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THERAPY IN PRACTICE

On the Optimal Diagnosis and the Evolving Role of Pimavanserin in Parkinson's Disease Psychosis

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Abstract

Parkinson's disease (PD) is associated with the development of psychosis (PDP), including hallucinations and delusions, in more than half of the patient population. Optimal PD management must therefore involve considerations about both motor and non-motor symptoms. Often, clinicians fail to diagnosis psychosis in patients with PD and, when it is recognized, treat it suboptimally, despite the availability of multiple interventions. In this paper, we provide a summary of the current guidelines and clinical evidence for treating PDP with antipsychotics. We also provide recommendations for diagnosis and follow-up. Finally, an updated treatment algorithm for PDP that incorporates the use of pimavanserin, the only US FDA-approved drug for the treatment of PDP, was developed by extrapolating from a limited evidence base to bridge to clinical practice using expert opinion and experience. Because pimavanserin is only approved for the treatment of PDP in the US, in other parts of the world other recommendations and algorithms must be considered.

Key Points

Patients with Parkinson's disease (PD) should be evaluated regularly for symptoms of psychosis to avoid progression to more severe psychotic symptoms.

Current treatment recommendations for PD with psychosis (PDP) involved tapering or discontinuation of dopaminergic medications, followed by treatment with atypical antipsychotics.

Our proposed algorithm involves the use of pimavanserin earlier in the treatment cycle of PDP and we recommend use of pimavanserin with or without other antipsychotics based on the severity of psychotic symptoms.

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1 Introduction

While Parkinson's disease (PD) is most often characterized by the cardinal motor symptoms (e.g., bradykinesia, resting tremor, rigidity) [1, 2], it is now clear that PD is both a neurodegenerative and neuropsychiatric disorder involving motor and non-motor symptoms. Patients with PD can present with a spectrum of non-motor symptoms, including depression, anxiety, apathy, impulse control disorder, dementia, and psychosis [3].

Parkinson's disease psychosis (PDP) is common, occurring in about 40% of the PD patient population [4]. The severity of PDP-associated psychotic symptoms can vary over a spectrum, with minor symptoms, including a sense of presence, passage hallucinations, and illusions, occurring in 25–50% of patients with PDP [5]. These more minor symptoms are often associated with maintained insight. The incidence of more bothersome psychotic symptoms in PDP is variable, with the most common being visual hallucinations (22–38%), auditory hallucinations (0–22%), and delusions (1–14%), and the less common being tactile, olfactory, and gustatory hallucinations [6]. These advanced symptoms are often distressing and can involve a lack of insight, potentially requiring treatment with antipsychotics.

While the mechanism of longitudinal progression of PDP from minor to advanced symptoms is unclear, evidence suggests a potential relationship between minor psychotic

phenomena and complex visual hallucinations [5]. Patients with PD can have concurrent visual hallucinations and minor psychotic phenomena nearly 60% of the time following PDP onset. Minor psychotic phenomena also reportedly occurs at the same time as visual hallucinations in 50% of patients with PD, while 25% experience minor psychotic phenomena before complex visual hallucinations and 22.2% experience them after [7]. This association between minor psychotic phenomena and visual hallucinations emphasizes the importance of educating patients with PD, and their caregivers, on the signs/symptoms and therapeutic options for PDP as early as possible to prevent, or quickly identify and manage, advanced psychosis.

Furthermore, psychosis may be associated with a more malignant form of PD, marked by rapid progression with cognitive impairment within 10 years from symptom onset; benign PD tends to progress slowly, with no accruing dementia after 20 years since disease onset [8]. In multivariate analyses, patients experiencing PDP-associated hallucinations were significantly more likely to have a malignant form of PD; 81.8% [126/154] of patients with malignant PD experienced concurrent hallucinations in comparison with 21% [44/210] of patients with more benign PD (odds ratio [OR] 49.2, 95% confidence interval [CI] 13.3–179.9; $p < 0.001$). Additionally, some small cohort studies suggest that psychotic symptoms can originate in early PD, sometimes before the onset of motor symptoms [9–12].

Patients with PD and concomitant dementia, or another severe cognitive impairment, are more likely to develop psychosis [13]. PDP is more likely to occur in patients of advanced age, with a long history of PD, and who experience sleep disturbances or disorders [13, 14]. Although the evidence for predictive–genetic biomarkers of PDP has been mostly inconclusive, recent findings suggest that polymorphisms in glucosylceramidase (*GBA*), cholecystokinin (*CCK*), and ankyrin repeat and kinase domain containing 1 (*ANKK1*) genes [15–17] may be promising predictors of PDP. PDP is also associated with a higher caregiver burden, risk for premature nursing home placement, hospitalization, and increased mortality [18–20].

While PDP has been studied for decades, there are limited treatment options that are efficacious and tolerable, without significantly worsening the PD-associated motor symptoms; current first-line options remain dopaminergic medication reduction and using other antipsychotic medications. In this paper, we assessed the current PDP treatment landscape and use currently available data to make recommendations for optimizing the diagnosis, follow-up, and treatment of PDP directed towards maximizing patient quality of life. It should be noted that the proposed treatment algorithm in this paper is for United States (US)-based practices, because pimavanserin, the only US FDA-approved treatment for PDP, is not approved outside the US; thus, other recommendations and algorithms must be considered.

2 Diagnosis and Follow-Up

The consensus guidelines for psychosis in PD, developed by the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health (NINDS/NIMH) working group, state that PDP requires a confirmed diagnosis of PD with the onset of one or more PDP-associated symptoms (e.g., hallucinations, illusions, delusions, or false sense of presence) including minor phenomena (MPs) with a duration of at least 1 month [21]. Additionally, treatment decisions must consider other associated features, including insight during hallucinations or illusions, concomitant dementia, prior PD medications, and the possibility of the patient becoming dangerous to themselves or to loved ones. Finally, psychosis can be associated with several psychiatric disorders, related to environmental changes, or induced by some drugs (Table 1). A diagnosis of PDP can be made if psychotic symptoms persist after addressing other potential disorders or drugs known to cause psychosis [21, 22].

While guidelines are not definitive on the frequency of follow-up for patients with PD, we suggest following up every 3–6 months, depending on the severity of PD, to assess both motor and psychiatric symptoms. Additionally, phone or virtual consultations may be used to follow up with patients if needed. We suggest that psychosis-related questions from Part 1 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [23] may be useful for overall psychiatric assessment. Moreover, the enhanced Scale for the Assessment of Positive Symptoms in PD (eSAPS-PD) [24] is also available for additional assessment of more MPs. A short list of questions, asked at each follow-up, could also elucidate a general sense of the patient's psychiatric wellbeing and detect psychosis (Table 2).

These questions, and others, could be asked separately between patients and their caregivers. Caregivers often witness both motor and psychiatric symptoms, of which patients are unaware or unwilling to discuss. In addition, a questionnaire evaluating motor and psychiatric symptoms may be sent, separately, to each patient and caregiver before a visit. This could allow for symptoms of psychosis to be more efficiently flagged for further discussion or evaluation. Finally, a more thorough psychiatric evaluation by a specialist might be conducted yearly, increasing the frequency (e.g., $\leq$ 6 months) depending on psychosis severity or the initiation of antipsychotic therapy. If hallucinations or delusions become distressing to either the patient or caregiver, especially if there is a lack of insight, pharmacological management could be warranted.

Table 1 Potential causes of psychosis beyond Parkinson's disease psychosis [21]

Other disorders or drug reactions associated with psychosis
Delirium (can be related to a variety of metabolic, toxic, or infectious causes)
Schizophrenia/schizoaffective disorders
Progressive supranuclear palsy
Cortico-basal ganglionic degeneration
Lewy body dementia
Brief psychotic disorder
Delusional disorder
Bipolar/unipolar mood disorders
Drug/substance-associated psychosis

3 Current Guidelines and Clinical Evidence for the Treatment of Parkinson's Disease Psychosis (PDP)

As noted above, before a diagnosis of PDP can be made, alternative causes of psychosis must be excluded [21]. Although differentiating PDP from other neurodegenerative disorders (e.g., Lewy body dementia, Alzheimer's disease) can be challenging due to comorbidity of neuropathology, assessing dementia, including its timing of onset and evolution, in relation to the onset of psychosis can often be a distinguishing factor. Other psychosis-associated psychiatric disorders (e.g., mood disorders, schizophrenia, etc.) can be more easily differentiated from PDP by their onset and longitudinal development, or types of psychotic symptoms. Finally, delirium- or substance-associated psychosis should be considered, and managed accordingly, before the diagnosis and treatment for PDP [21, 22]. If psychotic symptoms persist despite resolving any delirium or discontinuing psychosis-inducing medications, and other psychosis-associated disorders have been ruled out, management and treatment of PDP may be considered. The standard PDP management paradigm usually involves tapering or discontinuation of dopaminergic medications, followed by treatment with atypical antipsychotics (Fig. 1).

3.1 Tapering or Discontinuation of Antiparkinsonian Medications

Most medications used to manage motor symptoms in PD have been associated with hallucinations or delusions [22, 25]. A retrospective study of 52 PD patients without dementia showed that a high daily dose of levodopa (>750 mg daily equivalent) is associated with a sense of presence in PDP (OR 1.7, 95% CI 1.1–2.7; $p = 0.029$) [26]; however, an earlier case series of five patients with PDP who were treated with increasing amounts of levodopa found no association with hallucinations [27], although the differences seen in these two studies could be attributed to differences in sample sizes or inclusion criteria. Patients with PD who receive dopamine agonists (DAs) are reportedly more likely to experience symptoms of psychosis than patients receiving levodopa, when compared with untreated control patients with PD [28]. A meta-analysis of 25 trials evaluating DAs versus placebo or levodopa between 1990 and 2007 found that DAs are approximately five times more likely to be associated with hallucinations than placebo and twice more likely than levodopa [29]. Additionally, recent studies have found an association between the use of catechol-o-methyl-transferase (COMT) inhibitors and anticholinergic agents with PDP [30].

Table 2 Parkinson's disease psychosis screening questions

Detecting psychosis: questions to ask patients with PD/caregivers on follow-up visits
Are you/they feeling, hearing, or seeing anything, nearby or in peripheral vision, that is not being experienced by others?
Do you/they feel paranoid about being cheated or persecuted by your spouse/partner or others around you?
Do you/they feel like someone is stealing from you?
Do you/they think your spouse/partner is being unfaithful?

PD Parkinson's disease

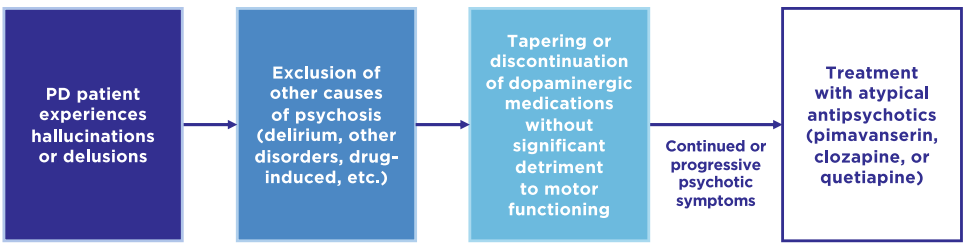

Fig. 1 Current treatment algorithm for Parkinson's disease psychosis based on guidelines and recommendations. *PD* Parkinson's disease

Current guidelines agree that when PDP symptoms become bothersome, antiparkinsonian medications should be optimized to diminish psychotic symptoms without significantly deteriorating motor function [22, 31–34]. However, there is no consensus on the order in which antiparkinsonian medications should be altered. Nevertheless, recent reviews have suggested that anticholinergic agents and DAs should be reduced, or stopped, first, followed by COMT and monoamine oxidase-B (MAO-B) inhibitors, leaving the alteration of levodopa formulations as a last resort [22, 31, 34].

If psychotic symptoms persist despite the adjustment of antiparkinsonian medications, in PDP patients with concomitant dementia or who are otherwise cognitively impaired, cholinesterase inhibitors (eg, rivastigmine, donepezil, and galantamine) should be considered [34, 35]. Cholinesterase inhibitors decrease the breakdown of acetylcholine, which allows for increased availability for acetylcholine in neuromuscular junctions to activate receptors associated with cognitive function. These agents are often approved for the treatment of dementia associated with PD and/or Alzheimer's disease and many have demonstrated activity against psychosis-related symptoms such as hallucinations [34]. For example, a recent meta-analysis of 34 randomized clinical trials evaluating the use of cholinesterase inhibitors to treat symptoms of psychosis in patients with Alzheimer's disease and PD showed an association between cholinesterase inhibitors and improvements in both delusions and hallucinations for both Alzheimer's disease and PD patients [36].

If antipsychotic symptoms still persist after these routes, it is then recommended to consider initiating therapy with antipsychotic drugs [22, 31, 33, 34].

3.2 Typical and Atypical Antipsychotics

Typical first-generation antipsychotics (e.g., haloperidol, prolixin, etc.) alleviate psychotic symptoms primarily by strongly inhibiting the D2 receptor [37]. These agents can be used to treat most psychotic disorders (schizophrenia, schizoaffective disorder, etc.), however they can severely worsen motor symptoms and are associated with increased mortality. A recent retrospective matched-cohort study found that patients exposed to typical antipsychotics had a significant increase in mortality over those patients not treated with an antipsychotic. Additionally, patients treated with typical antipsychotics had a 62% higher risk of mortality than those treated with atypical psychotics [38]. Typical antipsychotics are also the most common cause of drug-induced Parkinsonism and other extrapyramidal adverse effects in patients without PD, with approximately 80% of patients receiving typical antipsychotics experiencing more than one type of extrapyramidal adverse effect [39, 40]. All current guidelines and recommendations advise against using typical antipsychotics to manage PDP [22, 31, 33, 34]. Moreover, the American Geriatrics Society (AGS) specifically recommends avoiding all typical antipsychotics for elderly PD patients via the 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults [41].

Atypical antipsychotics can often inhibit the D2 receptor, but with a lower affinity than typical antipsychotics, and are serotonin 5HT2 receptor antagonists. While atypical antipsychotics such as risperidone [42–44], olanzapine [45, 46], and ziprasidone [47, 48] have shown promising antipsychotic efficacy in small PDP studies, they also worsened motor function. In a retrospective analysis by Weintraub and colleagues, atypical antipsychotics were associated with increased risk for mortality among patients with PDP, but to a lesser extent than typical antipsychotics [38]. Guidelines and recommendations, including the AGS Beers Criteria®, advise against using most atypical antipsychotics, for PDP, except for three agents, i.e. clozapine, quetiapine, and pimavanserin.

3.3 Clozapine

Clozapine was the first atypical antipsychotic shown to provide promising antipsychotic efficacy without significant worsening of PD-associated motor symptoms in a small cohort of PDP case studies [49]. Clozapine has since been evaluated in randomized placebo-controlled or active treatment comparator clinical trials for treating PDP-associated hallucinations and delusions (H&D), with clearly demonstrated efficacy (Table 3).

However, clozapine is associated with a high incidence of drowsiness (up to 53%) and orthostatic hypotension (up to 19%) when used to treat PDP [50, 51]. In other disease settings, clozapine has also been linked to a risk of agranulocytosis [52] and metabolic syndrome [53]. Additionally, more than 90% of patients receiving clozapine may experience drug-induced sialorrhea, either diurnally or nocturnally, which can negatively impact patient quality of life [54, 55]. In a randomized study evaluating the use of clozapine (12.5–50 mg/day, mean dose of 35.8 mg/day) versus placebo in 60 patients with PDP, a numerically higher rate of worsening of parkinsonism was observed with clozapine compared with placebo (13% vs. 4%); however, most worsening of motor function was mild and/or transient and may have occurred due to higher doses of clozapine (only 3 of 14 cases of worsening parkinsonism were considered a large [>10%] decrease based on the Schwab and England score, and 2 of the 3 cases received 50 mg/day dosing of clozapine) [51]. It should be noted that the dose of clozapine when used to treat PDP is typically much lower (6.25–50 mg/day) versus the target dose used to treat conditions such as schizophrenia (300–800 mg/day) [56].

Table 3 Evidence of clinical efficacy with clozapine in select placebo-controlled or active comparator randomized trials in Parkinson's disease psychosis

Trial designation	Patient population	Study design	Key efficacy results
Parkinson Study Group Trial (NCT00004826) [50]	Patients with PDP (baseline CGI ≥ 3) with no dementia severe enough to preclude assessment with psychiatric testing [$N = 60$]	Randomized (1:1) clozapine (6.25–50 mg/day) for 4 weeks	Significant improvements with clozapine relative to placebo in several psychiatric scoring measures, including CGI ($p < 0.001$), BPRS ($p = 0.002$), and SAPS ($p = 0.01$)
Pollak et al. study [51]	Patients with PDP (baseline MMSE ≥20, CGI > 3, and PANSS positive subscore ≥ 4) [$N = 60$]	Randomized (1:1) clozapine (6.25–50 mg/day) for 4 weeks	Significant improvements with clozapine relative to placebo in both the CGI score ($p = 0.001$) and the positive subscore of the PANSS scale ($p < 0.0001$)
Morgante et al. study [100]	Patients with PDP (baseline BPRS ≥3) with no history of severe dementia (MMSE <24) [$N = 40$]	Randomized (1:1) clozapine (6.25–50 mg/day) vs. quetiapine (25–200 mg/day) for 12 weeks	While both clozapine and quetiapine showed significant improvements from baseline in both CGI and BPRS scores ($p < 0.001$), there was no significant difference in improvement between the drugs
Merims et al. study [101]	Patients with PDP (mean MMSE score of 24) with no dementia at the first year after onset of PD symptoms [$N = 27$]	Randomized (1:1) clozapine (6.25–50 mg/day) vs. quetiapine (25–150 mg/day) for 22 weeks	While both clozapine and quetiapine showed significant improvements from baseline in CGI scores ($p < 0.001$), there was no significant difference in improvement between the drugs. There were however significant improvements in hallucinations and delusions (as assessed by the NPI score) with clozapine but only non-significant improvements with quetiapine
Ellis et al. study [42]	Patients with PDP [$N = 10$]	Randomized (1:1) clozapine (25–100 mg/day) vs. risperidone (1.0–1.5 mg/day) for 3 months	Mean BPRS psychosis cluster score improved significantly over baseline with risperidone ($p = 0.004$), but not with clozapine ($p = 0.032$); however, the difference in improvement between drugs was not significant ($p = 0.23$)
Pintor et al. study [47]	Patients with PDP with no dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria [$N = 16$]	Randomized (1:1) clozapine (12.5–100 mg/day) vs. ziprasidone (20–80 mg/day)	While both clozapine and ziprasidone improved psychotic symptoms from baseline using multiple metrics (BPRS, SAPS, and CGI), there was no significant difference in efficacy between the two agents

BPRS Brief Psychiatric Rating Scale, *CGI* Clinical Global Impression, *MMSE* Mini-Mental State Examination, *NPI* Neuropsychiatric Inventory, *PANSS* Positive and Negative Syndrome Scale, *PD(P)* Parkinson's disease (psychosis), *SAPS* Scale for the Assessment of Positive Symptoms

Recent International Parkinson and Movement Disorder Society (IPMDS) guidelines concluded that, with specialized monitoring, clozapine can be 'clinically useful' in the treatment of PDP because of its proven efficacy and acceptable risk [33]. These guidelines suggest that clozapine should be used in all patients with PDP who previously had treatment failure with quetiapine or pimavanserin. Furthermore, it may also be considered as a first-line option after tapering/discontinuing antiparkinsonian medication, despite onerous weekly blood count monitoring due to the risk of neutropenia. FDA guidance mandates weekly blood tests for patients receiving clozapine for the first 6 months along with absolute neutrophil count testing every 2 weeks for the following 6 months if an acceptable neutrophil count is maintained for the first 6 months. Absolute neutrophil count testing is required every 4 weeks thereafter [57]. Recent AGS Beers criteria include clozapine as an exception to the general recommendation to avoid antipsychotics in older patients with PDP because of its proven efficacy and minimal likelihood of worsening PD motor symptoms [41].

3.4 Quetiapine

Unlike clozapine, most small clinical studies evaluating low-dose quetiapine in PDP have demonstrated little to no improvement in psychosis in PDP when compared with either placebo or clozapine [58–61]. However, quetiapine (25–50 mg) seems more tolerable when compared with clozapine, with lower risk of orthostatic hypotension (up to 7% with quetiapine compared with up to 19% with clozapine) and agranulocytosis (a recent report from a drug surveillance program of over 300,000 patients with psychotic symptoms treated with atypical antipsychotics showed a relative incidence of neutropenia and agranulocytosis of 0.23% with quetiapine vs. 1.57% with clozapine) [50, 51, 62, 63]. In other disease settings, quetiapine is associated with drowsiness (up to 57%) and weight gain (up to 23%) and may increase the risk of metabolic syndrome [53, 62]. Low-dose quetiapine (12.5–50 mg) also has limited effects on motor functioning in PDP, as seen in a recent systematic literature review that demonstrated that overall, quetiapine did not significantly worsen motor function versus placebo across several randomized trials, as measured by the UPDRS motor scores [64].

Recent IPMDS guidelines concluded that quetiapine can be 'possibly useful' in the treatment of PDP because of its acceptable safety profile, with no need for specialized monitoring despite the lack of high-quality evidence of efficacy in this setting [33]. They suggest that low-dose quetiapine can be considered a pragmatic first choice for PDP, if pimavanserin is unavailable, after the optimization of antiparkinsonian medication due to its improved safety profile compared with clozapine. Recent AGS Beers criteria also include quetiapine as an exception to the general recommendation to avoid antipsychotics in elderly patients with PDP, although they note quetiapine has only been evaluated in low-quality studies with comparable efficacy to both placebo and clozapine [41].

3.5 Pimavanserin

Pimavanserin is a selective serotonin 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor inverse agonist and antagonist. Critically, pimavanserin also has no dopamine D2 receptor affinity [65] allowing it to, theoretically, be administered without altering the efficacy of dopaminergic agents that treat the motor systems associated with PD. In 2016, the FDA granted approval of pimavanserin for the treatment of H&D associated with PDP [66] based on the data from the ACP-103-020 (NCT01174004) trial.

3.5.1 Clinical Data

Pimavanserin was initially evaluated in two randomized placebo-controlled studies. The first study (ACP-103-006, NCT00087542) was a phase II, multicenter trial in 60 patients randomized 1:1 to receive 20–60 mg/day of pimavanserin versus placebo for a total of 4 weeks [67]. The key efficacy endpoint was improvement in the Scale for the Assessment of Positive Symptoms (SAPS). That was followed by two phase III trials evaluating pimavanserin versus placebo in PDP. The first, ACP-103-012 (NCT00477672), was a multicenter study in 259 patients with PDP randomized 1:1 to receive 10 or 40 mg/day of pimavanserin versus placebo for a total of 6 weeks [68]. The second, ACP-103-014 (NCT00658567) was a multicenter study in 123 patients with PDP randomized 1:1:1 to receive 10 or 20 mg/day of pimavanserin versus placebo for a total of 6 weeks [69]. The key efficacy endpoint for both phase III trials was improvement in the H&D component of the SAPS. While all three trials demonstrated the manageable safety profile of pimavanserin, including no worsening of parkinsonism as determined by the Unified Parkinson's Disease Rating Scale (UPDRS), neither trial showed a significant efficacy benefit over placebo in either the SAPS or SAPS H&D measurements, respectively. After completion of the phase III ACP-103-012 study, there were some concerns about the non-centralized assessment of psychotic symptoms globally versus in the US, in which there did appear to be a benefit with pimavanserin [68]. This led to the initiation of a subsequent North American-restricted phase III trial, ACP-103-020 (NCT01174004).

The ACP-103-020 trial was a phase III, randomized, double-blind, placebo-controlled study evaluating the use of pimavanserin for PDP [70]. After a 2-week lead-in phase of psychosocial therapy to induce a placebo response prior

to baseline, 199 patients were randomized (1:1) to receive once-daily 40 mg pimavanserin tartrate, equivalent to 34 mg pimavanserin free base ($n = 105$), or placebo ($n = 94$) for up to 6 weeks. No reductions in dopaminergic drugs were required during the study. The primary outcome was the antipsychotic benefit as determined by the newly developed PD-adapted scale for assessment of positive symptoms (SAPS-PD). Key secondary outcomes included improvements in the Clinical Global Impression-Improvement (CGI-I) scores as well as safety and tolerability.

In the ACP-103-020 trial, pimavanserin was reportedly associated with a 5.79-point decrease in SAPS-PD compared with a 2.73-point decrease with placebo (Δ − 3.06 points; 95% CI − 4.91 to − 1.2; $p = 0.001$) [70]. At the end of the 6-week period, 73.7% of patients who received pimavanserin achieved at least a 1-point improvement (i.e., decrease) in SAPS-PD from baseline, 33.7% achieved an improvement of at least 10 points, and 13.7% achieved a complete response, compared with 55.6%, 16.7%, and 1.1% with placebo, respectively [66]. Similarly, pimavanserin significantly improved CGI-I compared with placebo (2.78 vs. 3.45; $p = 0.0011$). The caregivers of patients receiving pimavanserin reported a larger reduction in burden-of-care than caregivers of patients in the placebo arm (4.34-point improvement in the Zarit 22-item caregiver burden scale; 95% CI − 7.00 to −1.67; $p = 0.0016$). These, along with other measurements, demonstrated that pimavanserin is efficacious when compared with placebo in the treatment of PDP [70].

The incidence of treatment-emergent adverse events in the ACP-103-020 trial was similar between the pimavanserin and placebo arms, with the most common being urinary tract infections (UTIs; 13% vs. 12%), falls (11% vs. 9%), hallucinations (7% vs. 4%), peripheral edema (7% vs. 3%), nausea (6% vs. 6%), and confused state (6% vs. 3%). Eleven percent of patients in the pimavanserin group, versus 4% in the placebo group, experienced serious adverse events. A mean increase of 7.3 ms in QT interval from baseline to 43 days was observed in the pimavanserin arm versus no change in the placebo arm. Unlike other noted atypical antipsychotics (e.g., clozapine and quetiapine), there was no association of pimavanserin with weight gain, somnolence, or metabolic syndrome. Notably, there was no evidence of treatment-related impairment of motor function in either the pimavanserin or placebo arms [70].

A more recent, open-label extension study (NCT00550238) demonstrated similar results [71, 72]. At the end of a 4-week extension period, the mean change in SAPS-PD at 10 weeks from baseline for all patients was − 1.8 (95% CI − 2.3 to − 1.2), and the subgroup of patients who had not received prior pimavanserin experienced a mean SAPS-PD benefit of − 2.9 (95% CI − 3.8 to − 2.1) [72]. 68.0% of patients in the extension study continued pimavanserin for 6 months and 18.1% continued pimavanserin for more than 4 years [71]. After prolonged exposure to pimavanserin, the adverse event profile resembled that observed in the placebo-controlled 6-week pimavanserin studies and most adverse events were mild or moderate. Additionally, early response to pimavanserin seemed to be durable with extended treatment.

3.5.2 Evaluating Mortality Risk with Pimavanserin

Recently, three insurance database retrospective analyses evaluated the risk of mortality associated with pimavanserin versus other atypical antipsychotics. One study using commercially insured patients receiving atypical antipsychotics to treat PDP found that there was no significant difference in the risk of mortality with pimavanserin versus the preferred atypical antipsychotics quetiapine and clozapine (adjusted hazard ratio [HR] 0.99, 95% CI 0.81–1.20) or non-preferred atypical antipsychotics (adjusted HR 0.98, 95% CI 0.79–1.22) [73]. A second study assessing Medicare beneficiaries with PD showed that the risk of mortality with pimavanserin was approximately 35% lower than with other atypical antipsychotics (quetiapine, risperidone, olanzapine, or aripiprazole) within the first 180 days of treatment (HR 0.65, 95% CI 0.53–0.79), but there was no significant difference in mortality with treatment beyond 180 days (HR 1.05, 95% CI 0.82–1.33) [74]. Another study assessing Medicare beneficiaries with PD showed a similar improvement in risk of mortality with pimavanserin versus other atypical antipsychotics (clozapine, quetiapine, risperidone, olanzapine, aripiprazole, or brexpiprazole) with an HR of 0.78 (95% CI 0.67–0.91) [75].

Finally, after evaluation of reported postmarketing adverse events, the FDA did not identify new or unexpected safety concerns with pimavanserin, and upheld their conclusion that benefits with pimavanserin outweigh its risks for patients with PDP [76, 77]. Taken together, these data demonstrate the durability of efficacy with pimavanserin without increasing the incidence of toxicities with longer dosing.

3.5.3 Comparing Pimavanserin with Other Antipsychotics

While there have been no head-to-head comparisons between pimavanserin and other atypical antipsychotics in PDP, a recent network meta-analysis of 19 studies assessing the use of atypical antipsychotics (including pimavanserin, clozapine, quetiapine, ziprasidone, olanzapine, aripiprazole, and risperidone) in the treatment of PDP evaluated the efficacy and safety of pimavanserin compared with other atypical antipsychotics in PDP [78]. This analysis found that the included pimavanserin studies demonstrated significantly greater odds of improving

PDP symptoms than placebo (OR 1.16, 95% CI 1.07–1.24) and showed numerically greater odds (not statistically significant) of improving PDP symptoms over clozapine (OR 1.14, 95% CI 0.98–1.31), olanzapine (OR 1.23, 95% CI 0.91–1.37), and ziprasidone (OR 1.13, 95% CI 0.91–1.37). Additionally, pimavanserin demonstrated similar odds of treatment discontinuation rates due to adverse events (ORs of 0.9 and 1.15 for pimavanserin vs. clozapine and quetiapine, respectively) and odds of deteriorating motor function via the UPDRS II/III versus other atypical antipsychotics (standardized mean differences of 0.67 and −0.02 for pimavanserin vs. clozapine and quetiapine, respectively) and showed numerically improved odds of not developing somnolence compared with clozapine and quetiapine (ORs of 0.23 and 0.46, respectively). Additionally, there is a clear difference between time to response for pimavanserin versus other atypical antipsychotics. For example, while pimavanserin typically takes 2–6 weeks to elicit a meaningful response in alleviating psychotic symptoms, response to clozapine is usually much faster, occurring within approximately 1 week after initiation of therapy [56]. This suggests a different utility for pimavanserin versus other atypical antipsychotics for the management of PDP, especially when patients require hospitalization due to their symptoms (see below). A phase IV comparative trial (C-SAPP, NCT04373317) has been initiated to investigate pimavanserin versus quetiapine in patients with PDP [79].

Despite the current lack of direct comparisons, the IPMDS recommends that pimavanserin is 'clinically useful' in the treatment of PDP and may be considered a preferable first choice after optimization of antiparkinsonian medications [33]. Like most antipsychotics or combinations of antipsychotics, the IPMDS noted the need to monitor QT intervals with pimavanserin, especially when used in combination with other antipsychotics. Similar to clozapine, the AGS recently listed pimavanserin as an antipsychotic that may be used for older patients with PDP [41].

4 Proposed Updated Algorithm for Treating PDP

Current guidelines and recommendations for PDP management suggest that before diagnosis and treatment of PDP, other potential causes for psychosis must be excluded (Table 1) [21, 22, 31, 33, 34]. After excluding these factors, current guidelines recommend alterations to antiparkinsonian medications to manage persistent bothersome psychotic symptoms if they do not significantly worsen motor symptoms. This can then be followed by antipsychotic therapy [32, 33]. While it has been shown that pimavanserin does not negatively impact motor function in PDP, even without reduction of antiparkinsonian medications, we agree that the regimen of antiparkinsonian drugs and other medications must first be optimized by removing any non-essential components (e.g., anticholinergic agents, amantadine, muscle relaxants, opioids, etc.) to assess whether psychotic symptoms may be alleviated without further intervention but without significantly affecting a patient's motor function. If antipsychotic symptoms persist after optimization of antiparkinsonian and other medications, we propose a modified treatment algorithm based on the relative impact of psychotic symptoms on patients or their caregivers, and whether patients are experiencing an episode of psychosis that requires hospitalization (Fig. 2). It should be noted that while pimavanserin is the only FDA-approved drug for the treatment of PDP in the US, it has not been approved in this setting elsewhere and some regions may experience significant financial costs with this type of new therapy, therefore alternative options and recommendations must be considered.

4.1 Patients with Minor/Non-distressing Symptoms

As noted above, PDP is symptomatically heterogenous. For patients whose symptoms are not distressing for themselves or their caretakers, or who can recognize the unreality of their condition, symptoms can be considered minor or non-distressing. We recommend that these patients should be managed with changes in lifestyle choices that minimize potential exacerbation of the psychosis (Fig. 2a). Table 4 lists possible lifestyle modifications that can be suggested for these patients.

Patients with minor or non-distressing symptoms, and their caregivers, can be educated about the disease, including the importance of symptom progression monitoring and the available therapeutic options. While there is no definite evidence that pimavanserin is more efficacious and/or adds quality-of-life benefit when used to treat mild or non-distressing PDP, treating psychosis associated with other disease states before the symptoms become distressing improves overall treatment efficacy and patient quality of life, while alleviating caregiver burden [80–82]. Additionally, it has been shown that patients experiencing PDP-associated hallucinations were more likely to have a malignant form of PD, and some small cohort studies have shown that psychosis can originate in early PD or before motor symptoms emerge [8–12]. Therefore, we suggest initiating the treatment for patients with mild or non-distressing PDP, upon their request, may be considered after a proper discussion of the risks and benefits. Since the onset of significant psychosis cannot be predicted, this approach may be helpful by reducing the risk of the minor symptoms becoming more significant.

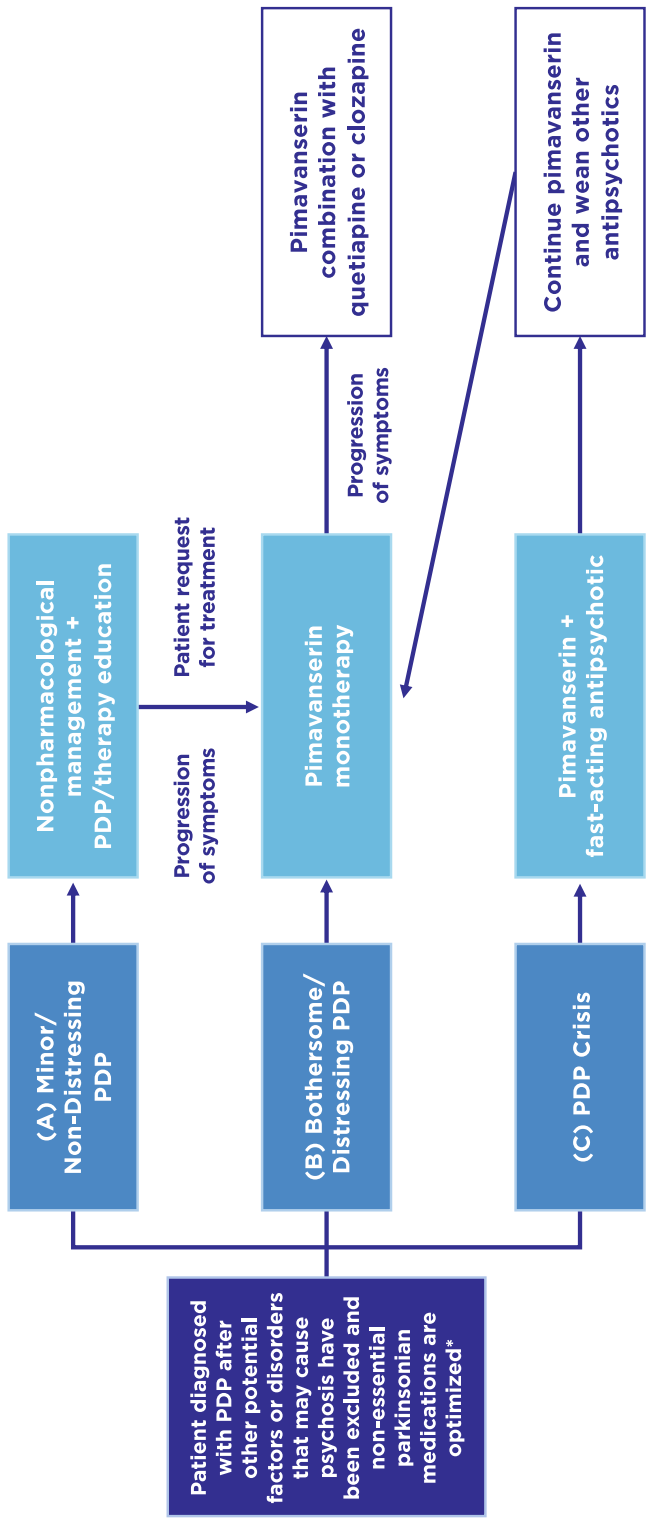

Fig. 2 Updated algorithm for the management/treatment of hallucinations and delusions associated with Parkinson's disease psychosis therapy for patients with (**a**) minor/non-distressing symptoms, (**b**) bothersome/distressing symptoms, or (**c**) are in psychotic crisis. * Cholinesterase inhibitors may be tried in PDP with dementia/cognitive impairment at any point as long as caution is exercised regarding QTc prolongation. *PDP* Parkinson's disease psychosis

Table 4 Non-pharmacologic management of minor/non-distressing Parkinson's disease psychosis

Lifestyle changes for non-pharmacologic management of minor/non-distressing PDP
Maintaining an optimal sleep/wake cycle and circadian rhythm
Maintaining familiar scenery around the home
Ensuring well-lit rooms during the day
Maintaining hydration and monitoring for symptoms of urinary tract infections
Avoiding medications that trigger neuropsychiatric issues (e.g., anticholinergics, benzodiazepines, opiates, sedating drugs)

PDP Parkinson's disease psychosis

4.2 Patients with Bothersome/Distressing Psychotic Symptoms

While overstimulation of dopamine receptors (exacerbated by dopaminergic medication) is a known contributor towards psychosis in PD [83], there are likely several other contributors (e.g., increased accumulation of 5-HT_{2A} receptors). Although studies of *de novo* PD are relatively small and limited because of difficulties in pathologic confirmation of PD, between 1% and 26% of treatment-naïve patients with PD have been reported to experience psychotic symptoms [9, 10, 12, 84, 85]. Additionally, there is minimal evidence supporting dose reduction of most dopaminergic medications for alleviating psychotic symptoms in PD [86], an approach that can be accompanied by deterioration of PD-related motor function [87]. Decreasing antiparkinsonian medications that have been optimized for motor control in patients with PDP has little to no effect on psychosis, but can negatively impact mobility, possibly leading to a net negative impact on patient quality of life. Thus, we recommend reducing dopaminergic medications for PDP management only after confirming the ineffectiveness of antipsychotic pharmacological regimens (see below).

We recommend treating all patients experiencing bothersome or distressing PDP-associated hallucinations or delusions with first-line pimavanserin (Fig. 2b), considering its demonstrated efficacy in managing PDP symptoms without negatively affecting motor function [70]. The efficacy of pimavanserin is sustainable with minimal safety concerns for long treatment durations [71, 72, 76]. Unlike clozapine and quetiapine, pimavanserin can also avoid causing adverse anticholinergic effects. Patients and caregivers should be instructed that observable therapeutic effects will occur approximately 4–6 weeks after the initiation of pimavanserin therapy. We recommend visiting with the patient at some point during this 4- to 6-week interval to evaluate clinical response and tolerability. Alternatively, phone or virtual consultations may also be used to follow-up with patients more frequently if needed.

Although pimavanserin provides a generally sustainable clinical benefit and a manageable safety profile, symptoms of psychosis can progress in some cases. There are no clinical data evaluating the best therapeutic options after progression on pimavanserin and no FDA-approved medications for PDP beyond pimavanserin. Recently, a single-center retrospective study of 27 patients with PDP who experienced regression of antipsychotic symptoms while taking pimavanserin were treated with subsequent clozapine (mean dose of 49.5 mg/day; range 25–100 mg/day) [88]. Of the 27 patients, 17 (63%) reported that clozapine was at least moderately effective in alleviating psychotic symptoms, with 5 (18%) patients reporting clozapine was somewhat effective. For patients who have progressive psychosis after pimavanserin, we suggest using pimavanserin in combination with other atypical antipsychotics that have some demonstrated efficacy in PDP, i.e. clozapine and low-dose (12.5–50 mg) quetiapine. There are limited data demonstrating the efficacy of these treatment combinations; however, case series evidence suggests potential efficacy benefits of pimavanserin in combination with both agents [89, 90]. The first series was a report of 11 patients with PDP who received pimavanserin for their psychotic symptoms, three of which received combination quetiapine and reported control of their psychotic symptoms [89]. The second series was a report of 10 patients with PDP who did not respond to prior antipsychotic therapy (including clozapine) and received subsequent pimavanserin, 6 of whom received combination clozapine with pimavanserin and reported the eventual complete alleviation of their psychotic symptoms [90].

If there is a robust response after adding clozapine or quetiapine during the early phases of combination therapy, or if adverse effects occur, cross-taper of the new agent should be attempted. This type of combination with the option of cross-taper could provide the benefit of continued management of antipsychotic symptoms and allow for patients to remain home and lessen the risk of hospitalization, as would be needed if further progression of psychotic symptoms occurred. This type of strategy could also avoid the risk of worsening motor function that a patient would experience if other atypical psychotics were required to manage more severe symptoms.

It should be noted that both clozapine and quetiapine increase drowsiness and orthostatic hypotension (in comparison with pimavanserin) and are associated with

potential risk of metabolic syndrome with long-term use [51, 53, 62]. Additionally, clozapine is associated with the risk of agranulocytosis [52], requiring frequent monitoring of white blood cell and neutrophil counts [57]. Finally, pimavanserin is associated with drug-induced QT interval (QTc) prolongation [66], which may worsen with the addition of other antipsychotics. While many typical and atypical antipsychotics are associated with QTc prolongation, the association with clozapine or quetiapine is limited and mostly occurs at high doses or in patients with QT prolongation-associated comorbidities [91]. Studies have shown that nearly 90% of patients with QTc prolongation and/or torsade de pointes have two or more identifiable risk factors, including heart disease, older age (>65 years), female sex, bradycardia, and concomitant use of drugs that interfere with drug metabolism [91, 92].

In recent postmarketing analyses, the FDA noted that combining pimavanserin with other antipsychotics can be concerning due to the increased risk of QTc prolongation and consequential heart rhythm disorder [76]. In patients where QTc prolongation is a concern, EKG data should be gathered at the beginning of pimavanserin monotherapy and again after 2 weeks. When pimavanserin is used in combination with other antipsychotics, an EKG should be obtained again at the beginning of therapy (with the second agent), then again after 2 weeks. Finally, it should be noted that if additional cholinesterase inhibitors are used to manage psychotic symptoms for PD patients with dementia or cognitive impairment, there are similar concerns about QTc prolongation, and thus extra monitoring should be considered if used with or before pimavanserin [93–95].

4.3 Patients in Psychotic Crisis

Patients with PD are rarely hospitalized for episodes of psychosis; in such rare instances, we strongly recommend against halting their motor-symptom medications. Abrupt discontinuation of dopaminergic medications for PD can trigger a neuroleptic malignant-like condition called Parkinsonism hyperpyrexia syndrome [96]. Antiparkinsonian medications may be gradually reduced in order to alleviate some psychotic symptoms; however, abrupt discontinuation should not be considered. The most important avenue for avoiding such episodes of psychosis is thorough education, for both patients and caregivers, on the potential for psychosis with PD, including signs of psychosis, management of mild symptoms with proper lifestyle changes, and what to do if crisis is unavoidable.

While there is no clinical trial evidence to guide the therapeutic approach for such a scenario, we recommend starting pimavanserin (if not already being taken) paired with a fast-acting antipsychotic that could differ depending on the nature of the psychotic crisis (Fig. 2c). For example, an atypical antipsychotic can be administered in combination with pimavanserin until the patient is less distressed, after which the fast-acting antipsychotic may be tapered off.

The paired antipsychotic could be one of many atypical antipsychotics, including quetiapine, clozapine, olanzapine, or ziprasidone. We suggest using quetiapine or clozapine first because of their short half-life, quickly developing steady-state equilibrium, and negligible motor adverse effects. Then, if needed, consider olanzapine, which was well tolerated and efficacious in some case reports and series, for PDP [97, 98]. Furthermore, a recent single-center case series of 7 patients with PD and/or Lewy body dementia with psychosis who were treated with ziprasidone demonstrated some efficacy in patients with PD, with manageable toxicity and a limited effect on motor function. Furthermore, ziprasidone may be especially useful for patients who are unable to take oral medications because of its ability to be administered intramuscularly [99]. However, long-term use of olanzapine and ziprasidone should be avoided to prevent worsening of motor function in patients with PDP. Ideally, in all contexts, monotherapy with one antipsychotic agent is preferred to reduce the risk of adverse effects and drug–drug interactions. It should also be noted that atypical antipsychotics, in general, have a black-box warning against their use in elderly patients with dementia-related psychosis, therefore prolonged use of these other antipsychotics with or without pimavanserin should not be considered beyond the alleviation of the severe psychotic symptoms requiring hospitalization.

It is unclear whether the non-pimavanserin atypical antipsychotics in this scenario work via an antipsychotic effect or via causing sedation in this scenario. Nevertheless, there could be a clear alleviation of distress experienced by the patient. When the psychosis becomes manageable, the atypical antipsychotics with greater risk of long-term adverse effects can be gradually tapered and removed.

5 Conclusion

Although a significant proportion of patients diagnosed with PD eventually develop symptoms of psychosis, there is a considerable unmet need for an effective therapeutic approach for this patient population. Patients with PDP have limited treatment options that are both effective and tolerable enough to maintain optimal motor control. These patients can also be misdiagnosed or have their disease mismanaged due to factors including the lack of education or potential stigmas. A strategically developed, patient-centered approach for the diagnosis and management of PDP is necessary to best improve patient quality of life. Of utmost importance is patient/caregiver education on PDP symptom awareness and overcoming health inequities through better access to healthcare providers for all PDP patients.

When following up with PD patients, it is important to monitor for signs of psychotic symptoms. A short list of questions may be used at every follow-up to assess PD patients for psychosis. Once symptoms of PDP have been identified, it is important to first rule out other potential causes of psychosis before proper management can be planned. Once other causes are excluded and a diagnosis for PDP can be made, it is important to extensively evaluate psychotic symptoms and regularly follow-up with patients. If psychotic symptoms are not bothersome, patients can be managed with lifestyle changes (although we note treatment may be considered at a patient's or caregiver's request after proper discussion of the risks and benefits). Treatment should be initiated if the psychotic symptoms become bothersome or distressing to patients or their caregivers.

Current guidelines and recommendations suggest that the first step in the management of PDP, after excluding other causes of psychosis, is to decrease or discontinue antiparkinsonian medications until the psychotic symptoms decrease (without significantly altering motor function, if possible) [22, 31–34]. Persistent psychotic symptoms should then be treated with typically recommended antipsychotics.

We have proposed a treatment algorithm for the management of PDP in which all patients with bothersome symptoms should be treated with first-line pimavanserin if available, as it is only approved for the treatment of PDP in the US. Pimavanserin is the only antipsychotic therapy approved by the FDA for the treatment of H&D associated with PDP [66] and has demonstrated sustainable improvements in psychotic symptoms, without negatively affecting motor function [70–72]. The most common adverse events that occurred in 5% or more of pimavanserin-treated patients and at twice the rate of placebo were peripheral edema, nausea, and confusional state. Hallucinations, constipation, and gait disturbances were also observed at an incidence of 2% or greater in pimavanserin-treated patients and at twice the rate of placebo. Treatment was discontinued in 8% (16/202) of pimavanserin-treated patients and in 4% (10/231) of placebo-treated patients due to hallucinations (2% vs. <1%), UTI (1% vs. <1%), and fatigue (1% vs. 0%).

Patients with bothersome PDP should receive first-line pimavanserin until progression of psychotic symptoms, at which point combinations with other atypical antipsychotics (quetiapine, clozapine) can be considered. For patients with PDP in a severe psychosis episode, it is important to not force the discontinuation of antiparkinsonian medication, but instead administer pimavanserin (if not already taking the medication) in combination with a fast-acting antipsychotic (first quetiapine, clozapine, or olanzapine, ziprasidone) to control the psychotic symptoms, after which the non-pimavanserin antipsychotic can be tapered off. We believe that compared with current standard practice, this treatment algorithm accompanied by increased patient/caregiver education and an optimized multidisciplinary approach, may better improve the quality of life for patients with PDP.

Declarations

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Conflicts of Interest Fernando L. Pagan is a speaker/consultant for Acorda, Acadia, Adamas, Amneal, Kyowa Kirin, Neurocrine, Supernus, Teva, and US WorldMeds. He has received educational and research grants from Novartis, US WorldMeds and Medtronic, as well as NIH/NIA and Sun Pharma funding for clinical trials. He is the cofounder and Board member of KeifeRx. Paul E. Schulz is funded by the McCord Family Professorship in Neurology, the Umphrey Family Professorship in Neurodegenerative Disorders, multiple NIH grants, and several foundations. He has served as a consultant and speaker for Eli Lilly, Biogen, and Acadia Pharmaceuticals, and has contracts with multiple pharmaceutical companies to perform clinical trials. Yasar Torres-Yaghi is a speaker and consultant for AbbVie, Acorda, Acadia, Amneal, Sunovion, Teva, Kyowa Kirin, and Abbott. Gregory M. Pontone is currently funded by NIH grants and in the past has received funding from foundations and participated in industry-sponsored clinical trials. He has consulted for Acadia Pharmaceuticals and GE Healthcare.

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