Factors Affecting the Efficacy of Pramipexole in Patients with Restless Legs Syndrome

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Abstract- Dopamine agonists, particularly nonergot dopamine agonists such as pramipexole, have become the mainstay of therapy for patients with symptoms of restless legs syndrome (RLS). This study was designed to evaluate the factors affecting the efficacy of pramipexole in patients with RLS. Fifty-nine eligible RLS patients referred to neurology clinic of Rasoul-e-Akram Hospital (Tehran, Iran) were recruited in this study. All of the patients received an oral dose of 0.18 mg pramipexole. The severity of RLS symptoms were evaluated including sleep disorder, symptomatic days per week and symptomatic hours per day, both at the beginning and at the end of follow-up time. Different baseline and follow-up variables were also recorded and their relationships with the outcomes were assessed. The mean severity values of different symptoms significantly decreased after treatment with pramipexole (P<0.001). Female gender (P<0.05) and duration of treatment (P<0.05) were significant factors to achieve >50% reduction in symptomatic days per week and symptomatic hours per day. Moreover, the cutoff point of 3.5 *mo* for duration of treatment could potentially differentiate >50% reduction in severity of sleep disorder from the ones with <50% reduction with sensitivity and specificity of 56.8% and 78.6%, respectively. Our findings show that female gender and duration of treatment were the factors affecting the effectiveness of pramipexole in RLS patients. If tolerated by the patients, a longer duration of treatment with pramipexole is more effective in RLS.

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Keywords: Efficacy; Pramipexole; Restless legs syndrome (RLS); Treatment

Introduction

Restless legs syndrome (RLS) is a common, distressing movement disorder, yet many sufferers are not diagnosed or managed adequately. This sensorimotor disorder affecting approximately 12% of the adult population (1, 2). The prevalence of RLS among Iranian patients who referred to neurology and orthopedic outpatient clinics was 9.7% and 11%, respectively, whereas, only 2.7% patients were admitted with chief complaint of RLS symptoms (3).

Restless legs syndrome is characterized by dysesthesia and an irresistible urge to move the legs, which may begin or worsen during periods of rest or inactivity and often affects sleep (4). Consequently, RLS often impacts patients' daytime functioning and therefore, is a major source of morbidity and lost productivity (5).

Treatment of RLS ranges from elimination of the predisposed factors (*e.g.* Iron deficiency and certain medications), through other nonpharmacologic measures (*e.g.* abstinence from caffeine, nicotine and alcohol) to pharmacotherapy (6). Until now, there have been limited pharmacologic treatment options available to alleviate the symptoms of RLS, which can significantly impact patients' quality of life. However, dopamine agonists, particularly nonergot dopamine agonists (NEDAs), have become the mainstay of therapy for patients with daily symptoms of RLS (7).

Pramipexole is an oral, nonergot dopamine agonist with a high selectivity for the dopamine D_2 and D_3 receptors, which was approved in the EU and the US for the treatment of idiopathic RLS in adults in 2006. Some evidences show that pramipexole is efficacious for

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treating RLS symptoms in patients with moderate to severe clinical RLS (8-12). Regardless of the effects of pramipexole on the symptoms of RLS, the factors affecting these effects are not still clearly defined. Therefore, this study was designed to answer this question and evaluate the factors affecting the efficacy of pramipexole in patients with RLS.

Materials and Methods

Subjects

This prospective study was conducted on a case series of 59 RLS patients referred to neurology clinic of Rasoul-e-Akram Hospital in Tehran, Iran, during the years 2005-2008. Eligible subjects were recruited with a consecutive enrolment of patients affected by restless legs syndrome (RLS). The diagnosis of RLS was established following the International Restless Legs Syndrome Study Group's (IRLSSG) revised criteria (4,13). Additionally, only patients free of medication at the time of the study, and never treated before for RLS (including dopaminergic agents, benzodiazepines, opioids, and anticonvulsants) were included in the study.

Reasons for exclusion were: other sleep disorders (*e.g.* narcolepsy, sleep terrors, sleepwalking, sleep disordered breathing), other movement disorders, or any other medical conditions that would affect the assessment of RLS. Pregnancy was another exclusion criterion (Figure 1).

This study has been accepted by the ethics committee of Iran University of Medical Sciences and all researchers undertake Helsinki's treaty.

Clinical assessments

The patients received an oral dose of 0.18 mg pramipexole (Sifrol, Boehringer Ingelheim, Germany). It was initiated with a half tablet of pramipexole, increased to a single full tablet after one week and to the maximum dose of two pills, received 2 hours before sleeping time. All patients underwent neurological examination with a one group of neurologists. Baseline and demographic characteristics were recorded for each patient including: current age and age at the onset of symptoms, family history of RLS and comorbidities (*e.g.* diabetes mellitus, hypothyroidism, hyperthyroidism, anemia, rheumatoid arthritis, renal failure, cancer, gastrectomy, uterine myoma etc).

The severity of RLS symptoms were evaluated using a 5-stage Likert scale questions both at the beginning and at the end of follow-up time. These were consisted of severity of sleep disorder (0=nothing, 1=mild, 2=moderate, 3=severe, 4=very severe), symptomatic days per week (0=nothing, 1=1 day, 2=2-3 days, 3=4-5 days, 4=6-7 days) and symptomatic hours per day (0=nothing, 1=less than 1 hour, 2=1-3 hours, 3=3-8 hours, 4=more than 8 hours). This was a simple list of questions; however, it was validated in our patients.

In addition, the duration of treatment and probable side effects (*e.g.* hallucination, sleepiness, orthostatic hypotension, nausea and vomiting, dyskinesia, insomnia and nightmares) were also questioned and recorded.

Regarding <50% or >50% relief or reduction in the severity of different symptoms, data were compared in different study groups.

Statistical analysis

The data were analyzed using SPSS v.16 software for Windows (Chicago, USA). In descriptive reports, parameters such as frequency, mean, mode and standard deviation (SD) were used. The analyses were performed using statistical tests. Kolmogronov Smirnov (KS) test was performed to evaluate normal distribution of the quantitative variables. To test the differences between non-parametric variable means in the two study groups, Mann–Whitney U-test and independent t-test were performed. Also, Chi-square and Fisher's exact tests were used for qualitative variables; and Wilcoxon rank test was performed to evaluate the within group changes of quantitative variables. Binary logistic regression analysis was used to evaluate the effects of different factors to predict different study outcomes.

Moreover, Receiver operating characteristics (ROC) curve analysis was performed to assess the predictability of <50% or >50% relief or reduction in the severity of different symptoms with quantitative values of the study, and the area under curve (AUC) and appropriate cutoff point were determined. Diagnostic values (*e.g.* sensitivity and specificity) of each cutoff point were also calculated.

A 5% probability of a type I error (two-tailed), and a power of 80% were considered in the analysis. All reported *P*-values are two-tailed.

Results

Baseline characteristics

The patients were consisted of 40 (67.8%) female and 19 (32.2%) male with the mean age of 53.15 (SD=12.10) yr ranges between 19 to 80 yr. The mean age at the onset of RLS symptoms was 38.93 (SD=15.71) yr and family history of RLS was reported in 23 (39%) of the cases. As shown in table 1, the most

common comorbid diseases were hypothyroidism and anemia in 8 (13.6%) patients. In addition, the most frequent scale for severity of sleep disorder, symptomatic days per week and symptomatic hours per day were "very severe" in 32 (54.2%), "6-7 days per week" in 43 (72.9%) and "3-8 hours per day" in 26 (44.1%) patients, respectively. The mean of quantitative values of these variables are also listed in table 1.

Follow-up assessment

The mean follow-up time of the patients was 8 months. As shown in table 1, the mean severity values of different symptoms decreased after treatment with pramipexole and the results of Wilcoxon rank test showed that these reductions were statistically significant (P<0.001). The mean percentage of reduction in severity of sleep disorder, symptomatic days per week and symptomatic hours per day were 67.16% (SD=38.92), 52.68% (43.70) and 56.50% (SD=41.84), respectively.

Fourteen patients (23.7%) had different side effects during treatment period. The most common side effects were sleepiness [in 8 (13.6%)], nausea and vomiting [in 3 (5.1%)], nightmares [in 3 (5.1%)], hallucination [in 2 (3.4%)] and insomnia [in 1 (1.7%)], respectively.

Regarding the 50% reduction in the severity of different symptoms as a treatment goal, table 2 shows the comparison of different factors among patients with <50% or >50% reduction after treatment. As illustrated in table 2, female RLS patients were significantly more achieved to >50% reduction in severity of sleep disorder (42.9% vs. 75.7%, P=0.027). Also, duration of treatment was significantly longer in patients with >50% reduction in severity of sleep disorder [4.41 (SD=6.34) *vs.* 10.45 (SD=10.71) *mo*, P=0.028]; while, the frequency of side effects was not statistically significant (P=0.082). Similar findings were observed for the other two indexes of disease severity. Female patients were significantly more achieved to >50% reduction in symptomatic days per week (50% *vs*. 80%, P=0.015) and symptomatic hours per day (47.6% *vs*. 78.9%, P=0.014), too. Additionally, duration of treatment was significantly longer in patients with >50% reduction in severity of symptomatic days per week [4.58 (SD=6.43) *vs*. 10.30 (SD=10.68) *mo*, P=0.021] and symptomatic hours per day [3.80 (SD=5.26) *vs*. 10.28 (SD=10.62) *mo*, P=0.010]. The incidence of side effects was also not statistically significant between the two groups (P>0.05).

In binary logistic regression analysis, female gender (*Exp(B)*=0.25, P=0.027) and duration of treatment (*Exp(B)*=1.1, P=0.044) were significant factors to achieve >50% reduction in symptomatic days per week (Model P=0.004). Moreover, female gender (*Exp(B)*=0.24, P=0.025) and duration of treatment with pramipexole (*Exp(B)*=1.1, P=0.032) were also significant factors to achieve >50% reduction in symptomatic hours per day (Model P=0.001).

Table 1. Demographic and follow-up variables in all patients.

Variable	*P*-value
Age at the onset of disease (year) *mean* ± *SD*	38.93 ± 15.71
Current age (year) *mean* ± *SD*	53.15 ± 12.10
Gender distribution (%)	
Male	19 (32.2%)
Female	40 (67.8%)
Family history of RLS (%)	23 (39%)
Comorbidities (%)	
Diabetes Mellitus	3 (5.1%)
Hypothyroidism	8 (13.6%)
Anemia	8 (13.6%)
Duration of treatment (month) *mean* ± *SD*	7.97 ± 9.55
Severity of sleep disorder (baseline) *mean* ± *SD*	3.00 ± 1.40
Severity of sleep disorder (after treatment) *mean* ± *SD*	0.97 ± 1.29
Symptomatic days/week (baseline) *mean* ± *SD*	3.56 ± 0.79
Symptomatic days/week (after treatment) *mean* ± *SD*	1.64 ± 1.56
Symptomatic hours/day (baseline) *mean* ± *SD*	3.17 ± 0.77
Symptomatic hours/days (after treatment) *mean* ± *SD*	1.36 ± 1.35
Side effects (%)	14 (23.7%)

Table 2. Comparison of different factors among patients with <50% or >50% reduction after treatment.

Variable	Relief in the severity of sleep disorder		*P*-value	Reduction of symptomatic days/week		*P*-value	Reduction of symptomatic hours/day		*P*-value
	<50% n=14	>50% n=37		<50% n=24	>50% n=35		<50% n=21	>50% n=38	
Age at the onset of disease (year) *Mean ± SD*	37.4 ± 14.7	36.4 ± 14.7	0.821	39.6 ± 16.1	38.5 ± 15.6	0.782	40.9 ± 16.6	37.9 ± 15.3	0.489
Current age (year) *Mean ± SD*	51.8 ± 10.9	51.9 ± 12.2	0.966	54.1 ± 11.8	52.5 ± 12.4	0.613	53.76 ± 12.4	52.8 ± 12.1	0.776
Gender distribution (%)									
Male	8 (57.1%)	9 (24.3%)	0.027*	12 (50%)	7 (20%)	0.015*	11 (52.4%)	8 (21.1%)	0.014*
Female	6 (42.9%)	28 (75.7%)		12 (50%)	28 (80%)		10 (47.6%)	30 (78.9%)	
Family history of RLS (%)	5 (35.7%)	18 (48.6%)	0.407	9 (37.5%)	14 (40%)	0.847	7 (33.3%)	16 (42.1%)	0.508
Comorbidities (%)									
Diabetes Mellitus	0	3 (8.1%)	0.552	0	3 (8.6%)	0.264	0	3 (7.9%)	0.546
Hypothyroidism	2 (14.3%)	5 (13.5%)	1	3 (12.5%)	5 (14.3%)	1	3 (14.3%)	5 (13.2%)	1
Anemia	0	5 (13.5%)	0.305	3 (12.5%)	5 (14.3%)	1	2 (9.5%)	6 (15.8%)	0.699
Duration of treatment (month) *Mean ± SD*	4.41 ± 6.34	10.45 ± 10.71	0.028*	4.58 ± 6.43	10.30 ± 10.68	0.021*	3.80 ± 5.26	10.28 ± 10.62	0.010*
Severity of sleep disorder (baseline) *Mean ± SD*	3.36 ± 0.74	3.51 ± 0.80	0.338	2.58 ± 1.56	3.29 ± 1.23	0.039*	2.43 ± 1.60	3.32 ± 1.19	0.015*
Severity of sleep disorder (after treatment) *Mean ± SD*	3.00±0.68	0.41 ± 0.60	<0.001*	1.88 ± 1.45	0.34 ± 0.64	<0.001*	2.00 ± 1.52	0.39 ± 0.64	<0.001*
Symptomatic days/week (baseline) *Mean ± SD*	3.43 ± 0.85	3.70 ± 0.70	0.200	3.42 ± 0.88	3.66 ± 0.72	0.295	3.33 ± 0.91	3.68 ± 0.70	0.118
Symptomatic days/week (after treatment) *Mean ± SD*	3.21 ± 0.89	1.00 ± 1.33	<0.001*	3.29 ± 0.86	0.51 ± 0.66	<0.001*	3.24 ± 0.89	0.76 ± 1.08	<0.001*
Symptomatic hours/day (baseline) *Mean ± SD*	2.86 ± 0.77	3.24 ± 0.68	0.097	3.04 ± 0.86	3.26 ± 0.70	0.373	3.05 ± 0.92	3.24 ± 0.67	0.527
Symptomatic hours/days (after treatment) *Mean ± SD*	2.71 ± 0.91	0.65 ± 0.82	<0.001*	2.67 ± 1.05	0.46 ± 0.56	<0.001*	2.90 ± 0.89	0.50 ± 0.56	<0.001*
Side effects (%)	1 (7.1%)	12 (32.4%)	0.082	3 (12.5%)	11 (31.4%)	0.125	2 (9.5%)	12 (31.6%)	0.108

ROC curve analysis

More detailed analysis was performed to find out the optimal duration of treatment in RLS patients. As shown in figure 2, duration of treatment with pramipexole had the AUC of 0.699 (*P*=0.030) to predict >50% reduction in severity of sleep disorder in RLS patients. The cutoff point of 2.5 *mo* for duration of treatment could potentially differentiate >50% reduction in severity of sleep disorder from the ones with <50% reduction with sensitivity and specificity of 78.4% and 50%, respectively. In addition, the cutoff point of 3.5 *mo* has the sensitivity and specificity of 56.8% and 78.6%, respectively.

Figure 3 shows that duration of treatment with pramipexole had the AUC of 0.676 (*P*=0.023) to predict >50% reduction in symptomatic days per week. The cutoff point of 3.5 *mo* for duration of treatment could potentially differentiate >50% reduction in symptomatic days per week from the ones with <50% reduction with sensitivity and specificity of 54.3% and 75%, respectively. In addition, the cutoff point of 4.5 *mo* has the sensitivity and specificity of 51.4% and 79.2%, respectively. Figure 4 shows that duration of treatment with pramipexole had the AUC of 0.702 (*P*=0.011) to predict >50% reduction in symptomatic hours per day. The cutoff point of 3.5 *mo* could potentially differentiate patients with >50% reduction in symptomatic hours per day from the ones who had <50% severity reduction with sensitivity and specificity of 55.3% and 81%, respectively.

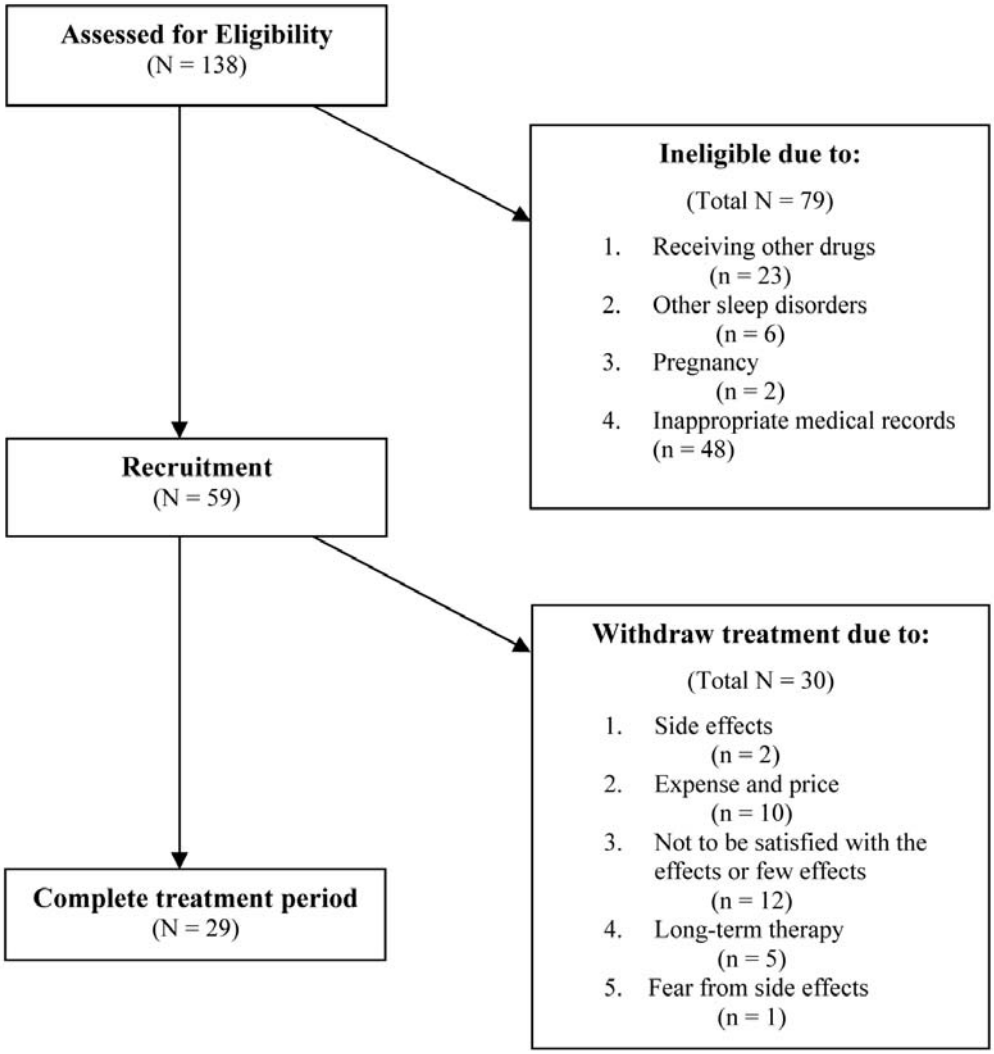

Figure 1. Flow diagram of recruitment and the follow-up of RLS patients.

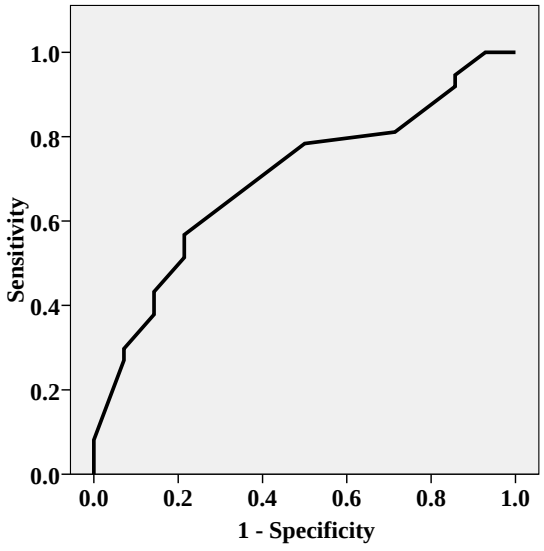

Figure 2. Receiver operating curve (ROC) analysis of duration of treatment with pramipexole to achieve at least 50% relief in the severity of sleep disorder in patients with RLS (Area under curve=0.699, *P*=0.030).

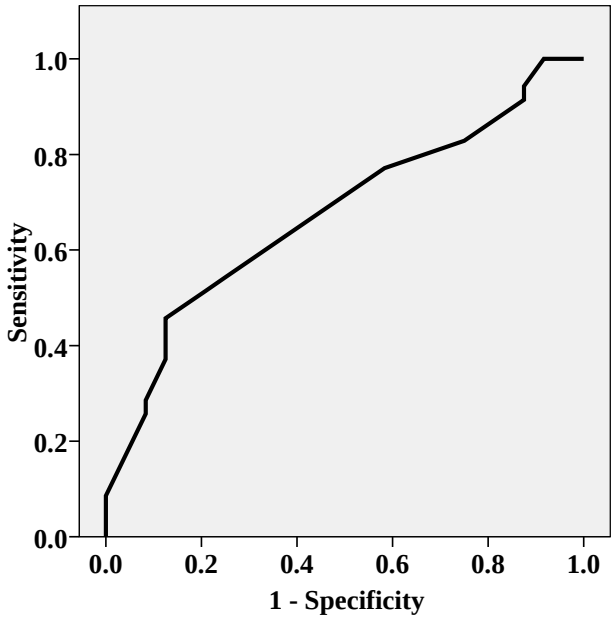

Figure 3. Receiver operating curve (ROC) analysis of duration of treatment with pramipexole to achieve at least 50% reduction in the number of symptomatic days per week in patients with RLS (Area under curve=0.676, *P*=0.023).

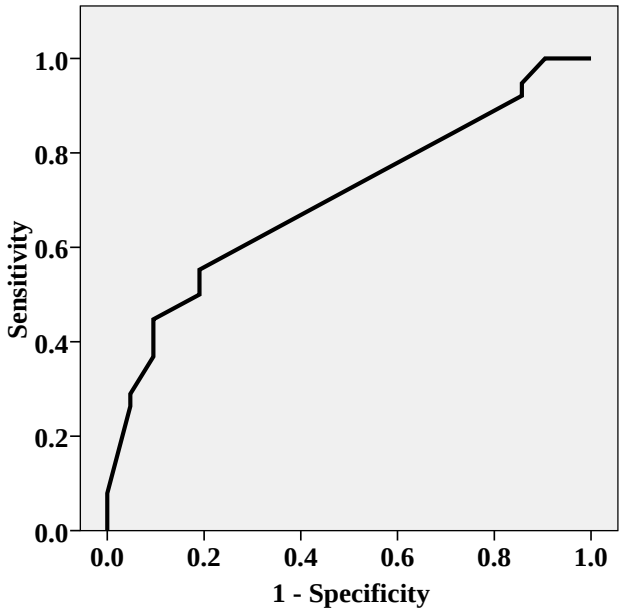

Figure 4. Receiver operating curve (ROC) analysis of duration of treatment with pramipexole to achieve at least 50% reduction in the number of symptomatic hours per day in patients with RLS (Area under curve=0.702, *P*=0.011).

Discussion

Not only the effects of pramipexole on the severity of symptoms in RLS was evaluated in our study, but, also the factors affecting this effectiveness were assessed. Our results show that severity of sleep disorders, symptomatic days per week and symptomatic hours per day were all decreased after treatment with pramipexole. Moreover, female gender and a longer duration of treatment were the factors affecting this effectiveness.

Two currently published meta-analysis have evaluated the results of numerous clinical trials on the efficacy of pramipexole in RLS patients (7,14). Including the results of 14 trials, Baker *et al*. (7)

concluded that use of NEDAs in patients with moderate-to-severe RLS resulted in significant reductions in symptom severity, but a significant portion of patients will discontinue their use as a result of adverse events. These trials were all evaluating the effects of NEDAs with placebo. Another meta-analysis by Quilici *et al.* (14) gathered trials comparing the effects of pramipexole versus ropinirole and placebo. The direct meta-analysis confirmed superior efficacy for both treatments versus placebo. Placebo comparisons showed a significantly higher incidence of nausea for pramipexole ($P<0.01$), whereas nausea, vomiting, dizziness, and somnolence were significantly higher for ropinirole (all $P<0.01$). Finally, they concluded that differences in efficacy and tolerability favouring pramipexole over ropinirole can be observed.

As shown in our study, 23.7% had different side effects during treatment period with pramipexole and the most common side effects were sleepiness (13.6%), nausea and vomiting (5.1%).

Recent studies further confirmed that pramipexole is generally well tolerated, with most adverse events being transient and of mild to moderate severity (15). However, Baker *et al.* (14) believed that the beneficial effects of NEDAs must be weighed against a statistically significant increase in withdrawals resulting from adverse events, as well as an increased incidence of individual adverse events. They added when evaluated separately, ropinirole significantly increased the number of withdrawals that were due to adverse effects and significantly increased the risk of nausea, dizziness, somnolence, and fatigue compared with placebo. In contrast, pramipexole did not increase the risk of withdrawals because of adverse effects and only increased nausea risk compared with placebo (14). In our study, only two patients (3.4%) withdrew treatment due to adverse effects and therefore, it is concluded that pramipexole was well tolerated.

Comparing with a 12-week study by Ferini-Strambi *et al*. (16) which nine percent of patients withdrew because of adverse events, the frequency of side effects was lower in our study. Even using a wide range of treatment dosage (0.125-0.75 mg/d) of pramipexole during a 3-week study period, Partinen *et al*. (9) showed that pramipexole was well tolerated and did not produce somnolence at any dose. In another study by *et al*. (17) it was concluded that no dose-dependent increase in adverse events of pramipexole, and no drug-related increase in daytime somnolence was observed.

Our results show that one of the most important factors affecting the efficacy of pramipexole on RLS symptoms was the duration of treatment. In a way that, the longer the treatment period is, the higher reduction in the severity of symptoms is occurred. In contrast, Baker *et al*. (7) explained the qualitatively greater improvements with pramipexole by the relatively short duration of pramipexole studies (3 to 6 weeks), because they believed it is during this time the drug's effects are most prominent; and also the beneficial effects of NEDAs, in terms of improvements in IRLS scores from baseline, are most prominent during the first few weeks of therapy ($P<0.001$). They added that these effects appear to diminish somewhat in trials evaluating a 12-week treatment period (7). On the other hand, some previously conducted longer-term follow-up extension studies (up to 2 years) have shown that NEDAs maintain their beneficial effects, although augmentation was seen in 33% to 50% of patients (18-20). In a 26-week, open-label trial by Partinen *et al.* (21) also it was shown that pramipexole is well tolerated and effective for long-term treatment of RLS. In addition to these findings, our study suggests that a treatment period of more that 3.5 months (14 weeks) could potentially lead to a higher reduction in severity of most of the symptoms in RLS patients.

However, as some others also declare (7), these results must be interpreted cautiously, given that confounders other than study duration may have an impact on effectiveness of pramipexole.

For the first time in literature, we have found a gender difference in the efficacy of pramipexole on the symptoms of patients with RLS. As shown in our study, female patients were significantly more achieved to a higher reduction rate in sleep disorder, symptomatic days per week and symptomatic hours per day. Only a few studies have evaluated the sex differences in pramipexole effects in Parkinson's disease patients. Kompoliti *et al.* (22) showed that significant sex differences occurred in the levodopa pharmacokinetic measures in Parkinson's disease; whereas, these sex differences were not seen in pramipexole pharmacokinetics. Experimental data suggest complex actions of estrogens in the basal ganglia with enhancement or suppression of striatal dopamine functions (23). Although pramipexole is absorbed by simple bulk diffusion and is eliminated without undergoing significant metabolism (24), more pharmacokinetic studies are needed to explain sex differences in its effectiveness in RLS patients.

To the best of our knowledge, our single group prospective study is one of the first to assess the factors affecting the efficacy of pramipexole in RLS patients.

Despite some limitations which may influence our results including small sample size, consecutively single center selection of the patients and not evaluating more confounding factors; we show that female gender and duration of treatment were significant factors to achieve a higher reduction rate in severity of symptoms. Additionally, the long-term treatment period and the recommended cutoff points for this duration are other considerable aspects of our study. Conclusively, if tolerated by the patients, a longer duration of treatment with pramipexole is more effective in RLS and also more studies are needed to evaluate the sex differences in the efficacy of this drug in patients with RLS.

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