%) patients taking pramipexole were also taking one or more additional medications to assist with RLS symptom control or sleep difficulties (sedating antidepressants = 15, gabapentin = 14, benzodiazepines = 7, opioid = 11). The majority of these patients (86%, 30/35) were on such medications at the baseline visit. There were no statistically significant differences in rates of augmentation or tolerance between those patients receiving additional medications versus those not getting such agents.

4. Discussion

This naturalistic case series provides the first detailed description of a large group of patients treated with pramipexole long-term for RLS. We found a rate of augmentation (32%) requiring earlier pramipexole administration, which was higher than that had been preliminarily reported for this agent, though similar to that described for pergolide, another dopaminergic agonist. What could account for this disparity between our results and those of others using pramipexole? Given Allen and Earley's [2,3] finding that the pretreatment severity of RLS predicted the subsequent appearance of augmentation, it is possible that

Table 3
Augmentation and tolerance with pramipexole

		Augmentation		
		No	Yes	
Tolerance	No	26	6	32
	Yes	14	13	27
		40	19	

$\chi^2 = 4.53$, *P* < 0.05.

our patients had more severe RLS than in previous reports investigating this phenomenon with pramipexole. Although we were unable to assess severity of RLS at baseline, as patients were immediately transitioned from previous RLS treatments to pramipexole without a baseline washout period, we did assess two corollaries of severity: time of initial daily dose of pramipexole [11] and the need for supplemental medications to control RLS. Neither of these potential indicators of RLS severity predicted the development of augmentation. Similarly, the baseline dose of pramipexole was not different in those with, versus those without, augmentation. These data suggest that our higher rates of augmentation with pramipexole are not related to a greater severity of RLS in our patient population.

The time course of augmentation observed in this case series (mean of 8.8 months) is nearly identical to that observed by Silber et al. [9]. On the other hand, Ferini-Strambi [8] found that no cases of augmentation occurred in his 102 patients after 15 weeks. Of note is that Silber found an augmentation rate more similar to ours than Ferini-Strambi did. Features of the patient population or of the methodology used in our study may be more similar to those of Silber than of Ferini-Strambi, accounting for these disparities.

Although the rate of augmentation found in our sample is higher than that previously found with pramipexole, it is lower than the 50% of patients who required an earlier time of L-Dopa administration in the original prospective case series describing augmentation [2]. Importantly, the course of pramipexole augmentation also appears to be less severe than that observed with L-Dopa. For most patients, augmentation was manageable by earlier, or twice per day, dosing. Few (3/59) patients had to adjust pramipexole dosing earlier more than once, and only one patient discontinued pramipexole due to augmentation. On the other hand, the nature of augmentation with pramipexole was similar to that observed with previous medications. Earlier appearance of RLS symptoms, and not extension of RLS to other body parts, was the principal manifestation of augmentation. In our study, only 5% (3/59) of patients had anatomical extension of symptoms, two of whom did not have concurrent temporal extension of symptoms. Those two patients did not require a medication increase.

Plasma half-life is, at this time, considered to be the major predictor of the augmentation propensity of a dopaminergic agent for the treatment of RLS [4]. Thus, it is not surprising that augmentation would be less frequent and less severe with pramipexole than with L-Dopa, given the much longer half-life (8–12 h) of the former agent. In addition, and again consistent with the long half-life of pramipexole, morning rebound or nocturnal breakthrough of RLS symptoms was either not seen or rare.

According to the most recent definition of augmentation [12], it is ambiguous as to whether a diminished response to a given dose of pramipexole (tolerance) is an independent phenomenon or a subtype of augmentation. If we had

included tolerance as an aspect of augmentation, 56% (33/59) of our sample would have had this complication. We distinguished these two phenomena for a number of reasons: (1) nearly all previous reports on augmentation have not included tolerance as a subtype of augmentation; (2) there is already a substantial literature on tolerance in pharmacology, denoting a decreased drug effect over time; and (3) although the biology of tolerance and augmentation may be similar (as our finding of a substantial overlap between the two processes suggests), further research will be required to determine the relationship between these two phenomena.

There are a number of limitations of this study that must be considered when interpreting the results. Some of the data (e.g. initial clinical response to pramipexole) were retrospectively inferred from chart review. However, the primary outcome variables in the study (augmentation and tolerance) were determined from the dose and time of administration of pramipexole. Although this allows for clearly operationalized definitions of augmentation and tolerance available in the patients' charts, it is possible that the rates of these two processes may reflect a systematic clinician bias in the decision to change the timing or the dose of pramipexole. It should be noted however that our standard for augmentation is more stringent than that used in previous studies on the subject, which did not require a change in time of administration but rather only a description of earlier appearance of symptoms. To more carefully assess augmentation and tolerance processes, future studies should assess RLS symptoms longitudinally under controlled conditions, using both subjective (diary) and objective (Suggested Immobilization Test) measures [13–15].

Because this was a naturalistic study, and not a clinical trial, most patients were using other RLS treatments immediately before and during pramipexole treatment. This prevents us from making definitive conclusions regarding the specific effects of pramipexole on RLS symptoms. In particular, augmentation and tolerance rates may have been systematically influenced by these other medications, either because they increased the likelihood of these complications or because they may have masked them. For instance, although previous L-Dopa use did not predict augmentation or tolerance, we did find statistical evidence that prior augmentation to L-Dopa was associated with augmentation to pramipexole. Another possibility is that addition of medications during the course of the treatment period may have been used to treat augmentation and tolerance. It is unclear whether the net effect of these other medications before and during pramipexole treatment would be to increase or decrease the apparent augmentation and tolerance rates. In the future, long-term studies of supplemental medications for RLS should be performed in the absence of the augmentation and tolerance processes.

The apparent development of augmentation and tolerance in our patients may alternatively either represent

the natural progression of RLS or a manifestation of fluctuations in underlying disease severity, rather than a complication of pramipexole treatment. Although we did not find a correlation between augmentation or tolerance and duration of pramipexole treatment, the long-term, uncontrolled nature of this study does not allow us to distinguish between these alternate interpretations of the results.

It is unclear to what extent these results can be generalized to the general population of individuals with RLS. Our patients were seen in a tertiary care setting, were composed of a heterogeneous group with primary and secondary RLS, included both treatment naïve and non-naïve patients, and included patients on monotherapy with pramipexole and polypharmacy. The effects of such heterogeneity on augmentation and tolerance rates are unclear. Future assessments of augmentation should use careful indices of baseline severity, such as the International Restless Legs Severity Scale or the Suggested Immobilization Test, as well as more homogenous patient populations.

In summary, augmentation and tolerance were observed in roughly one-third and one-half (respectively) of individuals with RLS treated with pramipexole for a mean of 2 years. Augmentation occurred on average 8 months after initiation of treatment. It was usually managed by earlier administration of pramipexole, and only rarely led to discontinuation of this treatment. Although this naturalistic study lacks the rigor of a clinical trial, it provides long-term data on the use of pramipexole unavailable in such clinical trials. Assessment of augmentation and tolerance under controlled conditions may produce insights into dopaminergic responsiveness and may eventually lead to a better understanding of the underlying pathophysiology of RLS.

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