Pimavanserin: A 2019 Clarification on the FDA Update

To the Editor: It was with great interest that we read the letter to the editor titled "Pimavanserin for Parkinson Disease Psychosis" by Mohanty et al[1] published in *The Primary Care Companion for CNS Disorders*. This letter discusses Parkinson disease psychosis (PDP) including the clinical features, pathophysiology, and treatments such as quetiapine, clozapine, and the recently introduced antipsychotic, pimavanserin. Although Mohanty and colleagues[1] provide a thorough overview of pimavanserin's mechanism of action and pharmacokinetics, we would like to elaborate on their discussion of pimavanserin's safety considerations.

The authors state, "As of May 2018, the drug's safety is currently being evaluated following reports of serious adverse events" and reference an article[2] published in *The Lancet* on May 5, 2018, titled "Pimavanserin Evaluated by the FDA" when discussing the drug's disadvantages. In September 2018, the US Food and Drug Administration (FDA) had already completed a thorough review of all postmarketing reports of deaths and serious adverse events reported with the use of pimavanserin and posted an online update titled "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."[3] We believe that the omission of this FDA drug safety update could add to pimavanserin's prescribing worries and possibly contribute to its underutilization.

We concur with Mohanty et al's description of pimavanserin's various side effects such as QT interval prolongation, peripheral edema, nausea, confusion, hallucination, constipation, and gait disturbance and that it is associated with increased risk of death in elderly patients with dementia-related psychosis.[1,3,4] Similar to pimavanserin, quetiapine is associated with increased risk of death in elderly patients with dementia-related psychosis and must be used cautiously with drugs that increase QT intervals and in patients with prolonged QT interval.[5] Additional side effects include neuroleptic malignant syndrome, suicidal thoughts and behavior, somnolence, orthostatic hypotension, dizziness, stroke, myocarditis, and coronary heart disease.[5] On the other hand, clozapine requires weekly complete blood count monitoring for the first 6 months followed by every other week for the next 6 months due to the rare but significant risk of agranulocytosis.[6] Black box warnings for clozapine include neutropenia, orthostatic hypertension, seizures, myocarditis, and dementia.[6]

According to a 6-week placebo-controlled trial,[3] no events of neuroleptic malignant syndrome, tardive dyskinesia, or serotonin syndrome were reported with pimavanserin (34 mg). Both clozapine and pimavanserin have demonstrated proven efficacy for PDP without impairing motor function.[7] Clozapine has a faster onset of action (1 week) compared to pimavanserin (4–6 weeks).[7] Although quetiapine is frequently used for PDP, its efficacy has not been demonstrated by double-blind, randomized trials.[7] Understandably so, pimavanserin is the only FDA-approved therapy proven to reduce delusions and hallucinations associated with PDP in elderly patients without impacting motor function.[3]

We would like to thank Mohanty and colleagues[1] for their discussion and bringing to light important facts about the role of antipsychotics in Parkinson disease and the pros and cons of antipsychotic use in PDP.

Zeeshan Mansuri, MD, MPH[a]
zeeshan.mansuri@ttuhsc.edu
Krupa Patel, MD[b]
Rupak Desai, MBBS[c]
Muhammad Khalid Zafar, MD[a]
Shailesh Jain, MD, MPH, ABDA[a]

Dr Mohanty and colleagues were shown this letter and declined to comment.

[a]Department of Psychiatry, Texas Tech University Health Science Center at Odessa/Permian Basin, Odessa, Texas
[b]Avalon University School of Medicine, Willemstad, Curaçao, The Netherlands Antilles
[c]Division of Cardiology, Atlanta Veterans Affairs Medical Center, Decatur, Georgia

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