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Pimavanserin versus quetiapine for the treatment of psychosis in Parkinson's disease and dementia with Lewy bodies

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ABSTRACT

Introduction: Psychosis is common among patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Limited data exist on the most effective therapies.

Methods: Retrospective cohort study comparing patients with PD or DLB initiated on quetiapine or pimavanserin for psychosis. Primary outcome was time to discontinuation of pimavanserin or quetiapine using Kaplan-Meier survival analysis. We hypothesized the rate of antipsychotic discontinuation would be lower in the pimavanserin group. Subjects were included if the indication for treatment was psychosis and excluded if there was a history of major mental illness or no follow up data were available.

Results: Forty-seven patients were included in the quetiapine cohort and 45 in the pimavanserin cohort. Patients in the pimavanserin cohort were more likely to have a diagnosis of DLB (33% vs. 11%, $P = 0.01$) and to have been prescribed an antipsychotic previously (62% vs. 6%, $P < 0.01$); otherwise, the groups were similar. Time to discontinuation analysis, which accounts for efficacy, safety and tolerability, revealed a lower early pimavanserin discontinuation rate and a higher late pimavanserin discontinuation rate (HR < 1 before day 43, HR > 1 after day 43; $P = 0.04$). There was no difference in mortality in the pimavanserin group compared to the quetiapine group (HR 0.37, 95% CI 0.06 to 2.45; $P = 0.88$). More individuals had a documented secondary indication for taking quetiapine than pimavanserin (38% vs. 4%; $P = 0.001$).

Conclusion: Accounting for efficacy, safety and tolerability, pimavanserin may be more clinically useful for promptly managing psychosis, while quetiapine may confer additional secondary benefits long-term.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting motor, cognitive, and psychiatric domains. Dementia with Lewy bodies (DLB) is a related disorder with similar pathophysiology and clinical features that is distinguished from PD by the onset of dementia within one year of motor symptoms. Psychosis is highly prevalent among patients with PD and DLB (collectively referred to as Lewy body disease), manifesting as hallucinations, illusions, false sense of presence or passage, or delusions [1,2]. Up to 60% of PD patients experience psychosis over the course of their disease and visual hallucinations are a core clinical feature for the diagnosis of DLB [3,4]. Psychosis in Lewy body disease (LBD) is associated with poorer patient outcomes including increased mortality, hospitalization and institutionalization rates, caregiver burden, and poorer quality of life [5–9].

Unfortunately, pharmacologic treatment options for psychosis in LBD are limited due to the risk of side effects from dopamine blockade, including worsening parkinsonism (bradykinesia, rigidity, tremor, postural instability) and severe neuroleptic sensitivity reactions (particularly in DLB) [10,11]. In addition, antipsychotics are associated with an increased mortality risk [12]. Despite limited evidence in PD psychosis [10], quetiapine – a mixed serotonergic and dopaminergic antagonist – is the antipsychotic most frequently used to treat PD psychosis [13]. Similarly, although it is used frequently in clinical practice for psychosis in DLB, studies of quetiapine in DLB are sparse [14,15], and current available evidence supports acetylcholinesterase inhibitor use as first line therapy [16].

Pimavanserin is a relatively new atypical antipsychotic and the first to be approved by the United States Food and Drug Administration (FDA) specifically for the treatment of PD psychosis. It represents a new class of antipsychotic that acts as an inverse agonist and antagonist of the serotonin 5-HT_{2A} receptor and lacks the dopamine receptor blocking effects of other antipsychotics [17]. Pimavanserin has been

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shown in a pivotal clinical trial to be well tolerated and effective for the treatment of hallucinations in patients with PD psychosis [18]. Pimavanserin was fast-tracked for FDA approval and more information is needed regarding real-world experience with this medication to optimize effective use in clinical practice. Since its FDA approval, small retrospective studies have confirmed safety and efficacy of pimavanserin in real-life cohorts of patients with DLB and PD psychosis [19–22], though limited data exist that directly compare pimavanserin to other antipsychotics. A recent study comparing mortality among PD patients with psychosis treated with pimavanserin and/or quetiapine did not show an increased risk of mortality among those taking only pimavanserin [23]. Differences in effectiveness between these medications is unknown. Though most clinical trials of pimavanserin and quetiapine enrolled exclusively PD patients, these antipsychotics are frequently used for both PD and DLB in clinical practice given that both entities likely represent different points on a common LBD spectrum [4]. In this study, we retrospectively compared clinical experiences and outcomes of patients treated with pimavanserin versus quetiapine for the treatment of psychosis in LBD at a single center, with a goal of better understanding of how to best manage this common and often difficult to treat sequela of PD and DLB.

2. Methods

This retrospective cohort study compared patients seen at the University of Pennsylvania Parkinson's Disease and Movement Disorders Center (PDMDC) with PD or DLB complicated by psychosis and treated with quetiapine and/or pimavanserin. The study protocol was approved by our local institutional review board.

2.1. Sample

Inclusion criteria were: 1) age ≥18 years; 2) diagnosis of PD or DLB made by a movement disorders specialist at the PDMDC; 3) psychosis as determined by documentation of hallucinations and/or delusions related to LBD; and 4) treatment initiation with quetiapine or pimavanserin between April 2016 (the time of FDA approval of pimavanserin) and May 2018. Patients were excluded if: 1) they had a history of bipolar disorder or schizophrenia; 2) there was no available follow-up data by October 2018; 3) they were prescribed the antipsychotic for an indication other than psychosis associated with LBD or; 4) they were not a patient at the PDMDC when the antipsychotic was started. All patients taking pimavanserin were included in the pimavanserin cohort, including those on combined therapy with quetiapine, to maximize the size of the sample.

We queried the electronic medical record (EMR) for potential eligible patients with 1) ICD diagnostic code for either PD or DLB; 2) no ICD code for schizophrenia or bipolar disorder; 3) who were seen in the PDMDC; and 4) prescribed quetiapine or pimavanserin within the time period specified. The identified records were then manually screened to confirm eligibility.

2.2. Data collection

Demographic and clinical data were abstracted from the medical record including diagnosis (PD or DLB), year of diagnosis, age, sex, race, date of antipsychotic prescription, medications, history of anxiety and depression symptoms, cognitive impairment (per report of the patient, caregiver, or physician), Montreal Cognitive Examination (MoCA) score, Hoehn and Yahr scale, Unified Parkinson Disease Rating Scale (UPDRS) motor score, psychotic symptoms, and adverse events. Total daily levodopa equivalent dose (LED) was calculated using standardized conversion factors [24,25]. For Rytary, a conversion factor of 0.7 was used, based on bioavailability data and use in prior studies [26–28].

The primary outcome was defined as time to medication discontinuation, as documented in the EMR. We hypothesized that the rate of antipsychotic discontinuation would be lower in the pimavanserin cohort. Secondary outcomes included mortality, reason for antipsychotic discontinuation, change in motor UPDRS score, and subjective improvement in psychosis as reported by the patient or caregivers and documented in the EMR.

2.3. Data analysis

Comparisons in baseline characteristics were made using T-test, Wilcoxon rank sum, Chi-square, and Fisher's exact tests. Cox proportional regression was used to adjust for potential confounders, selected based on clinical rationale, of time to discontinuation (including age, prior antipsychotic use, diagnosis, and LED) and mortality (including age, LED, diagnosis, and MoCA score). Because the proportional-hazards assumption was violated in the time to discontinuation analysis, a time by medication interaction was included in the model to account for non-proportionality of the hazards. A logarithmic function of time was used in the above interaction term. The overall effect of medication group was assessed using a likelihood ratio test. T-test, Wilcoxon rank sum, chi-square, and Fisher's exact tests were used to compare the remaining secondary outcomes. All statistical tests are two-sided. Statistical significance was set at < 0.05. Statistical analyses were performed using Stata/IC 15 and R software.

3. Results

3.1. Patients

EMR query identified the medical records of 202 patients, which were then screened by chart review for inclusion. Of those, 47 patients met both inclusion and exclusion criteria for the quetiapine cohort and 45 for the pimavanserin cohort (Fig. 1). Patients were followed for a mean of 317 days (SD 223). The age range of enrolled patients was 41–97 years with a mean of 73 (SD 8), with no significant between-group differences. Overall, 72 patients were diagnosed with PD and 20 with DLB. The percentage of patients with DLB was higher in the pimavanserin cohort. Patients in the pimavanserin cohort were more likely to have taken another antipsychotic medication previously or concurrently during the study period, the vast majority quetiapine. Otherwise, demographic data were similar (Table 1).

3.2. Efficacy

There was a significant difference in time to discontinuation between the two groups based on Cox regression analysis after adjusting for age, prior antipsychotic use, diagnosis, and LED, as well as adding a time by medication interaction in the model to account for non-proportionality of the hazards (coef of the main effect of pimavanserin relative to quetiapine is 1.98, 95% CI 0.27 to 3.69, $P = 0.02$ and coef of the interaction 0.92, 95% CI 0.02 to 1.83, $P = 0.05$; unadjusted coef of the main effect of pimavanserin relative to quetiapine is 1.60, 95% CI 0.03 to 3.16, $P = 0.05$ and coef for interaction 0.85, 95%CI -0.05 to 1.75, $P = 0.06$). Testing the overall effect of medication group, using the likelihood ratio test, revealed a lower early discontinuation rate in the pimavanserin cohort and a lower late discontinuation rate in the quetiapine cohort (HR < 1 before day 43 and HR > 1 after day 43; $P = 0.04$) (Fig. 2). In a subgroup analysis among patients in each cohort on pimavanserin (N = 35) or quetiapine (N = 47) monotherapy, the likelihood ratio test did not reach statistical significance (HR < 1 before day 48 and HR > 1 after day 48; $P = 0.07$). However, the direction of the association and magnitude were similar to the primary analysis. All potential confounders included in the model were not associated with time to discontinuation.

Patients in the pimavanserin cohort were more likely to discontinue the medication due to refractory psychosis, despite similar rates of

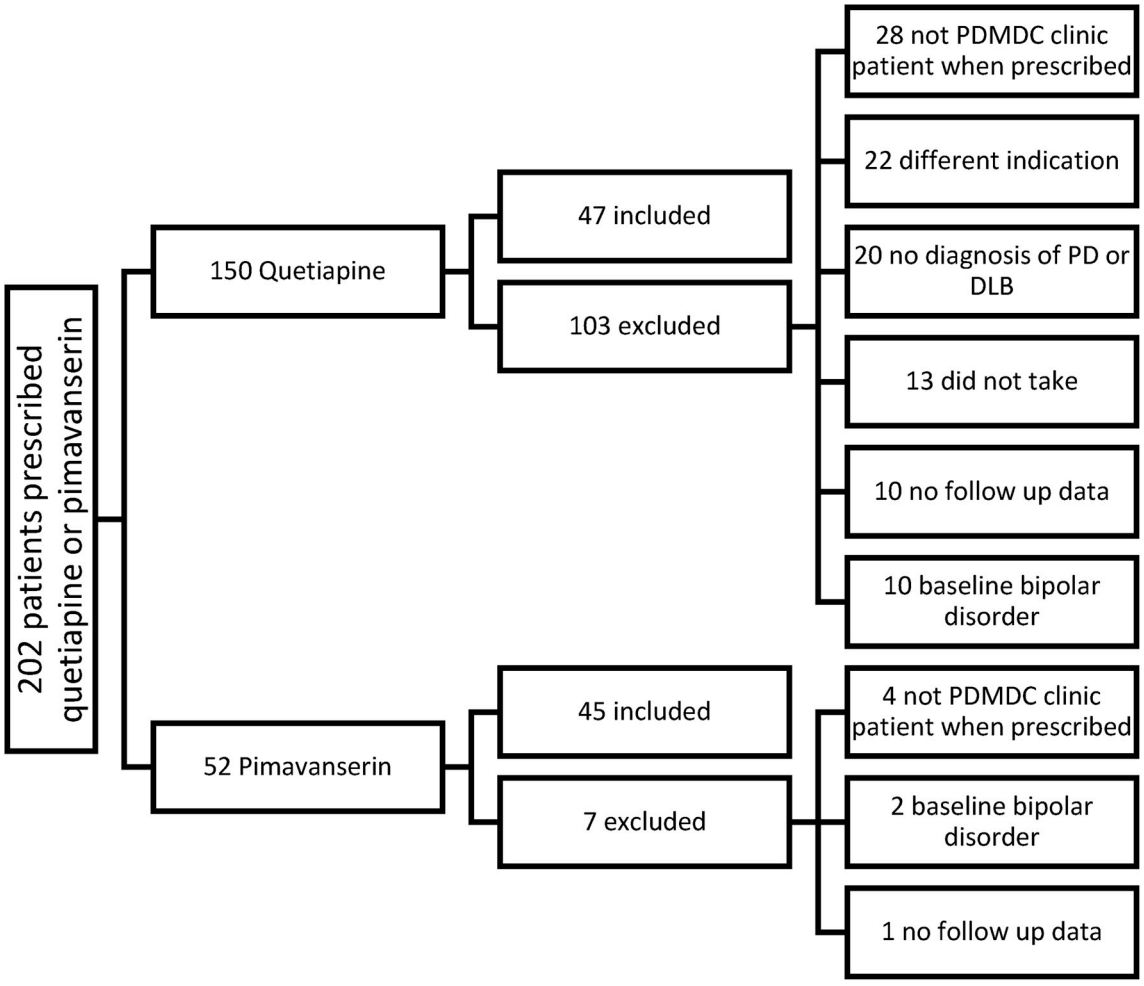

Fig. 1. Flowsheet of patient selection.

reported improvement in psychosis between groups (Table 2). Five of the 8 patients in the pimavanserin cohort who discontinued the medication due to lack of efficacy also took concurrent quetiapine at some point while on pimavanserin. Among patients who discontinued the antipsychotic (10 in the quetiapine cohort and 16 in the pimavanserin cohort), 7 (70%) in the quetiapine cohort and 2 (13%) in the pimavanserin cohort discontinued due to side effects ($P = 0.001$). A post hoc analysis showed that more individuals had a documented secondary indication for taking quetiapine (n = 18, 38%) than pimavanserin (n = 2, 4%), such as sleep disturbance, agitation, and anxiety ($P = 0.001$).

3.3. Adverse events

Mortality was not significantly different in the pimavanserin cohort compared to the quetiapine cohort (9% vs. 15%; HR 0.37, 95% CI 0.06 to 2.45; p = 0.88) (Table 3 and Fig. 3). Patients in the quetiapine cohort were more likely to experience new or worsening symptoms of orthostatic hypotension. Otherwise, there were no significant differences in side effects or hospitalization rate between the groups (Table 3).

4. Discussion

Data comparing efficacy and safety of treatments for psychosis in DLB and PD are limited, and optimal treatment of these patients remains unknown. This single center retrospective cohort study compared quetiapine and pimavanserin for the treatment of LBD-related psychosis and found a significant difference in time to discontinuation between patients taking these medications, with a lower early discontinuation rate in the pimavanserin cohort and a lower late discontinuation rate in the quetiapine cohort. Although most patients remained on the antipsychotic in both cohorts, patients in the quetiapine cohort were more likely to discontinue the medication due to side effects, while patients in the pimavanserin cohort were more likely to discontinue it due to lack of adequate improvement in psychosis. Symptoms of orthostatic hypotension were more common in the quetiapine group. There was no difference in mortality between the cohorts.

The pathophysiology of psychosis in LBD is poorly understood though hypothesized to be influenced by both extrinsic and intrinsic factors, including interplay between dopamine, acetylcholine, and serotonin neurotransmitters [29]. Antipsychotic options to treat psychosis in LBD are, in general, limited to clozapine, quetiapine, and the newly FDA-approved medication pimavanserin [10]. Given the risk for life-threatening agranulocytosis and requirement for frequent blood draws, clozapine is not often used in clinical practice [13]. Quetiapine, which has relatively less potent D_2-blocking activity than other atypical antipsychotics, is the most commonly used antipsychotic used to treat PD psychosis [13]. Randomized controlled trials to establish efficacy have been mixed and a meta-analysis of quetiapine trials found no significant improvement of psychosis in PD, though given small sample sizes and high dropout rates in the studies, these data should be interpreted with caution [30].

Because of the retrospective design of our study, without uniform follow-up assessments, we chose a practical endpoint of time to discontinuation of medication, which accounts for efficacy, safety and tolerability. While this endpoint limits direct comparison with other

Table 1
Baseline characteristics of subjects in each cohort.

	Quetiapine (N = 47)	Pimavanserin (N = 45)	*P* value
Demographics			
Sex, No. (%), male	27 (57)	26 (58)	> 0.99
Age, mean (SD), y	73.9 (10)	71.4 (6)	0.15
Race, No. (%)			0.11
White	37 (79)	34 (76)	
Non-White or unknown	10 (21)	11 (24)	
Clinical Characteristics			
Diagnosis			0.008
Parkinson's disease, No. (%)	42 (89)	30 (67)	
Dementia with Lewy bodies, No. (%)	5 (11)	15 (33)	
Time since diagnosis, mean (SD), years	8.5 (6)	8.9 (6)	0.72
Hoehn & Yahr score, No. (%)[a]			0.51
< 3	22 (49)	16 (40)	
≥3	23 (51)	24 (60)	
Baseline UPDRS, mean (SD)[b]	38 (15)	40 (13)	0.25
Psychotic features			
Hallucinations, No. (%)	44 (94)	43 (96)	0.68
Delusions, No. (%)	25 (53)	29 (64)	0.27
Cognitive impairment, No. (%)	43 (92)	40 (89)	0.74
MoCA (within 3 years), mean (SD)[c]	20.0 (4)	20.7 (5)	0.80
Anxiety, No. (%)	34 (72)	33 (73)	0.92
Depression, No. (%)	31 (66)	35 (78)	0.21
Medications			
Total daily LED, mean (SD), mg	702 (543)	665 (465)	0.98
PD medications, No. (%)			
Oral carbidopa-levodopa	42 (89)	39 (87)	0.37
Duopa	1 (2)	0 (0)	> 0.99
Dopamine agonists	8 (17)	5 (11)	0.42
Monamine oxidase inhibitors	7 (15)	7 (16)	0.93
Amantadine	3 (6)	3 (7)	> 0.99
Anticholinergics	1 (2)	0 (0)	> 0.99
Cognitive enhancing medication, No. (%)[d]	14 (30)	18 (40)	0.77
Benzodiazepine, No. (%)	16 (34)	17 (38)	0.71
Prior antipsychotic use	3 (6)	28 (62)	< 0.001
Concurrent antipsychotic use	0 (0)	10 (22)	0.001

[a] 45 observations in quetiapine group and 40 observations in pimavanserin group.
[b] 38 observations in quetiapine group and 43 observations in pimavanserin group.
[c] 20 observations in quetiapine group and 16 observations in pimavanserin group.
[d] donepezil, rivastigmine, and/or memantine; LED: levodopa equivalent dose. SD: standard deviation.

studies, it does provide real-world data comparing overall usefulness of these medications in a clinical setting. The lower early discontinuation rate in the pimavanserin cohort suggests that pimavanserin may be more effective at promptly managing psychosis. Therefore, accounting for efficacy, safety and tolerability, pimavanserin may be more clinically useful than quetiapine for the treatment of psychosis in PD and DLB in a real-world setting.

The lower late discontinuation rate in the quetiapine cohort, combined with the finding that more individuals had a documented secondary indication for taking quetiapine, suggests that patients remain on quetiapine long-term for delayed benefits, perhaps due to improvement in secondary indications such as agitation or insomnia. This may also explain why fewer patients taking quetiapine cited lack of improvement in psychosis as the reason for antipsychotic discontinuation despite having similar rates of non-responders in both groups. The higher rate of side effects in the quetiapine cohort (particularly

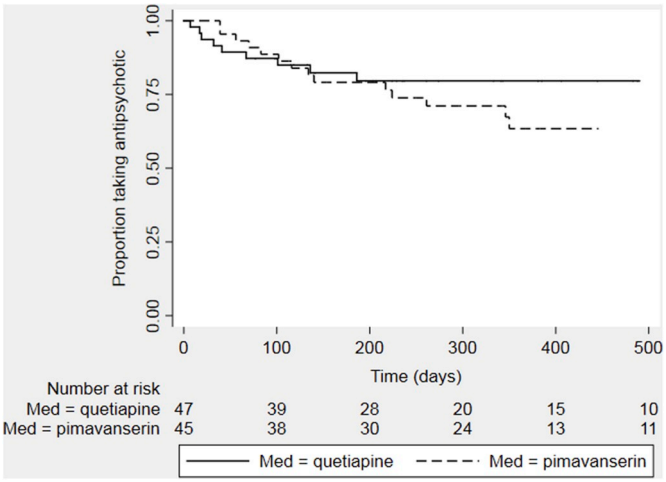

Fig. 2. Kaplan-Meier survival curves depicting time to discontinuation of the antipsychotic in each cohort.

Table 2
Secondary outcomes of subjects in each cohort.

	Quetiapine (n = 47)	Pimavanserin (n = 45)	*P* value
Discontinued Antipsychotic, No. (%)	10 (21)	16 (36)	0.13
Discontinue Reason, No. (%)			
Side effects	7 (15)	2 (4)	0.16
Cost	0 (0)	3 (7)	0.11
Lack of significant improvement	1 (2)	8 (18)	0.01
No longer needed	1 (2)	1 (2)	> 0.99
Other or unknown	1 (2)	2 (4)	0.61
Hallucination Outcome, No. (%)[a]			0.93
Improved	32 (73)	34 (79)	
No Change or Worse	10 (23)	8 (19)	
Delusion Outcome, No. (%)[b]			0.56
Improved	17 (68)	22 (76)	
No Change or Worse	7 (28)	6 (21)	
UPDRS change, mean (SD)	5 (16)	2 (8)	0.25

[a] Among those who reported hallucinations at baseline.
[b] Among those who reported delusions at baseline; SD: standard deviation.

Table 3
Side effects and adverse events attributed to the antipsychotic.

Adverse Events, n (%)	Quetiapine (n = 47)	Pimavanserin (n = 45)	*P* value
None	8 (17)	13 (29)	0.22
Sedation	9 (19)	9 (20)	0.56
Confusion	1 (2)	4 (9)	0.17
Insomnia	1 (2)	1 (2)	0.74
Worsening Psychosis	2 (4)	1 (2)	0.52
Dizziness/OH/syncope	12 (26)	2 (4)	0.007
Worsening parkinsonism	7 (15)	4 (9)	0.29
Nausea	0 (0)	1 (2)	0.49
Edema	0 (0)	2 (4)	0.24
Constipation	0 (0)	1 (2)	0.49
Headache	1 (2)	0 (0)	0.49
Fall	2 (4)	2 (4)	0.68
Worsening Behavior	1 (2)	0 (0)	0.49
Unknown	1 (2)	2 (4)	0.48
Hospitalization[a]	25 (53)	23 (51)	0.50
Death	7 (15)	4 (9)	0.88

[a] Patients who presented to the emergency department and/or were admitted to the hospital, including 4 admitted to inpatient psychiatry (all in the quetiapine cohort); OH orthostatic hypotension.

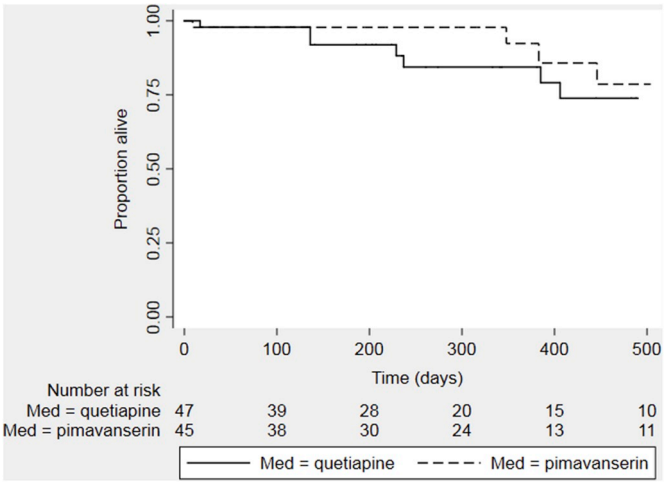

Fig. 3. Kaplan-Meier survival curves depicting mortality over time since initiation of the antipsychotic in each cohort.

orthostatic hypotension) may reflect sensitivity to dopamine receptor blockade in these patients and contribute to the higher early discontinuation rate in the quetiapine cohort.

The higher late discontinuation rate in the pimavanserin cohort could reflect more refractory psychosis in this group since the pimavanserin cohort had a higher percentage of patients with DLB and higher rate of prior antipsychotic failure; Kaplan-Meier survival curves depicting time to antipsychotic discontinuation in only PD or DLB patients are included in the Supplement (eFig. 1). The lower early discontinuation rate may be confounded by differences in prescribing guidance since patients prescribed pimavanserin are often encouraged to continue the medication for several weeks before discontinuation when ineffective. The late discontinuation rates may also reflect lack of sustained response to pimavanserin and could be confounded by survival bias.

Given recent concerns regarding mortality among those prescribed pimavanserin, it is reassuring that our study did not find a higher mortality rate in the pimavanserin cohort compared with the quetiapine cohort. These data are supported by a recent study by Moreno et al. that also found no increased risk of mortality in PD patients taking pimavanserin than in those taking quetiapine [23].

Our study had several limitations. It was retrospective and therefore limited by documentation in the medical record. We were unable to account for Seroquel doses in this analysis due to the large variation and frequent dose changes among patients and lack of statistical power in our small sample. Reflective of real-world experience, some of the patients in the pimavanserin cohort also took a concurrent antipsychotic (namely quetiapine) at some point during their pimavanserin course, which could have confounded the results. A subgroup analysis of patients on pimavanserin or quetiapine monotherapy did not reach statistical significance, probably due to underpowering. Kaplan-Meier survival curves depicting time to antipsychotic discontinuation in patients taking only pimavanserin or quetiapine are included in the Supplement (eFig. 2).

No systematic tool was used to evaluate response of psychosis, reason for discontinuation, or development of side effects in these patients, and there were missing data for some patients. Lack of randomization in retrospective studies can also introduce bias. As a single center study, the results may not be generalizable to the general population. The sample size was relatively small, though comparable to sizes of other studies in this population, likely reflecting inherent difficulties in studying psychosis in LBD [30].

This single center, retrospective cohort study suggests that pimavanserin may be more clinically useful for promptly managing psychosis, while patients may continue quetiapine long-term for secondary, delayed benefits. Given the incredible burden experienced by both patients and caregivers due to psychosis associated with LBD, as well as lack of strong evidence to guide treatment decisions, more study is needed to determine optimal management strategies in this population. More comparative effectiveness studies are needed to guide clinical care and improve quality of life for patients and families.

Declaration of competing interest

Dr. Horn received support from the Edmond J. Safra Fellowship in Movement Disorders. Dr. Weintraub has received research funding or support from Michael J. Fox Foundation for Parkinson's Research, Alzheimer's Therapeutic Research Initiative (ATRI), Alzheimer's Disease Cooperative Study (ADCS), the International Parkinson and Movement Disorder Society (IPMDS; honoraria for consultancy from Acadia, Alkahest, Bracket, CHDI Foundation, Clintrex LLC, F. Hoffmann-La Roche Ltd, and Ferring; and license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS. Dr. Dahodwala has received funding from Parkinson Foundation, Michael J Fox Foundation, Parkinson Council, AbbVie, Medtronic; served as site PI for clinical trials funded by Roche, Ely Lilly and Cala Health, and served on a Scientific Advisory Board for Acadia. The remaining authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.11.009.

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