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ORIGINAL RESEARCH

Comparison of nocturnal symptoms in advanced Parkinson's disease patients with sleep disturbances: pramipexole sustained release versus immediate release formulations

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Background: Nocturnal symptoms are common in Parkinson's disease (PD), which greatly affect the quality of life but are often overlooked in clinical settings. Treatment strategies that provide sustained dopaminergic stimulation may have sleep benefits.

Objective: To investigate the treatment effects of pramipexole (PPX) sustained release (SR) versus PPX immediate release (IR) on nocturnal symptoms in advanced PD patients with sleep disturbances.

Materials and methods: In this study, the PPX clinical trial (NCT00466167) was retrospectively analyzed for PD Sleep Scale (PDSS) total and domain scores in patients with advanced idiopathic PD receiving either PPX SR or PPX IR, who experienced motor fluctuations while on stable levodopa with a baseline PDSS total score of <90, indicating sleep disturbances. Analysis of covariance test was used to compare the adjusted mean changes at week 18 from baseline between treatment groups, after adjusting for pooled country and baseline scores.

Results: A total of 119 patients with PD reported sleep disturbances at baseline (PDSS <90; SR, n=59; IR, n=60). At week 18, patients receiving PPX SR reported numerically greater improvement of sleep disturbance than those receiving PPX IR, although the difference of 6.8 points was not statistically significant (adjusted mean changes in PDSS total score, SR=28.5 versus IR=21.7 points, P=0.165). Patients receiving PPX SR observed a numerically greater adjusted mean change in all PDSS domains compared with PPX IR. The overall proportions of patients with any adverse event were similar between both PPX SR and IR groups (62.7% versus 70.0%).

Conclusion: Both the PPX formulations showed improvements in nocturnal symptoms in advanced PD patients with sleep disturbances and were generally well tolerated. Given the known pharmacokinetic profile of an SR formulation and numerical advantage in PDSS mean change over IR formulation, these preliminary evidences support future prospectively designed studies to investigate the effects of PPX SR for improved sleep.

Keywords: dopamine agonist, efficacy, nonmotor symptoms, Parkinson's disease, Parkinson's Disease Sleep Scale, pramipexole extended release

Plain language summary

Beyond motor disabilities, patients with Parkinson's disease (PD) are also greatly impacted by nonmotor symptoms including sleep disturbances. Dopamine receptor agonists such as pramipexole (PPX) are the first-line treatment for PD; however, most studies focus on daytime treatment effects. Therapies that can ensure a constant stimulation of dopamine receptors throughout the night may help reduce nocturnal motor symptoms and improve sleep. This retrospective

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exploratory analysis investigated sleep outcomes of PPX sustained release versus immediate release in 119 adult patients with advanced PD experiencing motor fluctuations despite taking levodopa and reported sleep disturbances at baseline, which were identified from a Phase III PPX clinical trial (NCT00466167). The patients completed the PD Sleep Scale for sleep problems before and at the end of the 18-week treatment period; daytime sleepiness and adverse events were also recorded for safety evaluation. After 18 weeks of treatment, both the PPX formulations showed improvements in nocturnal symptoms and were generally well tolerated. Further research is necessary to investigate the effects of PPX sustained release for improved sleep in this clinical population.

Introduction

The impact of nonmotor symptoms of Parkinson's disease (PD) on patients' quality of life is comparable to the impact of the characteristic motor symptoms of PD.[1,2] Sleep disturbances are one of the major nonmotor complaints, and they often manifest even before the clinical onset of PD.[2,3] These sleep problems may worsen with disease progression and deterioration of motor-related abilities.[4–6] It is estimated that 74%–98% of patients exhibit symptoms of sleep disturbances, including insomnia, abnormal movements during sleep (eg, periodic leg movements and rapid eye movement sleep behavior disorders), and excessive daytime sleepiness.[1,6] However, sleep disturbances are often overlooked in clinical settings and are poorly examined in PD research.

Dopamine has a complex role in the sleep–wake cycle; therefore, several aspects of sleep-related problems are possibly related to dopamine.[7] As a common first-line strategy for treating PD, the use of dopamine receptor agonists such as pramipexole (PPX) may help with the sleep architecture and also improve nocturnal motor symptoms. Research has shown that treatment that is delivered continuously provides more constant stimulation of striatal dopaminergic receptors, which is associated with greater reduction in risk of motor complications and sleep disturbances, than the intermittent, short-acting dopaminergic agents.[6,8]

PPX, approved in the US and Europe since 1998 for both early and advanced PD, is a nonergot dopamine agonist with selective affinity for dopamine receptor of the D_2/D_3 subfamily. The early formulation is available as immediate release (IR) tablets and is orally administered three times daily due to the half-life of 8–12 hours. Since 2010, PPX has been available as once-daily sustained release (SR) formulation to meet the needs of patients, clinicians, and caregivers for an effective but simplified treatment regimen. Both PPX SR and IR contain the same active substance and possess identical receptor profile, efficacy, and receptor binding;[9,10] furthermore, the bilayer push–pull osmotic tablet of PPX SR ensures a continuous delivery of PPX at zero-order rate kinetics for an extended period of time, independent of pH and agitational intensity.[11] Studies in healthy volunteers have demonstrated that the once-daily PPX SR is bioequivalent to the three-times daily PPX IR, with respect to the area under the plasma concentration–time curve from time 0 to 24 hours (AUC_{24}) and the maximum plasma concentration (C_{max}).[12] Other than the advantage of less frequent dosing, PPX SR is also associated with linear pharmacokinetics and smaller peak–trough fluctuations in healthy volunteers, which suggest potentially better drug tolerability.[12] In randomized, double-blind, Phase III studies of early and advanced stage PD, PPX SR demonstrated similar efficacy to PPX IR and significantly greater efficacy than placebo, with or without background levodopa.[13,14] The adverse event (AE) profiles of both the formulations were similar, mostly of mild or moderate intensity, with no unique safety signals observed in PPX SR.[15] These earlier studies did not assess the treatment effects of different formulations on PD-related sleep problems.

In the present study, we retrospectively analyzed nocturnal symptoms of patients receiving PPX SR versus IR from a PPX clinical trial (ClinicalTrials.gov Identifier: NCT00466167) conducted in advanced PD patients with sleep disturbances while on stable levodopa.

Materials and methods

Patients and study design

This was a retrospective exploratory analysis of patients with advanced idiopathic PD experiencing motor fluctuations while on levodopa, who took part in the multicenter, double-blind, Phase III clinical trial on the efficacy, safety, and tolerability of PPX SR and IR.[14] The data were collected between May 2007 and November 2008 from 76 sites located across 14 countries. In each country, local institutional review boards and ethics committees approved the clinical trial; details are available from the original publication, and the clinical trial data are all publicly available.[14] The trial was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided their written informed consent.

The clinical trial included patients who were at least 30 years of age with a diagnosis of idiopathic PD at Hoehn and Yahr stage 2–4 (on time) for at least 2 years before the trial and were on a stable dose of levodopa at least 4 weeks before baseline. Patients were not allowed any dopamine agonists within 4 weeks before the start of the trial. Over 7 weeks after assignment of treatment arms, patients received

a stepwise uptitration of medication according to their ratings on the Patient Global Impression–Improvement scale. Patients then entered a maintenance phase at optimized dosage for the remainder of the study, administered as 0.375, 0.75, 1.5, 2.25, 3.0, 3.75, or 4.5 mg once daily for the SR formulation and 0.125, 0.25, 0.50, 0.75, 1.0, 1.25, or 1.5 mg three times daily for the IR formulation. Patients who took within 80%–120% of correct total dosage (calculated based on dose in mg), as assessed by physical count of returned study medication, were considered as compliant. Further details of this clinical trial have been reported.[14] For the purpose of this retrospective analysis, patients with sleep disturbances at baseline and received either PPX SR or PPX IR (optimized at 0.375–4.5 mg/day) were included from the trial. Patients with sleep disturbances were defined as those who scored <90 on the PD Sleep Scale (PDSS).[16,17]

Assessments

Baseline clinical information of patients was captured using the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr stage, and patient-rated questionnaires including the PDSS and the Epworth Sleepiness Scale (ESS).[18]

The main efficacy outcome measures were the adjusted mean changes at week 18 from baseline in PDSS total mean and domain scores. The PDSS is a patient-rated 15-item questionnaire that measures six domains of nocturnal sleep problems in PD, including global quality of night's sleep (questions 1–3, 14), nocturnal restlessness (questions 4 and 5), nocturnal psychosis (questions 6 and 7), nocturia (questions 8 and 9), nocturnal motor symptoms (questions 10–13), and daytime dozing (question 15).[19] Patients were asked to rate the severity of their sleep problems on a visual analog scale of 1–10, ranging from the worst score ("awful" or "always" at the left extremity) to the best score ("excellent" or "never" at the right extremity). A PDSS total score of <90 indicates sleep disturbances (score ranges from 0 to 150); a higher PDSS score reflects better sleep quality.

Overall safety and tolerability were based on AEs that occurred during the study. Since daytime sleepiness is a recognized adverse effect of dopamine agonists,[20] this was assessed by the adjusted mean changes at week 18 from baseline for both ESS total score and PDSS question 15 ("Have you unexpectedly fallen asleep during the day?"). The ESS is a patient-rated eight-item scale that measures a person's general level of daytime sleepiness in different situations commonly encountered in daily life. The chances of dozing off are rated on a scale of 0 (no chance) to 3 (high chance). A total score of >10 suggests the presence of possible excessive daytime sleepiness.

Statistical methods

The efficacy analysis included all randomized patients who received PPX SR or PPX IR and observed PDSS <90 at baseline. To assess the treatment outcomes of PPX SR and IR in terms of efficacy, the adjusted mean changes (ie, PDSS total score and six PDSS domains) at week 18 from baseline were compared using the analysis of covariance on the observed cases, after adjusting for the pooled country and the corresponding baseline scores. The safety analysis included all patients who were treated with PPX. The AEs were summarized descriptively. ESS and PDSS question 15 were analyzed using the same method as the efficacy analysis. All analyses were carried out using the SAS software version 9.4.

Results

Baseline and clinical characteristics

A total of 119 PD patients reported sleep disturbances at baseline (PDSS <90; PPX SR, n=59; PPX IR, n=60). Baseline characteristics were similar between PPX SR and IR; the only notable difference was that the proportion of off-time Hoehn and Yahr stage 4–5 was higher for the PPX IR group, although both the PPX groups reported similar mean scores across the UPDRS sections (Table 1).

Compliance

The proportion of compliant patients was 98.3% by week 18 for both the PPX groups. Only one patient in each group reported a compliance of <80%.

Efficacy outcomes

The mean PDSS total scores at baseline were 65.4 and 72.8 in PPX SR and IR groups, respectively (Table 2). Better recovery from sleep disturbances at week 18 from baseline was observed for PPX SR than for PPX IR (adjusted mean changes, 28.5 versus 21.7 points), at a difference magnitude of 6.8 points in the adjusted mean change of PDSS total scores (95% CI, –2.8 to 16.3; P=0.165); however, this difference did not achieve statistical significance (Table 2; Figure 1). At week 18, 55.1% of patients receiving PPX SR and 50.8% on PPX IR reported PDSS total scores of ≥90, that is, demonstrated improvements in sleep.

For each of the six individual PDSS domains, patients receiving PPX SR reported numerically greater adjusted mean change at week 18 from baseline than those receiving PPX

Table 1 Baseline demographic and clinical characteristics of PD patients with sleep disturbances

Characteristic	PPX SR, n=59	PPX IR, n=60
Men, n (%)	27 (45.8)	33 (55.0)
Age, years, mean (SD)	60.8 (9.9)	60.9 (10.1)
Race, n (%)		
White	31 (52.5)	31 (51.7)
Asian	28 (47.5)	29 (48.3)
BMI, kg/m^2, mean (SD)	24.4 (4.4)	24.6 (3.7)
Duration of illness, years, mean (SD)	6.9 (4.7)	8.0 (4.9)
On-time Hoehn and Yahr stage, n (%)		
2–3	57 (96.6)	58 (96.7)
4–5	2 (3.4)	2 (3.3)
Off-time Hoehn and Yahr stage, n (%)		
2–3	48 (81.4)	39 (65.0)
4–5	11 (18.6)	21 (35.0)
Concomitant PD therapies, n (%)	59 (100.0)	60 (100.0)
Levodopa	59 (100.0)	60 (100.0)
Amantadine	9 (15.3)	19 (31.7)
MAO-B inhibitors	8 (13.6)	12 (20.0)
Entacapone	0 (0.0)	8 (13.3)
Levodopa daily dosage, mg, mean (SD)[a]	658.9 (372.9)	713.5 (360.9)
UPDRS total scores, mean (SD)		
Part I	2.3 (1.9)	2.3 (1.8)
Part II	14.7 (6.6)	14.4 (5.6)
Part III	31.4 (13.5)	29.7 (13.4)
Part II+III	46.2 (18.9)	44.1 (17.8)
Part IV	5.9 (2.7)	6.3 (2.7)

Note: [a]The sample size was n=42 for PPX SR and n=56 for PPX IR.
Abbreviations: BMI, body mass index; IR, immediate release; MAO-B, monoamine oxidase type B; PD, Parkinson's disease; PPX, pramipexole; SR, sustained release; UPDRS, Unified Parkinson's Disease Rating Scale.

IR (differences in adjusted mean change, 0.4–2.3 points); however, none of the differences achieved statistical significance (Table 2).

Study drug exposure

The final mean (SD) PPX dosages at week 18, after flexible uptitration, were 2.9 (1.5) and 2.9 (1.4) mg/day for PPX SR and PPX IR groups, respectively.

Levodopa exposure

The mean (SD) levodopa dosages were 658.9 (372.9) and 713.5 (360.9) at baseline and 698.8 (488.0) and 742.5 (412.5) mg/day at week 18 for PPX SR and IR groups, respectively. Most patients (SR=83%, IR=75%) reported no change in levodopa dosages at week 18 from baseline.

Safety

Among all the 119 treated patients included in this retrospective analysis, the incidences of patients with any AE were similar between PPX SR and IR groups (62.7% versus 70.0%; Table 3). PPX SR group reported lower incidence of patients with drug-related AEs than PPX IR group (42.4% versus 55.0%). The numbers of patients who reported severe AEs and serious AEs were comparable between both PPX SR and IR groups. Among patients who were discontinued from treatment due to AEs, five were on PPX SR and one was on PPX IR.

In terms of daytime sleepiness, the adjusted mean ESS total score remained within the normal range of <10 at week 18 (8.9–9.5 points) for both PPX SR and IR groups (Table 4). Both the treatment groups did not differ in the magnitude of the adjusted mean change in ESS total scores at week 18 from baseline; however, the magnitude of the PPX SR group was reported to be slightly greater than that of PPX IR group (adjusted mean changes, −0.8 versus −0.1; P=0.457). Similarly, patients receiving PPX SR reported better improvements in PDSS question 15, although the overall difference from PPX IR group was not significant (adjusted mean changes, 3.4 versus 2.9; P=0.4161).

Discussion

The aim of this retrospective analysis was to assess the treatment effect of PPX SR and IR on nocturnal symptoms among advanced PD patients with sleep disturbances. At the end of the treatment, PPX SR observed improvements of nocturnal symptoms compared with PPX IR, and both the PPX formulations were generally well tolerated.

Earlier studies have demonstrated that both PPX SR and IR have comparable efficacy and safety profiles in patients with PD, including daily living and motor symptoms (as measured by UPDRS part II and part III). The treatment efficacy reported in most clinical studies was sustained by the multiple PPX IR dosages taken throughout the daytime. Since dopamine receptor agonists have been suggested to help and improve sleep quality through the effects on motor function and the reversal of nocturnal off-time related symptoms, a continuous dopaminergic stimulation (CDS) may mean an overall better sleep maintenance for patients with PD.[1,7,21] In rat models, early morning akinesia was better prevented by a continuous delivery of PPX via subcutaneously implanted minipumps compared with PPX via injections; the positive outcome was attributed to the availability of more CDS.[22] Previous single-arm or placebo-controlled clinical trials such as the SP826,[23] EASE-PD,[24] and the RECOVER[25] have shown benefits in the management of sleep disturbances in PD with sustained release nonergot dopamine agonist treatment with or without levodopa. To date, only one randomized,

Table 2 PDSS total and domain scores from baseline to week 18 of advanced PD patients with sleep disturbances

PDSS	PPX SR, n=49		PPX IR, n=59	
	Baseline	18 weeks	Baseline	18 weeks
PDSS total score	65.4±14.5	95.0±25.4	72.8±14.9	91.5±24.4
Adjusted[a] mean change[b]	28.5		21.7	
SR versus IR, *P*-value (95% CI)	6.8, *P*=0.1650 (−2.8 to 16.3)			
PDSS domains				
Nocturnal motor symptoms	14.7±8.1	25.6±8.1	18.7±8.1	25.6±7.7
Adjusted[a] mean change[b]	9.6		8.9	
SR versus IR, *P*-value (95% CI)	0.8, *P*=0.6422 (−2.5 to 4.0)			
Global quality of sleep	18.2±6.5	25.3±9.5	19.3±6.7	23.6±8.9
Adjusted[a] mean change[b]	6.6		4.3	
SR versus IR, *P*-value (95% CI)	2.3, *P*=0.1790 (−1.1 to 5.7)			
Nocturnal psychosis	11.9±4.9	15.2±4.1	12.5±4.4	13.9±4.7
Adjusted[a] mean change[b]	3.1		1.5	
SR versus IR, *P*-value (95% CI)	1.6, *P*=0.0547 (−0.0 to 3.2)			
Nocturnal restlessness	7.1±4.7	12.1±5.9	7.5±4.2	11.8±4.8
Adjusted[a] mean change[b]	4.7		4.3	
SR versus IR, *P*-value (95% CI)	0.4, *P*=0.7177 (−1.6 to 2.3)			
Daytime sleepiness	5.3±2.9	6.2±3.2	5.8±3.1	6.0±3.4
Adjusted[a] mean change[b]	1.5		1.0	
SR versus IR, *P*-value (95% CI)	0.5, *P*=0.4544 (−0.8 to 1.7)			
Nocturia	8.2±4.5	10.6±4.3	9.0±4.5	10.5±4.7
Adjusted[a] mean change[b]	2.6		2.1	
SR versus IR, *P*-value (95% CI)	0.6, *P*=0.5020 (−1.1 to 2.2)			

Notes: [a]Adjusted = Least-square means adjusted for pooled country and baseline scores; [b]positive change implies improvement. Data are presented as mean ± SD.
Abbreviations: IR, immediate release; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PPX, pramipexole; SR, sustained release.

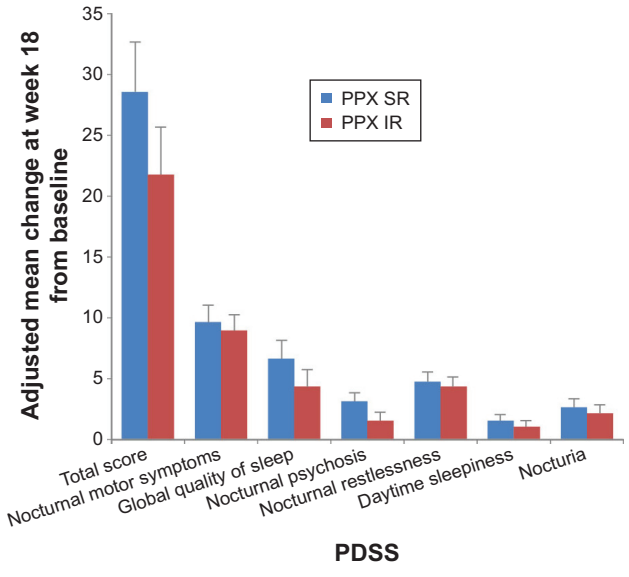

Figure 1 Advanced PD patients with sleep disturbances (PDSS <90): Adjusted mean changes at week 18 from baseline in PDSS total and domain scores.
Note: Error bars show the standard error.
Abbreviations: IR, immediate release; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PPX, pramipexole; SR, sustained release.

parallel-group study has compared the sleep outcomes of PD patients taking different release formulations of nonergot dopamine agonist; no statistical difference in adjusted mean change in PDSS total score at week 24 from baseline was observed between ropinirole prolonged release versus ropinirole IR in patients with PD (5.7 versus 5.8 points; *P*=0.937).[26] It is noted that the ropinirole study consisted

Table 3 Adverse event overall summary

Subgroup	PPX SR, n=59	PPX IR, n=60
Patients with any AE	37 (62.7)	42 (70.0)
Patients with severe AEs[a]	6 (10.2)	5 (8.3)
Patients with serious AEs[b]	3 (5.1)	3 (5.0)
Patients with drug-related AEs	25 (42.4)	33 (55.0)
Patients with AEs leading to discontinuation	5 (8.5)	1 (1.7)

Notes: [a]Incapacitating or causing inability to work or undertake usual activities; [b]fatal, life-threatening, requiring hospitalization, or resulting in significant disability. Data are presented as n (%).
Abbreviations: AE, adverse event; IR, immediate release; PPX, pramipexole; SR, sustained release.

Table 4 Daytime sleepiness from baseline to week 18 in advanced PD patients with sleep disturbances

Subgroup	PPX SR		PPX IR	
	Baseline	18 weeks	Baseline	18 weeks
ESS, n	42		56	
Total score[a]	7.9±3.9	8.9±4.6	8.9±4.5	9.5±5.3
Adjusted[b] mean change[a]	−0.8		−0.1	
SR versus IR, *P*-value (95% CI)	−0.6, *P*=0.4573 (−2.4 to 1.1)			
PDSS item 15, n	52		51	
Total score[c]	3.2±1.7	6.3±3.0	3.2±1.7	5.8±3.2
Adjusted[b] mean change[a]	3.4		2.9	
SR versus IR, *P*-value (95% CI)	0.5, *P*=0.4161 (−0.7 to 1.7)			

Notes: [a]Negative change implies improvement; [b]adjusted = Least-square means adjusted for pooled country and baseline scores; [c]positive change implies improvement. Data are presented as mean ± SD.

Abbreviations: ESS, Epworth Sleepiness Scale; IR, immediate release; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PPX, pramipexole; SR, sustained release.

of patients with generally normal sleep, which explains the smaller magnitude of sleep improvement after treatment compared with the current PPX study.

In the current retrospective analysis, an improvement in sleep was observed in PD patients with existing sleep disturbances for both PPX formulations. Although the PPX SR–IR difference of 6.8 points (adjusted mean changes in PDSS total score, SR=28.5 versus IR=21.7 points, *P*=0.16) did not meet statistical significance, this change does not necessarily preclude any clinically meaningful benefit to patients, and therefore, the latter remains to be evaluated. We noted that for studies in PD patients using PDSS second version (PDSS-2),[27] an improvement of >3.44 points or deterioration of >2.07 points on the PDSS-2 total score is recommended as the threshold for minimal clinically important difference in nocturnal sleep quality.[28] Consistently, we observed that the patients receiving PPX SR in this study reported a slightly greater proportion of recovery from sleep disturbances at week 18 compared with those on PPX IR (PDSS total scores of ≥90, SR=55.1% versus IR=50.8%). Further research comparing PPX SR with PPX IR and possible intervention trials including PDSS-2 are needed to help address these clinical gaps in PD patients with existing sleep disturbances.

The retrospective analyses confirmed the results of previous randomized controlled trials demonstrating that PPX SR and IR are equally safe and well tolerated by patients with advanced PD.[14,29] Both patient groups reported similar improvements in daytime sleepiness after 18 weeks of receiving PPX regardless of formulation, as measured by both ESS and PDSS question 15.

PD is a chronic disease that requires long-term treatment management; however, there is a significant concern of treatment nonadherence among patients with PD, varying between 10% and 67%, which leads to poor response to therapy.[30] Once-daily treatment regimens have been shown to significantly improve treatment adherence in chronic diseases compared with twice-daily or thrice-daily regimens, potentially increasing adherence days by up to 44%.[31] In another community survey, 83.1% of patients have ranked the need for a reduction in medication frequency as a high priority in their expectation toward treatment (rating of 1–3 on the 6-point scale).[32] In terms of symptoms alleviation, 76.8% ranked sleep disturbance as top three and 55.4% ranked early morning akinesia as "very important". According to these studies, a once-daily treatment regimen would contribute toward adherence to treatment, medication dosage, and timing to ensure that patients receive the available care. Considering the existing pool of patients who are already on PPX IR treatment, the success of switching from IR to SR formulations was evidenced by improvements in UPDRS Parts II+III in 86% of patients with advanced PD within 1 week after the switch.[33] Longer follow-up durations of switches to PPX SR from IR reported equal or better outcomes in the adherence and motor symptoms of patients with advanced PD, without severe adverse effects.[29,34,35]

The limitations of this analysis are inherent in the retrospective and exploratory design. The sample size of the study was not planned to confirm the efficacy outcomes, and only the actual observed data were used for analysis without any further imputations for dropouts (eg, last observation carried forward). Nonetheless, the positive and consistent sleep outcomes observed with PPX SR over PPX IR are encouraging and may serve as a pilot for prospectively designed studies to collect further supporting evidence.

In conclusion, in advanced PD patients with sleep disturbances and on stable levodopa, both the PPX formulations showed improvements in sleep disturbances. However, the current observations on the numerical difference between groups suggest that future prospectively designed research is necessary to confirm the effects of PPX SR for improved sleep.

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Author contributions

The authors fulfill the criteria for authorship as recommended by the International Committee of Medical Journal Editors; that is, they were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development including data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Wei Xiang, Ya Qing Sun, and Hui Chin Teoh are employees of Boehringer Ingelheim. The authors report no other conflicts of interest in this work.

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