Evidence for using pimavanserin for the treatment of Parkinson's disease psychosis

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Abstract
The aim of this editorial is to evaluate the evidence for using pimavanserin for the treatment of Parkinson's disease psychosis (PDP) from randomized controlled trials (RCTs). We only identified two published trials that evaluated the use of pimavanserin among individuals with PDP. Both studies found that pimavanserin improved psychotic symptoms among individuals with PDP when compared to placebo. Pimavanserin was fairly well tolerated in both studies and did not appear to cause significant sedation or worsen motor symptoms among individuals with PDP. However, given the limited data, additional confirmatory studies are required before pimavanserin can be considered as a first line agent for the treatment of psychotic symptoms among individuals with PD.

Key words: Pimavanserin; Parkinson’s disease; Parkinson’s disease psychosis; Psychosis; Antipsychotic
approved by the Food and Drug Administration for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). There are only two published trials that have evaluated the use of pimavanserin among individuals with PDP. Both studies are of good quality and found that pimavanserin improves psychotic symptoms among individuals with PDP when compared to placebo. Additionally, pimavanserin was fairly well tolerated in both studies and did not appear to cause significant sedation or worsen motor symptoms among individuals with PDP.

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INTRODUCTION

Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disorder that presents with tremors, bradykinesia, rigidity and postural instability[1]. After Alzheimer's disease (AD), PD is the second-most common neurodegenerative disorder in the United States[2]. Approximately 630000 individuals in the United States have a diagnosis of PD, with the diagnosed prevalence of PD likely to double by 2040. The prevalence for PD increases with age ranging from approximately 41 per 100000 people of 40 to 49 years of age to 1903 per 100000 population in individuals ≥ 80 years of age[3]. The economic burden of PD is reflected by the incurred medical expenses approximating $14 billion in 2010 which was $8.1 billion higher than expected for a similar population without PD[3].

Psychotic symptoms are not uncommon among individuals with PD with a prevalence rate of approximately 25%-30%[4,5]. The National Institute of Neurological Disorders and Stroke and National Institute of Mental Health combined work group used the term “PD psychosis” (PDP) to describe the various psychotic symptoms that present as a continuum of PD progression rather than representing a distinct symptom class[6]. For the diagnosis of PD psychosis to made, the following criteria should be met: (1) The presence of at least one of the following symptoms: illusions, false sense of presence, hallucinations or delusions; (2) A primary diagnosis of PD; (3) Meet the United Kingdom brain bank criteria for PD; (4) The psychotic symptoms occurred after the diagnosis of PD was made; (5) The symptom(s) are recurrent or continuous for 1 mo; (6) The symptoms are not better accounted for by another cause of Parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium; and (7) These symptoms could be associated with or without insight, with or without dementia, and with or without treatment for PD.

Risk factors for PDP include the presence of dementia, older age, reduced vision, longer duration of illness, high severity of illness, presence of depression, sleep disturbance and REM behavior disorder, axial rigidity subtype of PD, and exposure to dopamine agonists (DA)[7]. The presence of PDP is associated with greater caregiver stress, poorer quality of life for the individual with PD, higher rates of institutionalization or nursing home placement, and increased mortality[8]. A recent analysis of all health resource utilization (HRU) and total costs found that mean 12-mo HRU per patient was 2.3 times higher and costs were 2.1 times higher in the PDP cases, while falls were 3.4 times higher and fractures 2.3 times higher respectively[9].

The pathogenesis of PDP is yet to be clearly understood but present data indicates significant dysfunction in attention, executive functions, and visuospatial functions in these individuals[10]. Additionally, neuroimaging studies reveal grey matter atrophy in regions of the brain corresponding to dorsal and ventral visual pathways, the hippocampus, and cholinergic structures. Furthermore, functional imaging studies suggest the existence of an aberrant top-to-bottom visual processing system which dominates the normal bottom-to-top system in individuals with PD and visual hallucinations. Nucleotide polymorphisms of several genes have been studied among individuals with PDP, but thus far the 45C>T polymorphisms of the cholecystokinin gene (CCK) appears to have had the most potential in elucidating pathological pathways of PDP[10].
PDP may also occur partially due to medications that are used to treat the motor symptoms of PD\textsuperscript{[11]}. Hence, a part of treating PDP also involves the reduction or discontinuation of anticholinergic medications, monoamine oxidase inhibitors, levodopa, or DA which may be worsening or causing symptoms of PDP\textsuperscript{[12,21,22]}. If medication adjustments are not appropriate or they do not resolve the PDP symptoms, then available data from controlled trials indicate there is some benefits for use of antipsychotic medications, the acetylcholinesterase inhibitor-rivastigmine, and NMDA antagonist-memantine for treating PDP\textsuperscript{[11]}. Uncontrolled trials also indicate some benefit for low-dose apomorphine\textsuperscript{[14-17]} and electroconvulsive therapy (ECT)\textsuperscript{[15-20]} for treating PDP. However, none these therapies are approved by the United States Food and Drug Administration (FDA) for the treatment of PDP.

A recent systematic review by Wilby \textit{et al}\textsuperscript{[21]} that assessed the treatment for PDP included data from 16 studies. Eleven of these studies compared active drugs to placebo whereas 5 studies compared clozapine to another active drug. The placebo-controlled trials demonstrated benefit for clozapine and pimavanserin (Nuplazid) for the treatment of PDP with no definitive benefits noted for either quetiapine or olanzapine. The comparative studies demonstrated improvements in PDP symptoms when clozapine or comparator drug were assessed alone. However, the data did not suggest any superiority of one active drug over the other drugs.

Pimavanserin is an atypical antipsychotic medication and is now the first medication to be approved by the FDA for the treatment of hallucinations and delusions associated with PDP\textsuperscript{[21]}. Pimavanserin is a selective 5-HT2A inverse agonist that has low affinity for 5-HT2C and sigma-1 receptors. Additionally, pimavanserin lacks activity at dopaminergic, muscarinic, adrenergic, and histaminergic receptors. Pimavanserin is mainly metabolized in the liver through the cytochrome P450 system (CYP3A4 and CYP3A5) and is excreted primarily through the urine. Approximately 95\% of pimavanserin is protein bound. Pimavanserin has a mean peak onset in 6 h with a half-life of 55 to 60 h.

**EVIDENCE FOR USING PIMAVANSERIN FOR THE TREATMENT OF PARKINSON’S DISEASE PSYCHOSIS**

We identified and reviewed a total of two randomized controlled trials (RCTs) that evaluated the use of pimavanserin among individuals with PDP\textsuperscript{[2,4,14-17]}. Both studies were rated as being of good quality based on the center for evidence-based medicine criteria\textsuperscript{[23]} (Table 1). We discuss both studies in depth below, while a brief summary of both studies is outlined in Table 2.

*Meltzer \textit{et al}\textsuperscript{[4]} study*

The study by Meltzer \textit{et al}\textsuperscript{[23]} was a phase 2 multicenter, randomized, placebo-controlled, double-blind trial that compared pimavanserin to placebo among individuals with PDP. The trial was 4 wk in duration with a 4-wk follow-up period. The participants received pimavanserin or placebo in a 1:1 ratio, after completion of screening and baseline evaluations. The dosing of the study drug was 20 mg on day 1 with possible increases to 40 mg a day and 60 mg a day on study days 8 and 15, depending on the participants’ response to the medication. The staging of PD was done at baseline using the modified Hoehn and Yahr Unified Parkinson’s Disease Rating Scale (UPDRS Part V). The psychotic symptoms were evaluated using the Scale for the Assessment of Positive Symptoms (SAPS), the Parkinson’s Psychosis Rating Scale (PPRS) and the Clinical Global Impression-Severity (CGI-S) scale. The effect of treatment on mentation, behavior, mood, complications of therapy and activities of daily living were assessed using the UPDRS Parts I, IV and VI. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale. The motor symptoms were assessed using the UPDRS Parts II (Activities in Daily Living) and III (Motor Examination) respectively. An adverse event check list, vital signs, laboratory tests, physical examinations and electrocardiograms (ECG) were also completed.

The participants were assessed at screening/baseline (up to 14 d prior to study day 1). The study visits were days 1, 8, 15, 28, and 57. Visit day 57 was a safety data evaluation visit. The investigators completed a physical examination, vital signs and laboratory tests at each study visit. From day 1 to 57, the adverse events were noted and assigned severity and relationship to treatment.

The investigators noted improvements in the global rating of hallucination ($P = 0.02$, effect size 0.71), persecutory delusions domain score ($P = 0.009$, effect size 0.69) and in the ideas and delusions of reference domain score ($P = 0.05$, effect size 0.56) in the pimavanserin group when compared to the placebo group. Additionally, improvements were noted in the global rating of delusions ($P = 0.03$, effect size 0.58).
Table 1  Quality of studies reviewed

| Name of publication of study | Yr | Randomization? | Similar groups initially? | Equal treatments? | All participants accounted for? | Analyzed in groups to which they were randomized? | Objective/“blind” treatments? | Overall quality of the study |
|-----------------------------|----|----------------|--------------------------|------------------|--------------------------------|-----------------------------------------------|-----------------------------|---------------------------|
| Meltzer et al[23]           | 2010 | Yes           | Yes                      | Yes              | Yes                            | Yes                                           | Yes                         | Good                      |
| Cummings et al[24]          | 2014 | Yes           | Yes                      | Yes              | Yes                            | Yes                                           | Yes                         | Good                      |

and the sum of global ratings total (hallucinations and delusions) scores ($P = 0.02$, effect size 0.66) in the pimavanserin group when compared to the placebo group. Furthermore, a trend was noted in improvement in the sum of total (hallucinations and delusions) domain scores ($P = 0.09$, effect size 0.56) in the pimavanserin group when compared to the placebo group. The investigators also noted improvements in the UPDRS Part I total score ($P = 0.05$, effect size 0.43) in the pimavanserin group when compared to the placebo group. Improvements were also noted in the UPDRS IV (complications of therapy) scores ($P = 0.06$, effect size 0.55) in the pimavanserin group when compared to placebo but did not reach statistical significance. However, there were no significant improvements noted in the UPDRS Part II and III ($P = 0.83$, 0.40, 0.74 respectively), the PPRS scores ($P = 0.11$, effect size 0.48), the CGI-S ($P = 0.20$, effect size 0.58) and the UPDRS VI (activities of daily living) scores ($P = 0.22$, effect size 0.41) in the pimavanserin group when compared to placebo group.

The investigators did not identify any significant differences between the pimavanserin and placebo groups on the treatment-emergent adverse events (72.4% vs 77.4%). The most common adverse effects noted in the pimavanserin group were somnolence, edema and increase in blood urea nitrogen (all 10.3%). They noted that balance disorder and freezing phenomenon occurred in 6.9% of pimavanserin treated individuals when compared to none of the placebo treated individuals. Additionally, “on and off” phenomenon was noted in 3.4% of pimavanserin treated individuals when compared to none of the placebo treated individuals.

There are multiple weaknesses in this study to be highlighted. The study had a small sample size; only 44 total subjects (20 in pimavanserin group and 24 in placebo group) completed the study. There was also noted to be a relatively high attrition rate in the pimavanserin group ($n = 9$ or 31%) compared to placebo group ($n = 7$ or 23%) with the most common reason they dropped out being described as “other reasons”. The dropout rate was greater than the estimated 10% dropout rate the authors predicted in their analysis, although they report that ITT and PP analysis results were similar. It is also noteworthy that in the study design utilized relatively rapid dose escalation. Pimavanserin takes 10-14 d to reach steady state. Thus, escalating the dose after 1 wk of treatment may have led to insufficient time to achieve full efficacy. The study also did not assess the time of onset of delusions or hallucinations in relation to the duration of treatment with L-DOPA, which leaves a potential confounding factor.

An additional confounding factor to consider is that they also did not assess the efficacy of primavanserin in patients who were not receiving dopaminomimetic drugs. Also since the study is just placebo controlled, there is no comparison of efficacy/tolerability between pimavanserin and other antipsychotics such as clozapine.

Cummings et al[24] study

The study by Cummings et al[24] study was a randomized, double-blind, parallel group, placebo-controlled trial that enrolled participants with PDP from 52 centers (academic hospitals or neurology research centers) in the United States and two centers in Canada. The eligible participants were randomized to receive either pimavanserin (40 mg daily) or matched placebo in a 1:1 ratio in a double-blind manner. The assessments were completed at baseline and days 15, 29 and 43. The primary outcome was the change in total Parkinson’s disease-adapted scale for assessment of positive symptoms (SAPS-PD) score from baseline to day 43. The secondary outcomes were the change by day 43 in CGI-S and improvement (CGI-I) scale scores. The other measures were the Zarit 22-item care giver burden scale, scales for outcomes in PD-sleep (parts B and C) assessing night-time sleep quality (SCOPA-NS) and daytime wakefulness (SCOPA-DS) and the UPDRS II and III. Safety was assessed by evaluating the use of concomitant drug use, adverse events, physical examination, clinical laboratory tests, vital signs and ECG.
Table 2 Summary of studies

| Name of study       | Yr  | Country of origin          | Total number of participants | Age               | Type of setting                              | Comparators         | Duration |
|---------------------|-----|----------------------------|------------------------------|-------------------|----------------------------------------------|----------------------|----------|
| Meltzer et al[23]   | 2010| United States              | 60                           | Mean age 70.9 yr  | Unclear                                      | Pimavanserin vs placebo | 4 wk     |
| Cummings et al[24] | 2014| United States and Canada   | 199                          | Mean age 72.4 yr  | Academic hospitals and neurology research centers | Pimavanserin vs placebo | 6 wk     |

The investigators noted improvements in the total SAPS-PD score ($P = 0.0014$, effect size 0.50), the CGI-I score ($P = 0.0012$, effect size 0.50) and the CGI-S score ($P = 0.0007$, effect size 0.52) in the pimavanserin group when compared to placebo group. Additionally, improvements were noted in the SCOPA-night score ($P = 0.04$, effect size 0.31) and the SCOPA-day wake score ($P = 0.01$, effect size 0.39) in the pimavanserin group when compared to placebo group. Furthermore, improvements were noted in the Zarit Caregiver burden score ($P = 0.0016$, effect size 0.50) in the pimavanserin group when compared to placebo group. The investigators also noted non-significant improvements in both pimavanserin and placebo groups (-1.69 and -1.40) in the motor function (UPRDRS II and III) composite score.

There are some weaknesses to consider with this study. The study does not provide sufficient safety data or evidence about durability of response beyond 6 wk. The duration of the trial also limits the ability to look at long term benefits such as reduced nursing home admission and caregiver burden. A confounding factor to consider is that 99% of subjects in both placebo and pimavanserin group were using dopaminergic medications at baseline and throughout the RCT indicating they were not able to study efficacy of pimavanserin in patients not on dopaminergic drugs. Additionally, as with the Meltzer et al[23] study there is no comparison of efficacy/tolerability between pimavanserin and other antipsychotics such as clozapine.

**DISCUSSION**

Data available from these two well-designed studies indicates that pimavanserin improves psychotic symptoms (delusions and hallucinations) among individuals with PDP when compared to placebo[23,24]. Additionally, pimavanserin appears to be fairly well tolerated with no worsening of the motor symptoms of PD. Furthermore, no increase in mortality rates was noted among pimavanserin treated individuals in both studies.

A meta-analysis by Yasue et al[26] that included data from 4 RCTs that studied the use of pimavanserin for PDP. This meta-analysis included 417 pimavanserin-treated and 263 placebo-treated individuals with PDP. The investigators found that pimavanserin decreased the symptoms of hallucinations and delusions when compared to placebo [weighted mean differences (WMD) = -2.26, $P = 0.005$]. In addition, pimavanserin was found to be superior to placebo when evaluating the reduction in the symptoms of hallucinations (WMD = -2.15, $P = 0.001$) and delusions (WMD = -1.32, $P = 0.010$) independently. The investigators did not find any significant difference between pimavanserin and placebo on the all-cause discontinuation rates for adverse events, death, Parkinson motor symptoms and the incidence of individual adverse events. Pimavanserin was also associated with less orthostatic hypotension when compared to placebo (risk ratio = 0.33, $P = 0.008$, number needed to harm = 17, $P = 0.01$). The investigators concluded that pimavanserin is beneficial for the treatment of symptoms of PDP and is well tolerated.

In addition to the data from the two studies that we found from our literature search, Yasue et al[26] included data from two unpublished studies of pimavanserin
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The authors concluded that pimavanserin is the only FDA-approved treatment for the hallucinations and delusions among individuals with PDP. Despite pimavanserin’s different pharmacologic mechanism when compared to other atypical antipsychotics, the FDA remains concerned about the increased risk of death seen with other antipsychotic use among older adults. Thus Pimavanserin was also given the same boxed warning regarding the risk of death associated with antipsychotic use among older adults with dementia.

Pimavanserin’s package insert indicates that the drug prolongs QT interval and its use should be avoided among individuals with known QT prolongation or in combination with other drugs that can prolong the QT interval including antiarrhythmics (quinidine, procainamide, amiodarone), certain anti-psychotic medications (ziprasidone, chlorpromazine, thioridazine) and certain antibiotics (gatifloxacin, moxifloxacin)(33). Additionally, pimavanserin should be avoided among individuals with a history of cardiac arrhythmias, in situations that may increase the risk of torsades de pointes and/or sudden death including symptomatic bradycardia, hypokalemia or hypomagnesemia, and in the presence of congenital prolongation of the QT interval. However our review of the literature did not find any evidence of clinically significant increase in QTc with the use of pimavanserin among individuals with PDP. This data is consistent with the data from the Yasue et al meta-analysis.

A recent 6-wk randomized, placebo-controlled, double-blind study that included 181 participants who lived in nursing homes and had possible or probable AD and psychotic symptoms found that pimavanserin improved psychotic symptoms among these individuals at 6 wk when compared to placebo (Cohen’s d = -0.32; $P = 0.045$)(30). However, by week 12 the investigators found no significant advantage for pimavanserin when compared to placebo ($P = 0.561$). Common adverse events noted in the study when comparing pimavanserin vs placebo were falls (23% vs 23%), urinary tract infections (22% vs 28%) and agitation (21% vs 14%). Treatment discontinuation due to adverse events was seen in 9% of pimavanserin treated individuals when compared to 12% of the placebo treated individuals. There was no significant difference between the pimavanserin and placebo treated individuals on cognition or motor functioning.

A Pennsylvania-based non-profit organization published reports of post-marketing adverse events include hallucinations, confused states and deaths with the use of pimavanserin(34). The data published by Institute for Safe Medication Practices in November 2017 indicates that in total there were 2236 adverse events for the 12 mo post-marketing observation period ending in March 2017(35). The four most frequently reported adverse events were hallucinations 487 (21.8%) drug ineffectiveness 333 (14.9%), confused state 258 (11.5%) and death 244 (10.9%).

The United States FDA completed a review of all post-marketing reports of deaths and serious adverse events reported with the use of pimavanserin(36). The FDA did not identify any new or unexpected safety findings with pimavanserin or findings that were inconsistent with the established safety profile currently described for the drug. The FDA concluded that the drug’s benefits outweigh its risks for patients with hallucinations and delusions of PDP.

CONCLUSION
Data available from two well-designed studies indicates that pimavanserin improves psychotic symptoms among individuals with PD when compared to placebo. In addition, pimavanserin appears to be fairly well tolerated with no serious adverse effects and it does not appear to worsen the motor symptoms of PD. Additional well-controlled studies with positive data for both efficacy and safety are required before pimavanserin can be designated as the first line agent for use among individuals with PD.

REFERENCES

1 Sveinbjörnsdottr I. The clinical symptoms of Parkinson's disease. J Neurochem 2016; 139 Suppl 1: 318-324 [PMID: 27401947 DOI: 10.1111/jn.13691]
2 Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A. The current and projected economic burden of Parkinson's disease in the United States. Mov Disord 2013; 28: 311-318 [PMID: 23436720 DOI: 10.1002/mds.25292]
3 Pringsheim T, Jette N, Frolik S, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014; 29: 1583-1590 [PMID: 24976103 DOI: 10.1002/mds.25945]
4 Flyshe DH, Creer M, Politis M, Chaudhuri KR, Weintraub D, Ballard G, Aarsland D. The psychosis spectrum in Parkinson disease. Nat Rev Neurol 2017; 13: 81-95 [PMID: 28106066 DOI: 10.1038/nrneurol.2016.200]
5 Mack J, Rabins P, Anderson K, Goldstein S, Grill S, Hirsch ES, Lehmann S, Little JT, Margolis RL, Palanci J, Fontone G, Weiss H, Williams JR, Marsh L. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. Am J Geriatr Psychiatry 2012; 20: 123-132 [PMID: 21617321 DOI: 10.1097/JGP.0b013e31821f44]
6 Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, Aarsland D, Babcock D, Cummings J, Endicott J, Factor S, Galpern W, Lees A, Marsh L, Stacy M, Gwinn-Hardy K, Voorn V, Goetz C. Diagnostic criteria for psychosis in Parkinson’s disease. Mov Disord 2007; 22: 1061-1068 [PMID: 17266992 DOI: 10.1002/mds.2134]
7 Friedman JH. Parkinson disease psychosis: Update. Behav Neurol 2013; 27: 469-497 [PMID: 23243258 DOI: 10.3233/BEN-129016]
8 Ojo OO, Fernandez HH. Current Understanding of Psychosis in Parkinson's Disease. Curr Psychiatry Rep 2016; 18: 97 [PMID: 27629356 DOI: 10.1007/s11920-016-0730-1]
9 Fredericks D, Norton JC, Atchison C, Schoenhaus R, Pill MW. Parkinson’s disease and Parkinson’s disease psychosis: a perspective on the challenges, treatments, and economic burden. Am J Manag Care 2017; 23: 583-592 [PMID: 28719303]
10 Lenka A, Herath P, Christopher R, Pal PK. Psychosis in Parkinson's disease: From the soft signs to the hard science. J Neural Sci 2017; 379: 169-176 [PMID: 28716239 DOI: 10.1007/s10992-017-0111-1]
11 Chang A, Fox SH. Psychosis in Parkinson's Disease: Epidemiology, Pathophysiology, and Management. Drugs 2016; 76: 1093-1118 [PMID: 27312429 DOI: 10.1007/s40265-016-0600-5]
12 Cooney JW, Stacy M. Neuropsychiatric Issues in Parkinson's Disease. Curr Neurol Neurosci Rep 2016; 16: 49 [PMID: 27048443 DOI: 10.1007/s11910-016-0647-4]
13 Patel T, Chang F. Parkinson Society Canada. Parkinson’s disease guidelines for pharmacists. Can Pharm J (Ott) 2014; 147: 161-170 [PMID: 24847369 DOI: 10.1177/171563141297490]
14 Jauhar S, Veronese M, Rodega M, Bloomfield M, Natesan S, Turkheimer F, Kapur S, Howes OD. Regulation of dopaminergic function: an [-sup>18</sup>-F]-DOPA PET apomorphine challenge study in humans. Transl Psychiatry 2017; 7: e1027 [PMID: 28170002 DOI: 10.1038/tp.2016.270]
15 Muralidharan K, Thirumath R, Chakraborty V, Jain S. Bifrontal ECT for drug-induced psychosis in Parkinson's disease. Indian J Psychiatry 2011; 53: 156-158 [PMID: 21772651 DOI: 10.4103/0019-5545.82549]
16 Nishioka K, Tanaka R, Shimura H, Hiran K, Hatano T, Miyakawa K, Arai H, Hattori N, Urabe T. Quantitative evaluation of electroconvulsive therapy for Parkinson’s disease with refractory psychiatric symptoms. J Neural Transm (Vienna) 2014; 121: 1405-1410 [PMID: 24744048 DOI: 10.1007/s00702-014-1212-4]
17 Usui C, Hatta K, Doi N, Kubo S, Kaniangiichi R, Nakanishi A, Nakamura H, Hattori N, Arai H. Improvements in both psychosis and motor signs in Parkinson's disease, and changes in regional cerebral blood flow after electroconvulsive therapy. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35: 1704-1708 [PMID: 21605615 DOI: 10.1016/j.pnpbp.2011.05.003]
18 Factor SA, Molho ES, Brown DL. Combined clozapine and electroconvulsive therapy for the treatment of drug-induced psychosis in Parkinson’s disease. J Neuropsychiatry Clin Neurosci 1999; 11: 304-307 [PMID: 7580185 DOI: 10.1176/jnp.73.3.304]
19 Höflisch G, Burghoff KW, Kasper S, Möller HJ. [Electroconvulsive therapy in comorbidity of treatment refractory paranoid hallucinatory psychoses with Parkinson disease]. Nervenarzt 1994; 65: 202-205 [PMID: 7909917]
20 Ueda S, Koyama K, Okubo Y. Marked improvement of psychotic symptoms after electroconvulsive therapy in Parkinson's disease. J ECT 2010; 26: 111-115 [PMID: 20386461 DOI: 10.1097/YCT.0b013e3181c1826d]
21 Wilby KJ, Johnson EG, Johnson HE, Esmom MHH. Evidence-Based Review of Pharmacotherapy Used for Parkinson's Disease Psychosis. Am Pharmaco Ther 2017; 51: 682-695 [PMID: 28385039 DOI: 10.1177/0003364617693092]
22 Bozymski KM, Lowe DK, Pasternak KM, Gatesman TL, Crouse EL. Pimavanserin: A Novel Antipsychotic for Parkinson’s Disease Psychosis. Am Pharmaco Ther 2017; 51: 479-487 [PMID: 28375643 DOI: 10.1177/0003364617693092]
23 Meltzer HY, Mills R, Revell S, Williams H, Johnson A, Bahr D, Friedman JH. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. Neuropsychopharmacology 2010; 35: 881-892 [PMID: 19907417 DOI: 10.1038/npp.2009.176]
24 Cummings J, Isaacsen S, Mills R, Williams H, Chu-Birru K, Corbet A, Dhall P, Ballard C. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3
Tampi RR et al. Evidence for using pimavanserin for the treatment of PDP

25 Available from: http://www.cebm.net/critical-appraisal

26 Yasue I, Matsunaga S, Kishi T, Fujita K, Iwata N. Serotonin 2A Receptor Inverse Agonist as a Treatment for Parkinson's Disease Psychosis: A Systematic Review and Meta-analysis of Serotonin 2A Receptor Negative Modulators. J Alzheimers Dis 2016; 50: 733-740 [PMID: 26757194 DOI: 10.3233/JAD-150818]

27 ACADIA Pharmaceuticals Inc. A Study of Safety and Efficacy of Pimavanserin (ACP-103) in Patients With Parkinson's Disease Psychosis. [accessed 2018 May 20]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT00658567 ClinicalTrials.gov Identifier: NCT00658567/

28 ACADIA Pharmaceuticals Inc. A Study of the Safety and Efficacy of Pimavanserin (ACP-103) in Patients With Parkinson's Disease Psychosis. [accessed 2018 May 20]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT00477672 ClinicalTrials.gov Identifier: NCT00477672/

29 Mathis MV, Muoio BM, Andreason P, Avila AM, Farchione T, Atrakchi A, Temple RJ. The US Food and Drug Administration's Perspective on the New Antipsychotic Pimavanserin. J Clin Psychiatry 2017; 78: e668-e673 [PMID: 28493654 DOI: 10.4088/JCP.16r11119]

30 Cruz MP. Pimavanserin (Nuplazid): A Treatment for Hallucinations and Delusions Associated With Parkinson's Disease. P T 2017; 42: 368-371 [PMID: 28579723]

31 Ballard C, Banister C, Khan Z, Cummings J, Demos G, Coule B, Youakim JM, Owen R, Stankovic S; ADP Investigators. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study. Lancet Neurol 2018; 17: 213-222 [PMID: 29452664 DOI: 10.1016/S1474-4422(18)30039-5]

32 Webster P. Pimavanserin evaluated by the FDA. Lancet 2018; 391: 1762 [PMID: 29739555 DOI: 10.1016/S0140-6736(18)31002-X]

33 Institute for Safe Medication Practices. Hallucinations and Pimavanserin (NUPLAZID), a New Kind of Drug for Psychosis. ©Institute for Safe Medication Practices. 2017; 1-18 Available from: https://www.ismp.org/sites/default/files/attachments/2018-01/2017Q1_0.pdf/

34 FDA Analysis Finds No New or Unexpected Safety Risks Associated with Nuplazid (Pimavanserin), a Medication to Treat the Hallucinations and Delusions of Parkinson’s Disease Psychosis. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm
