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# Mortality in patients with Parkinson disease psychosis receiving pimavanserin and quetiapine

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Parkinson disease (PD) is a complex neurodegenerative disorder. Cognitive dysfunction and psychosis are leading contributors to nursing home placement.[1] Psychosis onset is associated with cognitive decline, levodopa supplementation, and visual dysfunction.[2] Treatment of PD psychosis (PDP) centers on levodopa dose adjustment, use of second-generation antipsychotics (SGAs), and cholinesterase inhibitors. SGAs function via serotonergic modulation and dopamine receptors blockade. Quetiapine, a structural analogue to clozapine, is often used to treat PDP, although evidence of its efficacy is mixed in randomized controlled trials.[3] Furthermore, there is a concern for increased morbidity and mortality with use of quetiapine and other SGAs in patients with dementia or those with PD, prompting a black box warning by the Food and Drug Administration (FDA).[4]

The FDA approved pimavanserin (Acadia Pharmaceuticals Inc., San Diego, CA) on April 29, 2016, as the first agent indicated for treatment of PDP. Its mechanism of action is novel, behaving as a selective inverse agonist of the serotonin 5-HT2A receptor and having no appreciable blockade of D2 receptors.[5] Pimavanserin's safety was recently highlighted in a report by the Institute for Safe Medication Practices,[6] including an expanded set of adverse events and risk of increased mortality. This report has led to concerns among prescribers, patients, and caregivers. Here we report on our institutional experience with pimavanserin for the treatment of PDP since its FDA approval.

## Methods

We conducted a retrospective study with inclusion criteria of (1) PD diagnosis and (2) prescribed pimavanserin, quetiapine, or both agents during April 29, 2016–April 29, 2018.

### Standard protocol approvals, registrations, and patient consents

All patients received their care at the University of California San Diego Health System. Anonymized records were obtained from the Epic electronic health record system. Since we only utilized de-identified electronic health records, no consents were required or obtained.

Data analyzed included age, sex, and whether patients were living or deceased. Descriptive statistics are reported for the group characteristics along with 2-sample *t* tests for significance ($p < 0.05$) (table). Logistic regression with adjustment for age and sex was used to calculate odds ratios for mortality between each drug exposure group and controls.

## Results

Of 4,478 patients with PD, 676 fulfilled the selection criteria. Despite a higher percentage mortality between quetiapine vs pimavanserin and combination vs pimavanserin, these differences were not different ($p = 0.17$ and $p = 0.28$, respectively). Mean age of the deceased cohorts was also similar

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**Table** Characteristics of pimavanserin vs quetiapine patient groups

| Characteristics | Pimavanserin | Quetiapine | Pimavanserin + quetiapine |
|---|---|---|---|
| **Sample size, n** | 113 | 505 | 58 |
| **Age, y, mean (SD)** | 75.9 (9.1) | 75.2 (12.4) | 74.1 (10.4) |
| **% Female** | 38.1 | 42.0 | 37.9 |
| **Total deaths (April 29, 2016–April 29,2018)** | 8 | 58 | 7 |
| **Mortality, %** | 7.1 | 11.5 | 12.1 |
| **Age of deceased, y, mean (SD)** | 81.4 (7.4) | 79.6 (8.7) | 82.0 (8.0) |
| **Odds ratio (95% confidence interval)** | 1.23 (0.57–2.68) | 1.74 (1.15–2.62) | 2.16 (0.93–5.01) |

between the groups, and age was similar to those not deceased ($p$ = 0.12). Recognizing that a control group not requiring use of these agents was likely to have milder symptoms and lower risk of complications, we nonetheless selected a cohort of individuals from our sample of patients with PD not receiving treatment with SGAs or pimavanserin and a similar mean age of 80 (range 78–82, n = 784) and found mortality to be 5.9%. Odds ratios showed an increased risk of mortality in the quetiapine group and a trend toward increased risk in the combination therapy group ($p$ = 0.07).

## Discussion

The use of SGAs to treat PDP is associated with an increased risk of mortality that is poorly understood.[4] This study was performed to determine whether recent press reports of increased mortality associated with use of pimavanserin warrant closer scrutiny. Our findings from a cohort of 676 patients showed a lower percentage of mortality for pimavanserin vs quetiapine or combination therapy, with only the quetiapine group having an odds ratio suggesting increased risk of mortality. Deceased individuals were older and more commonly male, though the male:female ratio we found was similar to the 1.5:1 ratio reported in PD, suggesting no sex-based mortality risk.[7] Despite the higher percentage mortality seen with pimavanserin and quetiapine compared to patients not receiving either medication, it is reasonable to assume that individuals requiring these medications have greater disease severity and are at higher risk of complications and death. Our data also highlighted a subset of patients receiving both pimavanserin and quetiapine who experienced the highest rate of observed mortality. While this observation was not statistically different, the safety of combination therapy is not established since the pivotal phase 3 trial of pimavanserin excluded individuals on antipsychotics.[8]

Our findings provide the largest comparative report of mortality risk in PDP; however, there are limitations in the study design. While selection bias is unlikely to lead to differences in reported mortality rates among the different agents, the mortality rates may be affected by the fact that at least 2 patients in this sample were known to have died prior to starting pimavanserin and possible underreporting of deceased patients. The focus of this study was on the relative mortality rates of pimavanserin and quetiapine, but the retrospective anonymized design of this study and our inability to conduct a case by case chart review limited our ability to determine the cause of death, duration of drug exposure, and whether unrelated factors were present. Our findings provide no new or unexpected concerns about the use of pimavanserin for the treatment of PDP. While the results pertaining to pimavanserin provide some reassurance for clinicians, patients, and families, future studies are needed to evaluate factors such as disease severity and cause of death to improve our understanding of the potential risks of treating PDP.

### Author contributions

G.M.M.: research project organization and execution, statistical analysis review and critique, writing of the first draft, manuscript review and critique. R.G.: research project organization and execution. S.L.L.: statistical analysis review and critique, manuscript review and critique. B.W.: statistical analysis review and critique, manuscript review and critique. I.L.: statistical analysis review and critique, manuscript review and critique. F.B.N.: research project conception, organization, and execution; statistical analysis design, execution, review, and critique; and manuscript review and critique.


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