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REVIEW

Pimavanserin: A Truly Effective Treatment for Parkinson's Disease Psychosis? A Review of Interventions

Beatrice Heim, Marina Peball, Florian Krismer, Atbin Djamshidian, Klaus Seppi

Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Correspondence: Beatrice Heim; Klaus Seppi, Department of Neurology, Medical University of Innsbruck, Anichstrasse 35, Innsbruck, 6020, Austria, Tel +43-512-504-81128, Email beatrice.heim@i-med.ac.at; klaus.seppi@i-med.ac.at

Abstract: Parkinson's disease (PD) is the second-most common neurodegenerative disorder with a long-term 60% cumulative prevalence of PD psychosis. Medical treatment is limited to few atypical antipsychotic drugs with low affinity to dopamine D2 receptors. In 2016, pimavanserin, a selective 5-HT2A inverse agonist/antagonist, was approved by the US Food and Drug Administration (FDA) as the only treatment for PD psychosis (PDP). This article provides an overview of the epidemiology, pathophysiology, and treatment options for PDP and illuminates the mode of action and therapy options with pimavanserin and the current study data.

Keywords: Parkinson's disease, psychosis, pimavanserin

Introduction

Parkinson's disease (PD) affects 2–3% of the population aged 65 years or above.[1]

Clinically, PD is defined by the presence of bradykinesia, and at least one additional cardinal motor feature, including rigidity and resting tremor.[2] Non-motor symptoms comprise a broad spectrum of problems including neuropsychiatric symptoms (such as depression, anxiety, apathy, hallucinosis and psychosis, impulse control and related disorders, cognitive impairment), autonomic dysfunction (eg, orthostatic hypotension, excessive sweating, urogenital and gastrointestinal dysfunction), disorders of sleep and wakefulness (such as sleep fragmentation and insomnia, rapid eye movement sleep behavior disorder and excessive daytime sleepiness) and others (such as pain, fatigue, olfactory and ophthalmologic dysfunction).[3] Long-term cumulative prevalence rates of psychosis in Parkinson's disease (PDP) were estimated to reach 60%[4] and can occur at any disease stage. However, it is most seen in advanced patients.[5,6] As a selective 5-HT2A inverse agonist/antagonist, pimavanserin is the first antipsychotic without affinity to dopamine receptors. Pimavanserin was first developed for PDP and approved in 2016 by the US Food and Drug Administration (FDA) for visual hallucinations and delusions due to PDP.[7,8] In addition to clozapine, the Movement Disorder Society Evidence-Based Medicine (MDS-EBM) review for non-motor symptoms (NMS) considers pimavanserin as the only antipsychotic drugs with proven efficacy for the treatment of psychosis in PD.

In this article, we review the literature and discuss the therapeutic approach of pimavanserin as a treatment of Parkinson's disease psychosis (PDP).

Parkinson's Disease Psychosis

Definition

Provisional consensus diagnostic criteria for PDP with descriptions of the full range of characteristic symptoms were established as there are no standardized diagnostic criteria.[9] These criteria require recurrent or continuous presence of symptoms for at least one month including delusions, hallucinations, or other 'minor hallucinations' along with the

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diagnosis of idiopathic PD. The symptoms may occur with or without insight, dementia, or medication-treated PD. Sensorium should be clear and there should be no other medical explanation.

Epidemiology and Clinical Description

In general, PDP occurs in more advanced disease stages and is associated with high mortality and morbidity, especially in elderly PD patients with dementia. Prevalence rates vary between 8% up to 60%.[4,10–13] This huge variability may be due to the lack of standardized diagnostic criteria.

PDP differs from other types of psychiatric psychosis. Visual hallucinations are typical and the most common symptom of PDP. These are often categorized into "minor" and "formed" variants, with "minor" hallucinations describing vague illusions like a sense of presence, or misperceptions as a sense of passage, and illusions, contrary to "formed" hallucinations, describing concrete hallucinations of persons, animals, or objects.[14]

Less common but more bothersome and complex than visual hallucinations are delusions: illogical, irrational, dysfunctional views or persistent thoughts, beliefs or worries that are not based on reality. Auditory hallucinations have also been reported in PDP, especially in patients with dementia.[14] Insight is not always preserved and often related to cognitive impairment.[14]

Furthermore, early PD patients without dopaminergic treatment or cognitive decline can develop hallucinations and delusions as well. Nevertheless, other studies found an association of visual hallucinations with dosage and duration of levodopa treatment,[15] with even higher rates in patients treated with dopamine agonists,[6] and a significant association of delusions and dopamine agonists.[16]

Pathomechanisms

The pathomechanism of PDP remains unclear and several factors may interact and contribute to PDP. Furthermore, co-morbidities such as co-existent dementia impact the interpretation of pathological studies.

Both extrinsic/exogenous (eg, drug-related) and intrinsic/endogenous (neurotransmitter dysfunction related to disease progression itself) factors are contributing to the development of PDP.

There are several hypotheses, which mechanisms are involved in the process of the generation of PDP and especially of visual hallucinations.

Overstimulation of striatal dopamine receptors,[17] degeneration of cholinergic neurons in the nucleus basalis of Meynert,[18,19] as well as an increase in serotonin levels are assumed to cause PDP. Some studies suggest an imbalance of serotonergic and dopaminergic transmitters,[20] while some others claim denervation and hypersensitivity of mesolimbic and mesocortical dopaminergic receptors responsible for psychosis.[21,22]

Degeneration of mesolimbic dopaminergic neurons for example consecutively contribute to degeneration in linked areas with acetylcholine and serotonin (5-hydroxytryptamine, 5-HT).[20]

The hypothesis of involvement of dopaminergic transmitters is supported by the fact that dopaminergic overactivity causes non-PD psychosis with antidopaminergic medication acting as antipsychotic treatment. Supportively, PDP improvement can be achieved by decreasing dopaminergic levels.[23]

The involvement of the serotonergic system is supported by the association of 5-HT1A receptor agonists including lysergic acid diethylamide (LSD) in producing visual hallucinations.[24] Moreover, the potent antipsychotic clozapine is known to have a strong affinity for the 5-HT2 receptor and also for its efficacy in treating PDP.[25] Apart from pharmacological interventions, PDP has been reported also in patients with subthalamic deep brain stimulation, possibly due to limbic hyperactivation.[26]

Taken together, the major risk factors for developing PDP are age, disease duration and severity, depression, and cognitive decline.[14] Moreover, all antiparkinsonian and other central nervous system active drugs are important triggers to be considered. In general, anticholinergics and amantadine have a greater potential to induce hallucinations and psychosis compared to dopaminergic agents.[27,28]

Assessment of PDP

In clinical trials of PDP, different inclusion criteria have been used which limits comparability and PDP is often used as an umbrella term for a spectrum of illusions, delusions, hallucinations, and confusion.[6,11]

Earlier trials in PDP used scales and questionnaires (such as the Clinical Global Impression Scale, CGIS; the Neuropsychiatric Inventory, NPI; the Schedule for Assessment of Positive Symptoms, SAPS; the Positive and Negative Syndrome Scale, PANSS, or the Brief Psychiatric Rating Scale, BPRS) designed for psychiatric diseases or dementia as outcome.[3,11]

Although several neuropsychiatric scales are recommended for the assessment of psychotic symptoms in PD, none of these scales were developed specifically PD and therefore may not reflect all phenomena relevant to PDP.[29] Different rating scales have been developed to assess PDP, but they can differ in the specific symptoms they assess, the severity levels they use, and the reliability and validity of the scale. This can lead to inconsistencies in how the condition is diagnosed and treated, as well as difficulty in comparing results across studies.

An International Parkinson Disease and Movement Disorder Society (IPMDS)-commissioned task force reviewed and made recommendations for the use of psychosis rating scales used in PD. Four instruments were listed as "recommended" for use in PD as primary outcome measures in clinical trials, including NPI (when a caregiver/informed other is available), SAPS, PANSS, and BPRS, and the CGIS as a secondary outcome measure.[30] Moreover, the IPMDS task force concluded that a novel PD specific scale is needed as no widely accepted scale exists.[30]

More recently, the SAPS-PD has been developed using clinical data of three failed trials with pimavanserin and the PSYCLOPS trial which reported effectiveness of low-dose clozapine compared to placebo in treating PDP.[25,31,32] As such, a PD-modified SAPS called SAPS-PD has been introduced as a measure of psychotic symptoms and treatment in PDP which seems to retain the reliability, sensitivity to change, and effect size of the SAPS while reducing administration time and score variability.[31] A relatively recent pivotal randomized controlled trial (RCT), indeed, used the SAPS-PD as primary outcome measure.[33]

Pimavanserin

Pharmacology

In 2016, the United States Food and Drug Administration (FDA) has approved pimavanserin for the treatment of PDP. Pimavanserin is a member of a new class of antipsychotics acting as an inverse agonist of the selective serotonin type 2A receptor (5-HT2A) and shows a 40-fold lower affinity for serotonine type 2C (5-HT2C) receptor[34] without dopaminergic, adrenergic, histaminergic, or muscarinic affinity.[33,35] Inverse agonists have the opposite effect of agonists on intrinsic activity and possibly decrease the receptor's intrinsic activity.[36]

Serotonin 5HT2A receptors are widely distributed in the brain.[37] The clinical significance in psychosis of this receptor was first noticed in psychedelic drugs such as lysergic acid diethylamide.[38] The relationship between serotonin receptors and psychosis, hallucinations, or delusions is poorly understood, but a recent study showed abnormalities in the 5-HT2A receptor gene in various neuropsychiatric disorders.[39]

Efficacy of Pimavanserin in PDP

An overview of completed clinical trials of pimavanserin PDP is given in Table 1.

To date, no clinical trial has directly compared atypical antipsychotics such as clozapine and pimavanserin for the management of PDP.

Therefore, a systematic meta-analysis was conducted to assess the relative efficacy and safety of pimavanserin compared to atypical antipsychotics for PDP including 17 studies.[40] Results showed that clozapine is effective against psychosis and has low impact on motor function but has safety issues, quetiapine is inferior to clozapine but superior to placebo with adequate safety, and pimavanserin may be less effective compared to clozapine but had a favorable safety profile for the treatment of psychosis in PD.

Table 1 Completed Efficacy Clinical Trials in Pimavanserin

Reference	Intervention vs Control	Design	Duration (Intervention Phase)	Inclusion Information	Patients (n)				Results	Safety		
					Screened	Randomised	Completed	ITT-Population (Intervention / Placebo)		Drop-Out Rate (Intervention / Placebo)	Adverse Events (Intervention / Placebo)	Comments on Safety
[30]	Pimavanserin (20–60 mg per day) vs Placebo	RCT, double-blind	28 days	Patients with Parkinson's disease psychosis (criteria by Ravina et al 2007) with moderate-to-severe visual and/or auditory hallucinations, and/or delusions for ≥4 weeks, Neuropsychiatric Inventory (NPI) hallucinations and delusions section ≥4	76	60	44	59 (28/31) Analyses done with "per-protocol"-population: 52 (24 / 28)	• Primary outcome: SAPS Total domain score for hallucinations and delusions showed a trend of greater improvement in the pimavanserin-group (p = 0.09, effect size 0.56) • Secondary outcome: SAPS global ratings total score (p = 0.02, effect size 0.66) and single scores for hallucinations (p = 0.02, effect size 0.71) and delusions (p = 0.03, effect size 0.58) improved greater in the intervention-group • Exploratory outcome: UPDRS I improved significantly compared to placebo (p = 0.05, effect size 0.43), particularly the item for thought disorder. No statistically significant improvement of UPDRS II, III, IV, VI, PPRS, CGI-S, ESS was found	n=9 (31%) / n=7 (23%)	n=21 (72%) / n=24 (77%)	There was no difference in the incidence of adverse events between the two study arms. In the pimavanserin-arm, the most common adverse events were somnolence, edema, and increase in blood urea nitrogen.
[31]	Pimavanserin (40 mg per day) vs Placebo	RCT, double-blind	43 days	Parkinson's Disease according to UK Brain Bank criteria, clinically-relevant psychotic symptoms for ≥1 month excluding other causes (eg, toxic, dementia), Neuropsychiatric Inventory (NPI) hallucinations and delusions section ≥6 or individual score of hallucination or delusion item ≥4	314	199	176	185 (95 / 90)	• Primary outcome: SAPS-PD scores improved psychosis in the pimavanserin-group compared with placebo (p = 0.0014, effect size 0.50) • Secondary outcome: SAPS Total domain score for hallucinations and delusions (p = 0.0012, effect size 0.50), hallucinations score (p = 0.0032, effect size 0.45), and delusions score (p = 0.0325, effect size 0.33) showed benefit for pimavanserin over placebo • Exploratory outcome: CGI-S (p = 0.0007, effect size 0.52) and CGI-I (p = 0.0011, effect size 0.51) reflected a greater antipsychotic benefit of pimavanserin than placebo. SCOPA-NS (p = 0.0446, effect size 0.31), SCOPA-DS (p = 0.0120, effect size 0.39), and CBS (p = 0.0016, effect size 0.50) reported improvements for pimavanserin compared to placebo • No significant improvement in UPDRS II and III.	n=16 (15%) / n=7 (8%)		Most common adverse events were nausea, peripheral oedema, urinary tract infection, fall, confusion, hallucinations, and headaches.

Abbreviations: RCT, randomized controlled trial; NPI, Neuropsychiatric Inventory; ITT, intention-to-treat; SAPS, Scale for the Assessment of Positive Symptoms; SAPS-PD, Scale for the Assessment of Positive Symptoms – Parkinson's Disease version; UPDRS, Unified Parkinson's Disease Rating Scale; PPRS, CGI-I/-S, Clinical Global Impression -Improvement / -Severity; ESS, Epworth Sleepiness Scale; SCOPA-NS/-DS, Scales for Outcomes in Parkinson's Disease -nighttime sleep problems / -daytime sleepiness; CBS, Caregiver Burden Scale.

We identified three published randomized controlled trials (RCTs) assessing pimavanserin in PDP.[33,35] Change in SAPS was defined as primary outcome in two published RCTS,[35] with influence on motor symptoms using the UPDRS Part II (Activities of Daily Living) and Part III (Motor Examination) as secondary endpoints.

Cummings et al[33] report a positive outcome for antipsychotic efficacy of pimavanserin. In the study of Meltzer et al,[35] no significant differences between the intervention groups regarding antipsychotic effects was found, possibly due to a too small number of participants,[3] and the HARMONY trial was stopped early for efficacy.[41] Moreover, there are two further trials, which have not yet been published, but whose results have been included in a recently published meta-analysis,[42] which included 4 studies comparing pimavanserin versus placebo in 680 patients with PDP (n = 263 placebo, n = 417 pimavanserin). Intriguingly, treatment with pimavanserin was associated with a significant reduction in scores using the Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions (SAPS-H+D) with a mean difference of 1.55 (95% CI 0.38, 2.71, p = 0.009) in favour of pimavanserine.

A recent systematic review of the MDS EBM group on non-motor symptom treatment in PD considers pimavanserin as "efficacious" and "clinically useful" despite the lack of controlled trials and safety data beyond 6 weeks of treatment.[3]

The use of pimavanserin for treatment of psychosis in PD patients has gained interest in the scientific community in recent years. Currently, pimavanserin in comparison to quetiapine is assessed for treatment of PD psychosis (NCT04373317, multi-centre, RCT, double-blind, https://clinicaltrials.gov/ct2/show/NCT04373317; NCT05590637, https://clinicaltrials.gov/ct2/show/NCT05590637) as well as psychosis in dementia with Lewy bodies (NCT05590637, single-centre, randomized, open-label).

Safety and Tolerability of Pimavanserin

There have been several concerns on pimavanserin's safety.[43] A retrospective analysis of 2186 pimavanserin users and 18,212 non-users between 2015 and 2018 showed an increased risk of hospitalization at one month of treatment initiation of pimavanserin and a higher risk of death for up to one year following initiation,[44] whereas other studies did not find higher mortality or morbidity rates in pimavanserin users.[45–47]

Although concerns associated with the use of atypical antipsychotics in the elderly frail population are believed to also apply to pimavanserin, as described in labeling, postmarketing commitments were obtained to supplement pre-approval safety information to better define other potential risks.[48]

One further study[43] summarized three randomized, double-blind, placebo-controlled trials analyzing PDP patients treated with pimavanserin (NCT00477672 (https://www.clinicaltrials.gov/ct2/show/results/NCT00477672?view=results), NCT00658567 (https://www.clinicaltrials.gov/ct2/show/results/NCT00658567), and NCT01174004 (https://clinicaltrials.gov/ct2/show/NCT01174004)), as well as a subgroup of patients with PD dementia and psychosis from the HARMONY trial.[41] Three studies (NCT00477672, NCT00658567, and NCT01174004) assessed motor-symptoms using the UPDRS II + III, or the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A), which was used in the HARMONY trial.[41] Furthermore, the HARMONY trial assessed cognitive function using the MMSE as a prespecified safety assessment, whereas the other three studies (NCT00477672, NCT00658567, and NCT01174004) investigated cognition using the MMSE only during the screening episode.

Taken together, 433 patients were included in the pooled analysis.[43] The authors found that pimavanserin was well tolerated without a negative impact on motor-symptoms or cognition. Moreover, a meta-analysis[42] which included four studies comparing 417 patients with PDP treated with pimavanserin versus 263 patients with PDP treated with placebo revealed that the groups had similar scores for Unified Parkinson's Disease Rating Scale II and III (UPDRS II and III) with a mean difference of 0.09 (95% CI–1.28, 1.46, p = 0.89).

Regarding safety-related endpoints, one long-term open-label extension study of pimavanserin (20–60 mg) in PD psychosis (NCT01518309, n = 39, https://clinicaltrials.gov/ct2/show/NCT01518309) is also yet to publish final results. Preliminary results revealed drug-related treatment-emergent adverse events in 44%, an all-cause mortality of 21%, serious adverse events in 46% (myocardial infarction, hip fractures, subdural haematoma, PD), and other adverse events in 87%. Similarly, results of another trial assessing tolerability with regard to motor symptom worsening, efficacy, and safety in psychotic PD patients on pimavanserin (n = 30) vs placebo (NCT00087542, multi-centre, RCT, double-blind, https://clinicaltrials.gov/ct2/show/NCT00087542) are pending.

The Use of Pimavanserin in Other Disorders

Apart from PD psychosis, pimavanserin is also currently tested for other indications, such as for the treatment of impulse control disorders in PD (NCT03947216, multi-centre, RCT, blinded, https://clinicaltrials.gov/ct2/show/NCT03947216). One randomized controlled study evaluated pimavanserin for the treatment of motor complications and levodopa-induced dyskinesia in advanced PD patients (NCT00086294, single-centre, https://clinicaltrials.gov/ct2/show/NCT00086294) based on a previously successful animal model. Pimavanserin or placebo were given on inpatient study days parallel to an intravenous levodopa application (individual dose titration of levodopa). Reporting of results is still pending.

Summary of Findings

Pimavanserin is a selective serotonin inverse agonist that acts through blocking of the 5-HT2A receptor, which is believed to play a role in the development of PDP.

Several clinical trials have been conducted to evaluate the efficacy of pimavanserin in treating PDP, revealing conflicting results.[33,35] In the pivotal Phase 3 trial, pimavanserin was shown to significantly reduce the severity and frequency of hallucinations and delusions in patients with PDP compared to placebo using the SAPS-PD.[33]

Nevertheless, results of larger head-to-head comparisons of pimavanserin and other antipsychotics are still pending. Based on these clinical trial results,[33] pimavanserin was approved by the FDA in 2016 for the treatment of hallucinations and delusions associated with PDP. Pimavanserin appears to be well tolerated but possibly less efficacious than clozapine in the treatment for PDP.[49] Nonetheless, with limited treatment options for PDP, pimavanserin represents a therapeutic option with little risk of worsening motor function.

Gaps and Recommendations for Future Studies

An overview of ongoing clinical trials of pimavanserin on PDP is given in Table 2.

Unfortunately, during the COVID-19 pandemic, not all trials were able to achieve their recruitment goal. Thus, one randomized double-blind study attempting to assess safety and daytime sedation of pimavanserin (2 x 17 mg) compared to low-dose quetiapine (25 to 100 mg) in PD patients with neuropsychiatric symptoms (NCT04164758,

Table 2 Ongoing Clinical Trials in Pimavanserin

Identifier	Intervention	Control	Patients	Status
NCT04373317	Pimavanserin 34 mg per day	Quetiapine 25 mg immediate release to 200 mg extended release per day	PD psychosis	Recruiting
NCT05590637	Pimavanserin (variable dose)	Quetiapine (variable dose)	PD psychosis Dementia with Lewy bodies	Recruiting (open-label)
NCT05357612	Pimavanserin	NA	PD psychosis	Recruiting (open-label)
NCT04292223	Pimavanserin 34 mg	NA	PD psychosis, activities of daily living	Completed – results pending (open-label)
NCT01518309	Pimavanserin 20–60 mg	NA	PD psychosis	Completed – results pending (open-label)
NCT00087542	Pimavanserin	Placebo	PD psychosis	Completed – results pending
NCT03947216	Pimavanserin 34 mg per day	Placebo	Impulse control disorders in PD	Recruiting
NCT00086294	Pimavanserin once weekly	Placebo	PD patients with motor complications and dyskinesia	Completed – results pending

Abbreviations: PD, Parkinson's Disease; NA, not applicable.

https://clinicaltrials.gov/ct2/show/results/NCT04164758) ultimately had to be terminated (n = 11). Another multicentre observational cohort study attempting to assess real-life data of patients with PD psychosis using pimavanserin, no- or another antipsychotic was also terminated for the same reason (NCT03152292, https://clinicaltrials.gov/ct2/show/NCT03152292).

Although pimavanserin met the primary endpoint and significantly improved the severity and frequency of hallucinations and delusions in patients with PDP compared to placebo in the pivotal phase 3 trial,[33] there are still some concerns and uncertainties on the role of pimavanserin in the treatment of PDP. These include long-term efficacy, long-term effects on motor and cognitive function, long-term effects on quality of life and caregiver burden, as well as long-term safety regarding potential adverse effects such as cardiovascular events.

Moreover, there is a need to understand the efficacy and safety of pimavanserin in different subgroups of PDP patients (eg, older versus younger patients; patients with more severe psychosis versus those with milder disturbing forms of psychosis, patients with comorbid conditions versus those without relevant comorbidities). Efficacy and safety aspects may vary between these subgroups. While pimavanserin has been shown to be effective in treating PDP in the phase 3 trial, more research is needed to compare its efficacy and safety to other antipsychotics such as clozapine or quetiapine or cognitive-behavioral therapy. Many studies feature a retrospective or observational study design, and there are no results of head-to-head studies comparing pimavanserin with other atypical antipsychotics such as clozapine and pimavanserin for the management of PDP.

Biomarkers to predict response to pimavanserin in patients with PDP are worth to be included in future studies. For instance, functional neuroimaging changes in response to pimavanserin using functional MRI and PET imaging are assessed in one single-centre, open-label trial (NCT05357612, https://clinicaltrials.gov/ct2/show/NCT05357612). This could help identify patients who are most likely to benefit from pimavanserin treatment and help personalize treatment approaches.

In conclusion, future studies should focus on investigating the long-term efficacy and safety of pimavanserin in PDP, including its effects on patient subgroups and comparisons to other treatments. The use of biomarkers could possibly help personalize treatment approaches for patients with PDP in the future.

Pragmatic Management of Psychosis in PD

Identification and removal of possible other explanations or triggering factors is crucial in the management of PDP. This includes medical conditions such as fever, infections, metabolic alterations (eg, dehydration, electrolyte imbalance), or (acute) structural brain lesions (eg, subdural hematoma or stroke), especially if symptoms appeared suddenly.[27] Next, concomitant medications should be evaluated. PD and many non-PD medications (eg, antibiotics, antidepressants, benzodiazepines, etc.) may all trigger psychotic symptoms.[50] Modifying PD treatment is suggested with gradual removal of PD medications (if motor function is maintained). Drugs with unfavorable risk benefit ratios regarding cognitive side effects versus antiparkinsonian efficacy should be tapered first, ie, anticholinergics, amantadine, MAO-B inhibitors before reducing dopamine agonists, catechol-o-methyltransferase (COMT) inhibitors, and lastly, levodopa.[39] As it is not always possible to reduce antiparkinsonian drugs to a level where psychotic symptoms improve while maintaining a sufficient motor control, antipsychotic treatment is required.

In this case, atypical antipsychotics, including quetiapine and clozapine, are primarily used in Europe.

Clozapine was the first antipsychotic to successfully treat drug-induced psychotic symptoms in PD without worsening of motor symptoms.[51] However, its usability is limited due to the safety warnings including agranulocytosis and metabolic disturbances.[52] The strict blood count monitoring required during treatment of clozapine is reported as the main reason for drug discontinuation in nursing homes,[53] albeit the effectiveness of extremely low doses of clozapine has been confirmed in several clinical trials.[3,11,25,54]

The use of quetiapine showed conflicting results regarding efficacy and safety in the treatment of PDP.[50] Nevertheless, as quetiapine does not require regular blood count monitoring and is generally well tolerated, it is widely prescribed and used for PDP treatment.[55] In one clozapine-controlled but not placebo-controlled trial, quetiapine showed similar efficacy as clozapine.[3,11]

However, the most frequent reported side effects of quetiapine but also clozapine include sedation and postural hypotension,[25,56,57] and one study even showed an increased mortality in PD patients treated with quetiapine but not with

clozapine.[58] A recent network meta-analysis compared efficacy, safety, and acceptability of different antipsychotic drugs including pimavanserin.[59] The authors conclude that in PDP, pimavanserin and clozapine showed significant improvement without affecting motor function in PDP patients, whereas quetiapine was associated with a significant decline in cognition.[59]

Moreover, a recent cohort study observed lower mortality rates in patients treated with pimavanserin compared with those patients treated with other atypical antipsychotics.[60]

Cholinesterase inhibitors like rivastigmin might be an alternative treatment of psychotic behavior specifically in demented patients,[3] albeit a recent RCT was terminated early due to slow recruitment and therefore could not properly evaluate the primary outcome.[61]

Conclusion

Management of PDP is based on careful assessment of triggering or contributing factors, including a rigorous review of the current antiparkinsonian treatment schedule, and frequently will include the addition of an antipsychotic agent, because dose reductions of antiparkinsonian drugs to a level that will lead to a resolution of psychotic symptoms while maintaining sufficient symptomatic motor control is not always feasible.[3] Pimavanserin, in countries where it is available, and low-dosage quetiapine can be considered a pragmatic first choice because of its easier application compared to clozapine. According to a recent EBM review of the MDS, quetiapine, however, is not formally established as efficacious in RCTs, while pimavanserin has been considered as "efficacious" in this instance with a lack of long-term efficacy and safety data.[3] The atypical antipsychotic clozapine has proven efficacy for the treatment of PDP and should be used in all cases that fail following treatment with quetiapine or pimavanserin, but can also be considered a first-line option despite onerous weekly blood count monitoring.[3]

In the US, pimavanserin is the first approved therapy for the treatment of hallucinations and delusions associated with PDP. Its mechanism of action as a selective 5-HT receptor subtype 2A inverse agonist and antagonist is thought to be unique compared to other antipsychotics due in part to its lack of consequential dopamine binding. A step forward given the unique mechanism of action of pimavanserin was represented by a new large phase 3, randomized discontinuation trial of the safety and efficacy of pimavanserin for the treatment of delusions and hallucinations associated with several types of dementia including dementia associated to PD.[41,62] This trial was stopped early for efficacy because patients with dementia-related psychosis who had a response to pimavanserin had a lower risk of relapse with continuation of the drug than with discontinuation.[41] These data support the use of pimavanserin for the treatment of PDP. Consideration of pimavanserin for the treatment of PDP should be based on the availability of efficacy data and its unique mechanism of action, which potentially confers a different risk profile than that of antipsychotics[62] which seems to result in decreased mortality risk compared with other atypical antipsychotics.[60]

Overall, pimavanserin represents a treatment option for patients with PDP when available, as available evidence suggests that it effectively reduce psychosis without worsening motor function or causing significant side effects.

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