Meta-analysis of the adverse events associated with extended-release versus standard immediate-release pramipexole in Parkinson disease

Zhengze Shen, MM, Deping Kong, MM

Abstract

Background: In order to increase treatment choices for patients with Parkinson disease (PD), we performed a retrospective assessment of adverse events associated with a novel once-daily extended-release (ER) formulation versus the standard immediate-release (IR) of the nonergolinic dopamine agonist, pramipexole.

Methods: The PubMed and Embase databases, as well as the foreign language medical information resource retrieval platform were searched from 2007 to 2017. The relative risks (RR) of various adverse events with 95% confidence intervals (95% CIs) were generated. The Modified Jadad score (MJs) was used to assess the quality of individual studies. Funnel plots were used to evaluate publication bias.

Results: Three randomized controlled trials involving 1021 patients were included in this meta-analysis. We evaluated common adverse events associated with pramipexole in the gastrointestinal and nervous systems. These included the typical gastrointestinal symptom of nausea (RR = 0.96, 95% CI: 0.72–1.28; P = .80 > .05) and nervous system symptoms of somnolence (RR = 1.16, 95% CI: 0.95–1.43; P = .14 > .05), dizziness (RR = 1.11, 95% CI: 0.80–1.54; P = .54 > .05), and dyskinesia (RR = 0.87, 95% CI: 0.47–1.60; P = .66 > .05).

Conclusion: Patients with PD treated with 2 different pramipexole formulations (ER and IR) had similar incidences of common adverse events.

Abbreviations: CI = confidence interval, ER = extended-release, IR = immediate-release, MJs = Modified Jadad score, PD = Parkinson disease, RCT = randomized controlled trial, RR = relative risk.

Keywords: adverse event, meta-analysis, Parkinson disease, pramipexole

1. Introduction

Parkinson disease (PD) is a chronic progressive neurodegenerative disorder. Demographic data estimate that cases of PD in the most populous nations will increase from 4.6 million in 2005 to 9.3 million by 2030. The main pathological feature of PD is the loss of dopaminergic neurons in the substantia nigra. The first primary clinical manifestation is static tremor, and subsequently the symptoms of dyskinesia, depression, anxiety, sleep disturbance, and cognitive impairment progress, respectively.

Pramipexole is a dopamine D2/D3 receptor agonist that is nonergot derived, which can be used for monotherapy in patients with early and advanced PD, or as adjunctive therapy together with levodopa. The pharmacodynamic properties of pramipexole reveal a stronger affinity to D3 receptors than the ergot agonists. On the basis of a pharmacokinetic experiment in healthy male volunteers, 1.5 mg of immediate-release (IR) pramipexole administered 3 times daily was bioequivalent to 4.5 mg of extended-release (ER) pramipexole taken once daily. A growing body of evidence supports ER formulations as equal to IR formulations in terms of efficacy, safety, and tolerability in early and advanced PD patients. Although increasing numbers of studies have shown efficacy and safety, from a clinical perspective, doctors and patients still have concerns about differences in adverse events between IR and ER treatments, including so-called “sleep attacks” that are reported to have caused car accidents. The aim of this study was to analyze the incidences of adverse events associated with the 2 types of treatment programs, providing clear options for patients and doctors.

2. Materials and methods

2.1. Data sources and literature search

In order to collect clinical data systematically, we carefully searched the NCBI PubMed and Elsevier Embase databases, as
well as the foreign language medical information resource retrieval platform. The search included literature published from 2007 to 2017, with the keywords pramipexole [title] and Parkinson's disease [title] or PD [title]. Grey studies were carefully identified from the references of included literature. No language restrictions were imposed. As the data included in our study were extracted from published literatures, no ethical approval and patient consent were required.

2.2. Inclusion and exclusion criteria
All trials were identified by 2 reviewers independently. Any disagreement was resolved through discussion with a third investigator. Primary studies were included if they met the inclusion criteria as follows. First, the study was a double-blind randomized controlled trial (RCT); second, the subjects were diagnosed with PD; third, the subjects with PD at Hoehn and Yahr stage ≥ 1, PD duration ≥ 2; fourth, grouping of subjects included those treated with ER and IR pramipexole; and fifth, outcomes of nausea, dizziness, somnolence, and dyskinesia were recorded. Articles were excluded if they were, or contained, any of the following: incomplete data, letters, case reports, review articles, conference abstracts, or duplicate studies and publications.

2.3. Data extraction
Data were extracted from each included study using a pre-designed extraction form. The following items were recorded: first author’s surname, publication year, country, study design groups, Hoehn and Yahr stage, mean or median age, sex, incidence of adverse events. All extracted data were performed by 2 reviewers independently. Any disagreement was settled by discussion with a third investigator.

2.4. Quality assessment
A modified Jadad score (MJ), which was based on the Cochrane Handbook for Systematic Reviews of Interventions, was calculated for the assessment of the quality of the RCTs. We carried out quality assessment based on 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

**Table 1**

| Characteristics of the included randomized controlled trials. |
| --- |
| Ref. | Country | Age (mean), y | Male/Female | Hoehn and Yahr stage | PD duration, y | Group | ER | IR | Outcome measure (adverse events) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Wang et al[13] | China | ≥30 | 300/175 | 2–5 | 2 | ER/IR | Y | Somnolence, dyskinesia, dizziness, nausea |
| Poewe et al[2] | Austria | 62 | 247/189 | 1–3 | 2–5 | P:ER/IR | Y | Dyskinesia, dizziness, nausea |
| Mizuno et al[11] | Japan | 67.5 | 42/70 | 2–4 | 3 | ER/IR | Y | Somnolence, dyskinesia, dizziness, nausea |

* "* stands for no completed data.
ER = extended-release, IR = immediate-release, P = placebo.
2.5. Data analysis and statistical methods

The analysis of adverse events was based on 2 factors using the RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark), which was developed and produced by the international Cochrane collaboration, and updated by the Nordic Cochrane Center. Statistical heterogeneity between studies was assessed by the value of $P$ and $I^2$. If the $I^2$ test showed a result indicating high heterogeneity ($I^2 \geq 50\%$), a random effect model was performed, otherwise, a fixed effect model was adopted.[10]

3. Results

3.1. Search results

From the keyword database search, we found 81 total articles. Eleven duplicated articles were excluded, as well as 12 non-RCTs and 43 studies based on title/abstract content. Thus, only 15 eligible studies underwent full-text review. Among these 15 articles, 1 was excluded due to incomplete data, and 3 were ruled out because study groups did not include ER versus IR treatments. Another 5 were excluded for other reasons and 1 article[12] was excluded for repeat study leaving only 3 RCTs involving 1021 patients who were examined in this meta-analysis (Fig. 1).

3.2. Description of the included studies

The 3 included trials[2,11,13] were published from 2011 to 2014. The patients in the remaining 3 trials ranged in age from 30 to 67.5 years, including both males and females. One trial was of a 2-group design (ER vs IR) (Poewe et al[2]) and the other 2 examined 3 groups (Placebo vs ER vs IR) (Wang et al[13] and Mizuno et al[11]). The detailed characteristics of the 3 analytical studies are summarized in Table 1.

3.3. Quality assessment and publication bias

The MJ score revealed that the quality of the 3 individual studies was sufficient for further analysis (Fig. 2). In addition, funnel plots were used to evaluate publication bias (Fig. 3). There was no significant publication bias found except in the analysis of dyskinesia.

Figure 2. Quality assessment of included studies using the Modified Jadad score.

Figure 3. Funnel plots for publication bias for somnolence (A), dizziness (B), dyskinesia (C), and nausea (D).
3.4. Meta-analysis of somnolence and dizziness as well as dyskinesia

All 3 trials reported the incidence of somnolence. However, we detected no significant difference in somnolence between the ER and IR groups [relative risk (RR) = 1.16, 95% confidence interval (95% CI): 0.95–1.43; P = .14 > .05] (Fig. 4A). All studies also reported the incidence of dizziness. Again, no significant difference was detected when comparing the combined ER and IR groups (RR = 1.11, 95% CI: 0.80–1.54; P = .54 > .05) (Fig. 4B). Only 2 of the articles recorded the incidence of dyskinesia. Not surprisingly, no difference was found between the ER and IR group by this metric either (RR = 0.87, 95% CI: 0.47–1.60; P = .66 > .05) (Fig. 4C).

3.5. Meta-analysis of nausea

All 3 trials reported the incidence of nausea. Similar to the nervous system symptoms, there was no significant difference in nausea between the ER and IR groups (RR = 0.96, 95% CI: 0.72–1.28; P = .80 > .05) (Fig. 5).

4. Discussion

PD is the second most common neurodegenerative disorder. Pramipexole, an agonist of the dopamine receptor, is the second most widely used treatment after L-DOPA for patients with PD.\(^{14}\)

Nausea, an uncomfortable feeling in the epigastrium, occurs in advance of vomiting, both of which impact the quality of life.\(^{15}\) Almost all gastrointestinal drugs are associated with the adverse reaction of nausea and pramipexole is no exception. ER formulations are dosed once a day, whereas IR formulations are dosed 3 times a day, but nausea caused by either treatment has been reported to be similar.\(^{14}\) In agreement, our analysis found a low incidence of nausea caused by pramipexole, with no apparent difference between ER and IR treatment.

Dizziness is a nonspecific symptom that can be defined as lightheadedness, faintness, imbalance, or the sensation of moving or spinning.\(^{16}\) On the basis of the degree of the progression of symptoms, we divided “dizziness” into 4 groups: vertigo; disequilibrium without vertigo; presyncope, and physiological dizziness, which is often associated with anxiety and panic.\(^{17,18}\) Dizziness is the most common symptom of the central nervous system and incidence ranges from 1.8% in young adults to more than 30% in the elderly.\(^{19}\) Dizziness impacts the quality of life by increasing the risk of falls and fractures, especially in the elderly.\(^{20}\) Incidentally, PD also usually occurs in the elderly. Fortunately, there is a low incidence of dizziness associated with pramipexole, with ER and IR formulations having an occurrence rate of 11% and...
12%, respectively. Therefore again, our analysis failed to detect any difference between ER and IR treatments.

The gold standard PD therapy, chronic L-3,4-dihydroxyphenylalanine (levodopa), does not sufficiently and thoroughly arrest dopaminergic neuronal degeneration and has toxic side effects when used long-term, such as levodopa-induced dyskinesia.\(^{[21,22]}\) Levodopa-induced dyskinesia was seen in both a phase I and IIb clinical trial.\(^{[23]}\) Preclinical and clinical research have shown that pramipexole can alleviate LID.\(^{[24–26]}\) In our analysis, both the ER and IR group had dyskinesia incidence rates of ~7.5% indicating no difference between the treatments. This conclusion is consistent with previous study that has reported that initial pramipexole treatment leads to the risk of developing dyskinesia decrease significantly.\(^{[27]}\)

Somnolence is a common complaint in patients with PD, especially excessive daytime somnolence.\(^{[28,29]}\) This symptom had been largely ignored until the description of sudden sleep attacks, which were linked to car accidents involving PD patients taking both ergot and nonergot dopamine agonists, including pramipexole.\(^{[30]}\) In our analysis, there was a higher incidence of somnolence linked to pramipexole than other symptoms, with the frequencies being 26.1% and 23.3% of PD patients treated with ER and IR, respectively. Although the difference between ER and IR is not significant, these somnolence events have caught people’s attention.

There are some limitations of this meta-analysis that should be pointed out. First, publication bias was present because only 3 trials were included in the analysis and additional clinical studies are needed to reduce this. Second, there is no detailed information regarding the complete data that were withdrawn, which may have been due to short observation periods. Third, the incidence of some adverse events in PD differs among types of patients. For instance, young patients on pramipexole showed a higher incidence of somnolence when compared with patients given a placebo.\(^{[30,31]}\) Therefore, it is important to explore adverse events in both early and advanced PD separately.

In conclusion, we found no significant differences in the common adverse events associated with ER versus IR pramipexole treatment in patients with PD. However, there is no doubt that these symptoms affect quality of life and attract the attention of patients and doctors. Considering the pathologic development of PD, and the clinical trials currently in progress, there is still a need for the development of novel therapies to combat the progression of neurodegeneration in PD.

**Author contributions**

Data curation: Zhengze Shen, Deping Kong.

Formal analysis: Zhengze Shen, Deping Kong.

Investigation: Deping Kong.

Project administration: Deping Kong.

Resources: Zhengze Shen, Deping Kong.

Software: Zhengze Shen.

Supervision: Deping Kong.

Validation: Deping Kong.

Visualization: Zhengze Shen.

Writing – original draft: Zhengze Shen.

Writing – review & editing: Deping Kong.

**References**

[1] Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68:384–6.

[2] Poewe W, Rascol O, Barone P, et al. Extended-release pramipexole in early Parkinson disease: a 33-week randomized controlled trial. Neurology 2011;77:759–66.

[3] Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson’s disease. Mov Disord 2011;26(suppl 3):S2–41.

[4] Fishman PS, Pramipexole R, and its extended release formulation for Parkinson disease. J Cent Nerv Syst Dis 2011;3:169–78.

[5] Piercey MF. Pharmacology of pramipexole, a dopamine D3-preferring agonist useful in treating Parkinson’s disease. Clin Neuropharmacol 1998;21:141–51.

[6] Jenner P, Könen-Bergmann M, Schepers C, et al. Pharmacokinetics of a once-daily extended-release formulation of pramipexole in healthy male volunteers: three studies. Clin Ther 2009;31:2696–711.

[7] Hauser RA, Schapira AH, Barone P, et al. Long-term safety and sustained efficacy of extended-release pramipexole in early and advanced Parkinson’s disease. Eur J Neurol 2014;21:736–43.

[8] Feucht S, Rogers JD, Greene PE, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908–10.

[9] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.

[10] Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, Chichester, England; 2011.

[11] Mizuno Y, Yamamoto M, Kuno S, et al. Efficacy and safety of extended-versus immediate-release pramipexole in Japanese patients with advanced and L-dopa-undertreated Parkinson disease: a double-blind, randomized trial. Clin Neuropharmacol 2012;35:174–81.

[12] Hametner EM, Sepp K, Poewe W. Role and clinical utility of pramipexole extended release in the treatment of early Parkinson’s disease. Clin Interv Aging 2012;7:83–8.

[13] Wang Y, Sun S, Zhu S, et al. The efficacy and safety of pramipexole ER versus IR in Chinese patients with Parkinson’s disease: a randomized, double-blind, double-dummy, parallel-group study. Transl Neurodegener 2014;3:111.
[14] Rosa MM, Ferreira JJ, Coelho M, et al. Prescribing patterns of antiparkinsonian agents in Europe. Mov Disord 2010;25:1053–60.
[15] Canziani BC, Uestuenen P, Fossali EF, et al. Clinical practice: nausea and vomiting in acute gastroenteritis: physiopathology and management. Eur J Pediatr 2018;177:1–5.
[16] Heyer GL, Young JA, Fischer AN. Lightheadedness after concussion: not all dizziness is vertigo. Clin J Sport Med 2018;28:272–7.
[17] Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. Neurologist 2008;14:355–64.
[18] Chawla N, Olshaker JS. Diagnosis and management of dizziness and vertigo. Med Clin North Am 2006;90:291–304.
[19] Dros J, Maarsingh OR, Beem L, et al. Impact of dizziness on everyday life in older primary care patients: a cross-sectional study. Health Qual Life Outcomes 2011;9:44.
[20] Pluijm SMF, Smits JH, Tromp EAM, et al. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. Osteoporos Int 2006;17:417–25.
[21] Obeso JA, Grandas F, Vaamonde J, et al. Motor complications associated with chronic levodopa therapy in Parkinson’s disease. Neurology 1989;39:11–9.
[22] Ziv I, Zilkha-Falb R, Ofen D, et al. Levodopa induces apoptosis in cultured neuronal cells: a possible accelerator of nigrostriatal degeneration in Parkinson’s disease? Mov Disord 1997;12:17–23.
[23] Van Gerpen JA, Kumar N, Bower JH, et al. Levodopa-associated dyskinesia risk among Parkinson disease patients in Olmsted County, Minnesota, 1976-1990. Arch Neurol 2006;63:205–9.
[24] Tayaranzibandizir KA, Jackson MJ, Rose S, et al. Pramipexole combined with levodopa improves motor function but reduces dyskinesia in MPTP-treated common marmosets. Mov Disord 2010;25:377–84.
[25] Utsumi H, Okuma Y, Kano O, et al. Evaluation of the efficacy of pramipexole for treating levodopa-induced dyskinesia in patients with Parkinson’s disease. Intern Med 2013;52:325–32.
[26] Constantinescu R, Romer M, Mcdermott MP, et al. Impact of pramipexole on the onset of levodopa-related dyskinesias. Mov Disord 2007;22:1317–9.
[27] Holloway RG, Shoulson I, Fahn S, et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 2004;61:1044–53.
[28] Abdulla AJJ, Pearce VR. The nighttime problems of Parkinson’s disease. Clin Neuropharmacol 1988;11:512–9.
[29] Ferreira J, Pona N, Costa J, et al. Somnolence as an adverse drug reaction of antiparkinsonian drugs: a meta-analysis of published randomized placebo-controlled trials. Mov Disord 2000;15:128.
[30] Emmanou M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson’s disease. Drug Saf 2001;24:863–8.
[31] Schapira AH, Mcdermott MP, Barone P, et al. Pramipexole in patients with early Parkinson’s disease (PROUD): a randomised delayed-start trial. Lancet Neurol 2013;12:747–55.