DOI: 10.14744/DAJPNS.2021.00164
Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2021;34:396-397

LETTER TO THE EDITOR

Pimavanserin in psychiatry- novel facts vs fiction

Sheikh Shoib[1], Alaa Baiou[2], Sana Javad[3], Doménica Nathaly Cevallos-Robalino[4], Fahimeh Saeed[5]

[1]Jawaharlal Nehru Memorial (JLNM) Hospital, Srinagar, Kashmir, India
[2]University Road, Faculty of Medicine, University of Tripoli, Furnaj, Tripoli, Libya
[3]Nishtar Medical University Multan, Pakistan
[4]One Health Research Group, Universidad de las Américas UDLA, Quito, Ecuador
[5]University of Social Welfare and Rehabilitation Sciences, Psychosis Research Center, Department of Psychiatry, Tehran, Iran

Dear Editor,

Parkinson's disease (PD) is characterized by gradual neural degeneration in the substantia nigra, a region of the midbrain, which results in motor abnormalities, e.g., bradykinesia, resting tremor, cogwheel rigidity, and postural instability. The neuropsychiatric symptoms can include depression, dementia, apathy, hallucinations, and delusions (1). Some 20% to 50% of PD patients develop psychosis, with hallucinations and/or delusions being the most prevalent symptoms (2).

Pimavanserin (Nuplazid; Acadia Pharmaceuticals Inc., San Diego, CA, USA) is a 5-HT2A receptor antagonist. It differs from other antipsychotic medications commonly used in Parkinson's disease psychosis (PDP) due to the selectivity for 5-HT2 receptors, a lower binding-affinity at the serotonin-2C receptor and the sigma 1 receptor, and because it spares dopamine post-synaptic receptors. It was approved by the US Federal Drug Administration in 2016 to treat Parkinson's-related delusions and hallucinations (1). Development of the drug as a treatment for schizophrenia was attracted researchers and pimavanserin is currently in phase 3 clinical trials for the treatment of schizophrenia (2,3).

Two 17 mg tablets (total of 34 mg) each day have been recommended for treatment of Alzheimer's disease-related psychosis. For patients taking strong CYP3A4 inhibitors (e.g., ketoconazole), the recommended dosage is a single 10 mg tablet daily (4). Patients taking heavy 3A4 inducers (e.g., rifampin) should be checked for decreased efficacy. In such situations, a dose increase could be required, but no clear guidelines have yet been provided (5).

While pimavanserin has not been tested in those with severe renal impairment (creatinine clearance 30 mL/min), there is no known need for a dosage change in those with mild to moderate renal dysfunction. It has not yet been studied in patients with hepatic impairment. However, current line of evidence indicated that there is no need to change the dosage according to age, gender, race, or weight (1).

Side effects profile. Pimavanserin is not approved for the treatment of patients with dementia-related psychosis that is unrelated to PDP. It has a black box warning about increased mortality in elderly patients suffering from dementia-related psychosis. A secondary meta-analysis of 4 studies concluded that, compared to a placebo, pimavanserin demonstrated no significant variation in the incidence of confusion, edema, nausea, dizziness, fall, headache, somnolence, or hallucinations. Furthermore, pimavanserin treatment was not associated with a significant difference in severe adverse effects, such as bronchitis, sepsis, bone fracture, or increase in PD symptomatology, and that pimavanserin was associated with less orthostatic hypotension (6).

Treatment with pimavanserin has been associated with a doubled risk of mortality in comparison with a

How to cite this article: Shoib S, Baiou A, Javad S, Cevallos-Robalino DN, Saeed F. Pimavanserin in psychiatry- novel facts vs fiction. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2021;34:396-397.

Correspondence: Sheikh Shoib, Department of Psychiatry, Jawahar Lal Nehru Memorial Hospital, Srinagar, Kashmir, India
E-mail: Sheikhshoib22@gmail.com

Received: August 31, 2021; **Revised:** September 22, 2021; **Accepted:** October 07, 2021

placebo. In the majority of cases, the cause of death was a cardiovascular event or infection (2). There is a risk of QT interval prolongation, so it should be avoided in patients at high risk of this cardiac disturbance (4). Nonetheless, due to the distinct mechanism of action, it appears to have an acceptable tolerability profile without adverse cognitive or motor effects (7,8).

Parkinson's disease psychosis. Pimavanserin 34 mg/day was found to be effective at decreasing the incidence and/or severity of PDP associated psychosis. It was also reported to significantly improve sleep efficiency and quality, caregiver burden, and other clinical and exploratory outcome indicators (9,8).

Schizophrenia. Phase 2 trials showed that pimavanserin treatment has demonstrated a significant improvement in negative symptoms (34-mg dosage), depressive effects, and social functioning, and was well tolerated (10,11).

Major depression disorder. Pimavanserin has proved to be effective in patients with major depression disorder (MDD) who have had an inadequate response to antidepressants (12). It was not found to cause an increase in the risk of suicide. Future studies should further evaluate pimavanserin as adjunctive therapy in non-responsive cases of MDD (13).

Peer-review: Externally peer-reviewed.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Bozymski KM, Lowe DK, Pasternak KM, Gatesman TL, Crouse EL. Pimavanserin: a novel antipsychotic for Parkinson's disease psychosis. Ann Pharmacother 2017;51:479-487. [CrossRef]
2. Markham A. Pimavanserin: first global approval. Drugs 2016;76:1053-1057. [CrossRef]
3. ACADIA Pharmaceuticals Inc. Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE-2). https://clinicaltrials.gov/ct2/show/NCT04531982. Accessed October 25, 2021.
4. Combs BL, Cox AG. Update on the treatment of Parkinson's disease psychosis: role of pimavanserin. Neuropsychiatr Dis Treat 2017; 13:737-744. [CrossRef]
5. Kitten AK, Hallowell SA, Saklad SR, Evoy KE. Pimavanserin: a novel drug approved to treat Parkinson's disease psychosis. Innov Clin Neurosci 2018; 15:16-22.
6. 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.
7. Ballard C, Banister C, Khan Z, Cummings J, Demos G, Coate B, et al. 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. [CrossRef]
8. Hacksell U, Burstein ES, McFarland K, Mills RG, Williams H. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. Neurochem Res 2014; 39:2008-2017. [CrossRef]
9. Black KJ, Nasrallah H, Isaacson S, Stacy M, Pahwa R, Adler CH, et al. Guidance for switching from off-label antipsychotics to pimavanserin for Parkinson's disease psychosis: an expert consensus. CNS Spectr 2018; 23:402-413. [CrossRef]
10. Bugarski-Kirola D, Arango C, Fava M, Nasrallah H, Liu IY, Abbs B, et al (editors). Advance: Phase 2, Randomised, Double-Blind, Placebo-Controlled Study of Adjunctive Pimavanserin in Patients with Negative Symptoms of Schizophrenia. In European Neuropsychopharmacology. Amsterdam: Elsevier Radarweg, 2020, 328-329. [CrossRef]
11. Nasrallah HA, Fedora R, Morton R. Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. Schizophr Res 2019; 208:217-220. [CrossRef]
12. Fava M, Dirks B, Freeman MP, Papakostas GI, Shelton RC, Thase ME, et al. A Phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder and an ınadequate response to therapy (CLARITY). J Clin Psychiatry 2019; 80:19m12928. [CrossRef]
13. Shelton RC, Fava M, Freeman MP, Thase ME, Papakostas GI, Jha MK, et al. Effect of adjunctive pimavanserin on suicidal ideation in patients with major depression: analysis of the CLARITY study. J Affect Disord 2020; 277:478-485. [CrossRef]