CrossMark

CASE REPORT

Investigation of the Pharmaceutical Care in One Elderly Parkinson's Disease Patient with Psychotic Symptoms

Chun-Ping Gu[1,2] · Yue-Liang Xie[1] · Yin-Juan Liao[1] · Cui-Fang Wu[1] ·
Sheng-Feng Wang[1] · Yu-Lu Zhou[1] · Su-Jie Jia[1]

Abstract A 66-year-old male patient with a 10-year course of Parkinson's disease (PD) was admitted for hallucination lasting a half a month. After treatment with levodopa/carbidopa, selegiline, and piribedil, the patient's motor symptoms were improved while no significant effects were observed on psychotic symptoms. A clinical pharmacist analyzed the pharmacologic and pharmacokinetic characteristics of selegiline and piribedil, summarized the scheme of PD with psychotic symptoms in the literature, and discovered that selegiline might potentiate psychotic side effects of piribedil, while the use of levodopa/carbidopa cannot be ruled out either. Finally, the clinical pharmacist proposed to reduce the dosage of levodopa/carbidopa, increase the dosage of selegiline and quetiapine, and discontinue piribedil. The clinician accepted this suggestion. After the adjustment of medication, the patient's motor symptoms were absolutely improved and the psychotic symptoms were notably improved. This case study suggests that long-term treatment with levodopa/carbidopa and piribedil, along with the progression of the disease itself, could contribute to the emergence of psychotic symptoms in PD. Additionally, selegiline could potentiate psychotic side effects of piribedil. Neurology clinical pharmacists should work alongside neurology clinicians at the bedside to optimize pharmacotherapy, improve patient safety, and contribute to scholarly efforts.

✉ Su-Jie Jia
sujiejia@csu.edu.cn

1 Department of Pharmaceutics, The Third Xiangya Hospital, Central South University, Tongzipo Road #138, Changsha 410013, China

2 Department of Pharmaceutics, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

Key Points

Psychotic symptoms tend to emerge in the late stage of Parkinson's disease (PD), most commonly manifesting as visual hallucinations.

Long-term treatment with anti-PD medications could contribute to the emergence of psychotic symptoms in PD; in particular, elderly patients in the late stages of PD are more vulnerable to hallucinations with long-term treatment with levodopa/carbidopa and piribedil.

Selegiline could potentiate piribedil psychotic side effects.

Neurology clinical pharmacists should work alongside neurology clinicians at the bedside to optimize pharmacotherapy, improve patient safety, increase efficiency, educate patients and clinicians, and contribute to scholarly efforts.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, presenting with motor symptoms including bradykinesia, rigidity, static tremor, and postural instability [1, 2]. Psychotic symptoms are common in PD and may surpass motor symptoms as the major factors impacting quality of life [3, 4]. Mood symptoms such as depression, anxiety, and apathy may precede the

△ Adis

development of motor symptoms, while other psychotic symptoms such as cognitive dysfunction, dementia, and psychosis are more common in later stages of the disease. PD-related psychosis is characterized by hallucinations (primarily visual), delusions, and other sensory disturbances such as illusions and 'sense of presence' hallucinations. These psychotic symptoms occur in 20–40% [5–7] of PD patients and significantly affect patients' quality of life, and most commonly manifest in visual hallucinations. The clinical pharmacist should work alongside clinicians at the bedside to optimize pharmacotherapy, improve patient safety, and contribute to scholarly efforts. Polypharmacy is common in geriatric PD patients in advanced disease stages with multiple comorbidities, bearing multiple risks for drug safety in theory [8]. Recent efforts have aimed to explore the complex pathophysiology of PD psychosis, which was recently found to involve an interaction between extrinsic, drug-related and intrinsic, disease-related components [9]. Removal or reduction of anti-PD medications is the first step to improve psychotic symptoms. Secondly, antipsychotic agents are recommended for the treatment of psychotic symptoms. While quetiapine has not been determined as efficacious in two randomized controlled trials, it is a common first-line treatment for PD psychosis because of its tolerability, ease of use, and high bioavailability in numerous open-label reports. Here, we present a case of PD in one elderly patient with psychotic symptoms intending to illuminate the process of a clinical pharmacist participating in treatment of psychotic symptoms in one elderly patient with Parkinson's disease, probably induced by piribedil and selegiline.

Case Report

Case Presentation

A 66-year-old male patient was admitted to the Third Xiangya Hospital of Central South University for bradykinesia and hallucination lasting for half a month. He was diagnosed with PD 10 years earlier. Since 2012, the patient was regularly hospitalized once per year. After his last hospitalization (for the half-month prior to the current admission), he was treated with levodopa/carbidopa (250 mg every 6 h) and piribedil (50 mg every 6 h). On examination, he showed mask face, lower body rigidity, and festinating gait. The patient had a history of chronic viral hepatitis B, splenomegaly, portal hypertension, esophagogastric varices, and interventional therapy of hepatoma.

The following clinical metric was performed: Hoehn and Yahr evaluation scale, a descriptive staging scale of the progression of PD symptoms, placing the patient in a stage

3: "Mild to moderate bilateral disease; some postural instability; physically independent" [10–12].

Search Strategies

The clinical pharmacist analyzed the pharmacology and pharmacokinetics of the medication, and performed a literature search on PD with psychotic symptoms and the drug–drug interaction of piribedil and selegiline by searching the Medline database via PubMed for relevant articles including review articles, randomized and non-randomized trials, as well as case reports.

Design

This study was performed at the Third Xiangya Hospital of Central South University, Changsha, China, from June 14 to June 23, 2016.

Pharmaceutical Care Service

On examination, the patient showed upper and lower body stiffness, rigidity, bradykinesia, and festinating gait. In addition, the patient displayed psychotic symptoms and visual hallucinations. He was treated with levodopa/carbidopa 200 mg/50 mg (half a pill every 6 h), piribedil (50 mg every 6 h), and selegiline (5 mg/day), with little improvement in his symptoms. In the meantime, the patient was treated with intravenous monosialoterahexosylganglioside sodium injections (MSI) (60 mg/day) to protect brain neurons, and cinepazide injections (320 mg/day) to improve microcirculation. The patient was also treated with alprazolam (0.4 mg per night) for its sedative-hypnotic effects. Given that selegiline can produce insomnia if taken later in the day [13], the clinical pharmacist recommended that selegiline should be taken earlier in the day.

On the second day of admission, the patient continued to have visual hallucinations, dizziness, insomnia, and impaired mental health. In order to improve the psychotic symptoms, the clinician prescribed quetiapine (25 mg per night). The clinical pharmacists performed a literature search looking for the pharmacokinetics profiles of quetiapine. They found that the patient must start with the lowest dose of quetiapine (25 mg/day) and gradually increase (25–50 mg/day), until the maintenance dose is reached. Quetiapine is primarily metabolized by cytochrome P450 3A4. The initial doses of quetiapine should be lower in elderly patients, as the metabolism of quetiapine decreases concurrently with decreased liver function [14]. This patient was a 66-year-old man with a history of chronic viral hepatitis B and interventional therapy for hepatoma. Therefore, the clinical pharmacist recommended that the patient should be treated with a lower initial dosage

of 12.5 mg per night, with the dosage gradually increased per day until the maintenance dose is reached. The clinician accepted these suggestions.

On the third day of admission, the patient still had bradykinesia, with no significant improvement in hallucinations. As a result of a literature review and evidence-based approaches, the clinical pharmacist found that psychotic symptoms are frequently caused or worsened by levodopa [15, 16]. Therefore, the therapeutic dosage of levodopa/carbidopa 200 mg/50 mg orally was reduced from half a pill every 6 h to quarter of a pill every 6 h. Additionally, large neutral amino acids (e.g., phenylalanine, tyrosine, and tryptophan) have been shown to compete with levodopa for absorption and brain penetration [17–20]. It is reported that clinically significant protein interaction with levodopa may reduce its effectiveness and therefore lead to worsened motor fluctuations of PD, taking hallucinations, gait freezing, and dyskinesias as markers of motor fluctuations [21]. This means that allowing the patient to take levodopa before or after meals, to avoid reducing levodopa effectiveness and developing motor fluctuations, could get a significantly increased benefit. Based on the above literature and the patient's usual routine, the clinical pharmacist recommended that levodopa/carbidopa should be administered at 5 a.m., 11 a.m., 5 p.m., and 10 p.m.

On the sixth day of admission, the patient showed slight improvement in hallucination but found it hard to change his in-bed body posture. The clinician considered that the maintenance dose of quetiapine had not been reached. The clinical pharmacist suggested that the therapeutic dosage of quetiapine should be gradually increased during the first week of treatment. The patient has been taking quetiapine 12.5 mg per night for four nights, and it was time to increase the dosage. Finally, the therapeutic dosage of oral quetiapine was increased from 12.5 mg per night to 25 mg per night.

On the seventh day of admission, the patient complained that he was still suffered from upper and lower body stiffness and rigidity in the morning and hallucination was improved slightly. Given that the therapeutic dosage of selegiline had not been reached, the clinician treated the patient with higher dosage of selegiline (5 mg twice a day) earlier in the day. The clinical pharmacist performed a literature search looking for the scheme of PD with psychotic symptoms, and found that psychotic symptoms were frequently caused or worsened by dopamine agonists, such as piribedil. In addition, selegiline would aggravate the psychotic symptoms induced by piribedil [22]. Therefore, the clinical pharmacist advised that piribedil be discontinued and the clinician accepted this suggestion.

On the tenth day of admission, the motor and psychotic symptoms of the patient were improved after the following adjustments: reducing the dosage of levodopa/carbidopa, increasing the dosage of selegiline, the addition of quetiapine, and discontinuing piribedil. The patient was discharged from hospital in a fair physical condition.

Discussion

Psychotic symptoms in PD tend to emerge in the late course of PD, and patients with a long history (> 10 years) of PD are more susceptible to these symptoms. Researchers are increasingly characterizing the psychotic symptoms of the disease such as depression, apathy, dementia and psychosis. The mechanisms underlying psychotic symptoms in PD have been identified as Lewy body deposition in the amygdala and cortical areas, neurochemical abnormalities, and visual processing abnormalities [23]. The prevalence for hallucinations ranges from 6 to 87% [24], in which the most common symptom is visual hallucinations. Visual hallucinations can occur at any time of the day, although they are most commonly reported in the evening hours during periods of low stimulation [25]. The content of visual hallucinations usually consists of people or animals but may also feature inanimate objects. Visual hallucinations generally last seconds to minutes at a time, and most studies have found them to occur at least once a week, although they can occur much more frequently.

It is now well accepted that, in addition to disease-related processes, antiparkinsonian therapy also contributes to the emergence of psychotic symptoms in PD. The use of dopaminergic medications was the first factor implicated in the development of psychosis in PD. Long-term levodopa/carbidopa treatment could induce psychotic symptoms. The prevalence of psychotic complications of levodopa treatment was assessed in 198 PD patients [26]. Psychotic complications were observed in 44 patients (22.2%), 27 (61.4%) of whom developed psychotic complications during first 5 years of the treatment.

It appears that dopamine agonists, like piribedil in particular, put patients at highest risk for developing psychotic symptoms. Piribedil has the unique cellular signature of signal-specific partial agonist actions at dopamine D_2 and D_3 receptors, antagonist properties at α_2-adrenoceptors, and minimal interaction with serotonergic receptors [27]. The utility of piribedil in the treatment of PD, both as monotherapy and as an adjunct to levodopa, has recently been underpinned by extensive clinical studies, including a long-term, placebo-controlled trial of monotherapy for early PD. Due to its long half-life, long-term efficacy of piribedil in the control of motor symptoms is well established. Dopamine-deprived striatal D_2 receptors are supersensitive in PD, so partial agonism is sufficient for relief of motor dysfunction. However, long-term use or overdose of

D_2 receptor agonists appear to increase the risk of triggering psychosis [28]. It is reported that piribedil, like any other dopamine agonist, may worsen levodopa-associated dyskinesias and in fact may induce dyskinesias in levodopa-naïve marmosets [29]. Additionally, piribedil may potentially worsen or induce visual hallucinations [30, 31]. Forty-nine Filipino PD patients with motor fluctuations were enrolled in an 8-week trial of piribedil of up to 150 mg/day. The most common side effects were hallucinations (20%), dyskinesias (20%), dizziness (8%), and sleepiness (6%) [31]. As piribedil has relatively strong anticholinergic properties, the potential exists for significant anticholinergic side effects (e.g., hallucinations, sicca symptoms, tachycardia, or urinary difficulty) to develop, especially with long-term use. Thus, caution is required in prescribing the drug to the elderly.

Selegiline protects nigral dopaminergic neurons and is recommended for the treatment of patients in the early stage of PD. Kamakura and his researchers [32] treated 112 PD patients and noted that those given selegiline had a high incidence of hallucination. When selegiline is given to patients who have PD of long duration and a high Hoehn and Yahr stage, and who are already receiving levodopa and a dopamine agonist, the doses of levodopa and the dopamine agonists given, as well as the presence of constipation, may be related to the incidence of hallucination. From 1988 to 1992, Vermersch and Petit [33] performed a prospective study to assess the clinical and therapeutic factors that may influence the tolerability of selegiline. In this study, 168 patients were treated with selegiline in combination with levodopa or with levodopa and a dopamine agonist (bromocriptine, lisuride, or piribedil). After an average of 19 months, 23 adverse effects (13.7%) were noted during the first 3 months of treatment with selegiline. Discontinuation was required in only ten cases (5.9%) with nine out of ten for a psychotic episode. While selegiline with levodopa or with bromocriptine and levodopa appeared to be safe antiparkinsonian combinations, significant psychotic side effects occurred with piribedil in combinations with selegiline and levodopa. A possible explanation was that selegiline potentiated piribedil side effects. Piribedil has the unique cellular signature of signal-specific partial agonist actions at dopamine D_2 and D_3 receptors. Selegiline, as an MAO-B inhibitor, could improve the dopamine deficient state. Therefore, the accumulation of dopamine was enhanced after administration of piribedil and selegiline. The mechanism of psychotic symptoms (hallucination) is unclear but could be related to loss of selectivity for MAO-B after chronic selegiline treatment with increased levels of circulating dopamine or metabolism into amphetamines [34].

Before treating psychosis in PD, it is important to rule out an underlying medical illness as the cause of the symptoms. If the patient is in the early stage of the disease, it is likely the psychotic symptoms are attributable to a pre-existing psychiatric disorder or another Parkinsonian syndrome such as dementia with Lewy bodies (DLB). Another important consideration in the management of PD psychosis is the issue of polypharmacy, which has been shown to be an independent risk factor for the development of psychotic symptoms in PD [35].

It is generally accepted that the most effective first-line strategy in the treatment of psychosis in Parkinson's disease is a reduction in anti-PD medications. If the patient is on multiple medications, most authorities would recommend the gradual removal of anti-PD drugs in the following order: anticholinergics, selegiline, amantadine, dopamine agonists, then catechol-O-methyltransferase (COMT) inhibitors, and lastly, levodopa [36, 37]. Clinicians should also consider using the short-acting formulation of levodopa rather than the continued-release or long-acting version because the former carries a lower risk for the accumulation of adverse side effects. If the reduction in anti-PD medications to the lowest dose tolerable without the exacerbation of motor symptoms does not improve psychosis, the addition of an antipsychotic agent should be considered.

Four non-traditional or 'atypical' antipsychotic drugs can be considered for the treatment of psychosis in PD: clozapine, risperidone, olanzapine, and quetiapine. The differences between these agents lie in their relative tendencies to worsen motor symptoms, and their unique side effect profile. Despite its demonstrated efficacy, clozapine is often avoided because of its potential for producing agranulocytosis, which is thought to occur in 0.38% of recipients [38]. Due to numerous reports of motor worsening in PD patients treated with risperidone, and the agent's 'typical' antipsychotic behavior, many movement disorders specialists are reluctant to use this agent to treat PD psychosis [39]. Olanzapine appears ineffective in the treatment of psychosis in PD and can lead to intolerable motor deterioration even at low doses [40]. Quetiapine is a dibenzothiazepine derivative, a strong 5-HT$_2$ receptor antagonist, and a moderate D_2 receptor antagonist [14]. Quetiapine appears to be less effective than clozapine for the treatment of PD psychosis. It does not improve tremor, and it may induce mild motor worsening [41]. However, unlike olanzapine and risperidone, no declines in motor functioning reported in PD patients have required hospitalization [42]. In addition, quetiapine does not carry an associated risk of agranulocytosis, and thus it does not require the vigilant monitoring that clozapine requires [23]. In summary, quetiapine is recommended for the treatment of psychosis in PD. The patient discontinued quetiapine and the psychotic symptoms did not relapse during follow-up, which suggested that improvement of psychotic

symptoms may also be due to the other effects such as the discontinuation of piribedil.

A 66-year-old male patient, with a diagnosis of PD established 10 years ago, was admitted to the Third Xiangya Hospital of Central South University for bradykinesia and hallucination lasting for half a month. Based on the Hoehn-Yahr Scale descriptions, it was likely that this patient was at stage 3. Upon physical examination, mask face was noted as well as upper and lower body rigidity, and a festinating gait. According to the patient's description, his motor symptoms began to worsen 2 months ago and hallucination appeared half a month ago. Therefore, disease-related processes might have contributed to the emergence of psychotic symptoms in this patient.

Long-term treatment of levodopa/carbidopa and piribedil was used in this patient. Considering that psychotic symptoms were frequently caused or worsened by levodopa, the therapeutic dosage of levodopa/carbidopa was reduced to the lowest dose tolerable without the exacerbation of motor symptoms. Additionally, the dosage of selegiline and quetiapine was increased. However, the patient showed slight improvement in hallucination. Finally, based on relevant literature and pharmacokinetic profiles, the clinical pharmacist performed the intervention to discontinue piribedil, which was accepted by clinician. The patient was discharged from the hospital with a notable improvement of hallucinations and bradykinesia.

Conclusion

In summary, psychotic symptoms tend to emerge in the late stage of PD, most commonly manifesting as visual hallucinations. The mechanisms underlying psychotic symptoms in PD have been identified as Lewy body burden in the amygdala and cortical areas, neurochemical abnormalities, and visual processing abnormalities. Long-term treatment with anti-PD medications could contribute to the emergence of psychotic symptoms in PD; in particular, elderly patients in the late stage of PD are more vulnerable to hallucinations with long-term treatment with levodopa/carbidopa and piribedil. Additionally, selegiline could potentiate piribedil psychotic side effects.

Compliance with Ethical Standards

Consent Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent may be requested for review from the corresponding author.

Conflict of interest Chunping Gu, Yueliang Xie, Yinjuan Liao, Cuifang Wu, Shengfeng Wang, Yulu Zhou, and Sujie Jia have no conflicts of interest that are directly relevant to the content of this report.

References

1. Lee A, Gilbert RM. Epidemiology of Parkinson disease. Neurol Clin. 2016;34:955–65.
2. Kubota KJ, Chen JA, Little MA. Machine learning for large-scale wearable sensor data in Parkinson's disease: concepts, promises, pitfalls, and futures. Mov Disord. 2016;31:1314–26.
3. Cooney JW, Stacy M. Neuropsychiatric issues in Parkinson's disease. Curr Neurol Neurosci Rep. 2016;6:49.
4. Castrioto A, Thobois S, Carnicella S, Maillet A, Krack P. Emotional manifestations of PD: neurobiological basis. Mov Disord. 2016;31:1103–13.
5. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. Visual symptoms in Parkinson's disease and Parkinson's disease dementia. Mov Disord. 2011;26:2387–95.
6. Goetz CG, Stebbins GT, Ouyang B. Visual plus nonvisual hallucinations in Parkinson's disease: development and evolution over 10 years. Mov Disord. 2011;26:2196–200.
7. Gibson G, Mottram PG, Burn DJ, Hindle JV, Landau S, Samuel M, Hurt S, Brown RG, Wilson KCM. Frequency, prevalence, incidence and risk factors associated with visual hallucinations in a sample of patients with Parkinson's disease: a longitudinal 4-year study. Int J Geriatr Psychiatry. 2013;28:626–31.
8. Muller-Rebstein S, Trenkwalder C, Ebentheuer J, Oertel WH, Culmsee C, Hoglinger GU. Drug safety analysis in a real-life cohort of Parkinson's disease patients with polypharmacy. CNS Drugs. 2017. https://doi.org/10.1007/s40263-017-0478-0 (Epub ahead of print).
9. Zahodne LB, Fernandez HH. A review of the pathophysiology and treatment of psychosis in Parkinson's disease. Drug Aging. 2008;25(8):665–82.
10. Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology. 1967;17:427–42.
11. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, Giladi N, Holloway RG, Moore CG, Wenning GK, Yahr MD, Seidl L. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. The Movement Disorder Society Task Force on rating scales for Parkinson's disease. Mov Disord. 2004;19:1020–8.
12. Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, Lau PN, Pica EC, Li SC, Luo N, Tan LC. Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. Mov Disord. 2010;25:710–6.
13. Pae C, Bodkin J, Portland K. Few serious adverse events in transdermal selegiline. Brown University Psychopharmacology Update. 2012;10:4–4.7/8.

14. Dando Toni M, Keating Gillian M. Quetiapine: a review of its use in acute mania and depression associated with bipolar disorder. Drugs. 2005;65:2533–51.

15. Pagonabarraga J, Martinez-Horta S, Fernández de Bobadilla R, Perez J, Roser RN, Marin J, Berta PS, Garcia C, Gironell A, Kulisevsky J. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. Mov Disord. 2016;31:45–52.

16. Fenelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. Neurology. 2006;66:93–8.

17. Leenders KL, Poewe WH, Palmer AJ, Brenton DP, Frackowiak RS. Inhibition of L-[18F]fluorodopa uptake into human brain by amino acids demonstrated by positron emission tomography. Ann Neurol. 1986;20:258–62.

18. Daniel PM, Moorhouse RS, Pratt OE. Letter: do changes in blood levels of other aromatic aminoacids influence levodopa therapy? Lancet. 1976;1:95.

19. Oldendorf WH. Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am J Physiol. 1971;221:1629–39.

20. Wade LA, Katzman R. Synthetic amino acids and the nature of L-DOPA transport at the blood–brain barrier. J Neurochem. 1975;25:837–42.

21. Virmani T, Tazan S, Mazzoni P, Ford B, Greene PE. Motor fluctuations due to interaction between dietary protein and levodopa in Parkinson's disease. J Clin Mov Disord. 2016;3:1–7.

22. Vermersch P, Petit H. Long-term selegiline tolerance in the treatment of Parkinson's disease. Therapie. 1992;47:75–8.

23. Zahodne LB, Fernandez HH. A review of the pathophysiology and treatment of psychosis in Parkinson's disease. Drugs Aging. 2008;25:665–82.

24. Urwyler P, Nef T, Killen A, Collerton D, Thomas A, Burn D, McKeith I, Mosimann UP. Visual complaints and visual hallucinations in Parkinson's disease. Parkinsonism Relat Disord. 2014;20:318–22.

25. Fenelon G, Mahieux F, Huron R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain. 2000;123:733–45.

26. Friedman A, Sienkiewicz J. Psychotic complications of long-term levodopa treatment of Parkinson's disease. Acta Neurol Scand. 1991;2:111–3.

27. Millan Mark J. From the cell to the clinic: a comparative review of the partial D_2/D_3 receptor agonist and α_2-adrenoceptor antagonist, piribedil, in the treatment of Parkinson's disease. Pharmacol Ther. 2010;128:229–73.

28. Martien S, Josephine P, Gaynor B, Megan G. Pharmacological lactation suppression with D_2 receptor agonists and risk of postpartum psychosis: a systematic review. Aust N Z J Obstet Gynaecol. 2016;56:336–40.

29. Smith LA, Tel BC, Jackson MJ, Hansard MJ, Braceras R, Bonhomme C, Chezaubernard C, Signore SD, Rose S, Jenner P. Repeated administration of piribedil induces less dyskinesias than L-dopa in MPTP-treated common marmosets: a behavioral and biochemical investigation. Mov Disord. 2002;17:887–901.

30. Robbana L, Belarbi A, Nasri A, Moula O, Bouasker A, Ghachem R. EPA-1699—hallucinations and Parkinson disease: a report case. Eur Psychiatry. 2014;29:1.

31. Evidentea VGH, Estebanb RP, Domingoc FM, Carbajalc LO, Parazod MA. Piribedil as an adjunct to levodopa in advanced Parkinson's disease: the Asian experience. Parkinsonism Relat Disord. 2003;10:117–21.

32. Kamakura K, Mochizuki H, Kaida KI, Hirata A, Kanzaki M, Masaki T, Nakamura R, Motoyoshi K. Therapeutic factors causing hallucination in Parkinson's disease patients, especially those given selegiline. Parkinsonism Relat Disord. 2004;10:235–42.

33. Vermersch P, Petit H. Long-term selegiline tolerance in the treatment of Parkinson's disease. Therapie. 1992;47:75–8.

34. Montastruc JL, Chaumerliac C, Desboeuf K, Manika M, Bagheri H, Rascol O, Maryse LM. Adverse drug reactions to selegiline: a review of the French pharmacovigilance database. Clin Neuropharmacol. 2000;23(5):271–5.

35. Henderson MJ, Mellers JDC. Psychosis in Parkinson's disease: 'between a rock and a hard place'. Int Rev Psychiatry. 2000;12:319–34.

36. Fernandez HH, Friedman JF. The role of atypical antipsychotics in the treatment of movement disorders. CNS Drugs. 1999;11:467–83.

37. Friedman JH, Fernandez HH. The non-motor problems of Parkinson's disease. Neurology. 2000;6:18–27.

38. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry. 1998;59:3–7.

39. Factor SA, Molho ES, Friedman JH. Risperidone and Parkinson's disease. Mov Disord. 2001;12:364–9.

40. Goetz CG, Blasucci LM, Leurgans S, Pattert EJ. Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. Neurology. 2000;55:789–94.

41. Fernandez HH, Trieschmann ME, Friedman JH. The treatment of psychosis in Parkinson's disease: safety considerations. Drug Saf. 2003;26:643–59.

42. Klein C, Prokhorov T, Miniovich A, Dobronevsky E, Rabey JM. Long-term follow-up (24 months) of quetiapine treatment in drug-induced Parkinson disease psychosis. Clin Neuropharmacol. 2006;29:215–9.