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REVIEW ARTICLE

Implications of Pimavanserin in Patients with Dementia-related Psychosis: A Systematic Review

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Psychosis in patients with dementia-related disorders has long been a challenging issue to be tackled by the medical fraternity. Although atypical antipsychotics (AP) are in use for the same reason, there has always been a question regarding their safety and tolerability in this group of patients. Pimavanserin, a serotonin receptor inverse agonist or antagonist, is the only drug that is Food and Drug Administration-licensed to be used for the treatment of Parkinson's disease psychosis. This systematic review, which was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020, had the objective of examining the effects of pimavanserin in patients with dementia-related psychosis (DRP). Among the publications (January 1, 2013–July 12, 2023) we gathered and examined were case–control and cohort studies, systematic reviews, meta-analyses, clinical trials, literature reviews, and randomized and nonrandomized control trials. The databases used to construct this list of publications were PubMed, Cochrane Library, and Google Scholar. These three databases yielded 157 reports in total once the relevant filters were applied. They were then further screened and put through quality evaluation processes, which led to the final nine papers that were included in this systematic review. We concluded from our review that pimavanserin proves to be a promising alternative for the treatment of DRP, showing significant improvements and fewer side effects compared to other atypical AP.

Key words: Pimavanserin, dementia, psychosis

INTRODUCTION

Psychosis, a typical characteristic of dementia that worsens as the disease progresses, is widespread in neurodegenerative conditions such as Parkinson's disease (PD), frequently occurring in conjunction with cognitive decline, nonmotor symptoms, and sleep difficulties. Other neurodegenerative disorders with a varied prevalence of psychosis include dementia with Lewy bodies (DLBs), Alzheimer's disease (AD), vascular dementia (VaD), and frontotemporal dementia (FTD).[1] The estimated prevalence of psychosis across all dementia illnesses is about 20%–70%.[2] In PD dementia (PDD), its prevalence is around 75%, resulting in significant morbidity and increased death.[3] Psychosis is distinguished by the presence of delusions, delusional misidentification, and hallucinations. Delusions, which affect around 35% of the population, are typically basic; common symptoms include delusions of theft, persecution, adultery, desertion, or that departed relatives are still alive.[4,5,6] The ones in AD are more along the lines of misidentifications, such as believing that one's home is not one's home; that a family member is someone else; that one has been copied or is an imposter (Capgras delusion); or that someone else is living in the house (phantom border hallucination).[4,7] Mistaking television, mirror, or photographic images for real people or objects is an even more common symptom.[4]

The most frequent causes of dementia-related psychosis (DRP), including AD, DLB, PDD, VaD, and FTD, result in behavioral disorders, greater caregiver load, poorer quality of life (QoL), nursing home placement, and faster

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cognitive loss.[4,8-13] Stern *et al*. demonstrated in seminal research that psychosis is related to faster cognitive deterioration.[14] Notably, some studies have revealed that among those who acquire psychosis, there is a steeper trajectory of deterioration even before the start of frank psychotic symptoms, with one study revealing that faster cognitive loss was evident a year before the development of psychosis.[4,12,15,16] Once present in dementia, two-thirds of people experience psychotic symptoms that last at least a year.[4,17] Furthermore, psychotic symptoms are frequently associated with or preceded by other neuropsychiatric symptoms such as agitation, aggressiveness, and depression, compounding the impact on the individual and others.[4]

There are no authorized pharmacological medicines for treating individuals with DRP, and antipsychotics (AP) pharmaceuticals are frequently used off-label for treating psychosis despite safety concerns with their usage in this group.[1] Their usage is linked to impaired cognition, extrapyramidal symptoms, drowsiness, falls, and a higher risk of mortality, and their effectiveness is at best questionable.[2] According to current recommendations, second-generation AP should only be used as a last resort and for a maximum of 12 weeks to treat agitation and psychosis in AD. Long-term use of these medications is linked to an increased risk of mortality and an increased frequency of cerebrovascular events.[18] The Clinical AP Trials on Intervention Effectiveness-AD trial demonstrated a substantial decrease in cognitive performance with AP usage,[19] and a meta-analysis of AP in dementia patients discovered a similar negative effect on cognitive function.[20] All APs licensed by the US Food and Drug Administration (FDA) carry a boxed warning about an increased risk of death in elderly individuals with DRP.[21] As a result, there is a critical unmet need for pharmaceutical DRP therapy that successfully controls psychotic symptoms without impairing cognition and has a favorable safety and tolerability profile.[1]

The new AP medication pimavanserin lacks dopaminergic, cholinergic, or histaminergic activity and works through a highly selective 5-HT2A pathway.[4] Contrary to traditional APs, which bind to D2 dopamine receptors and exhibit varied degrees of action at other receptors, such as histaminergic and muscarinic receptors, this profile is distinct from that of other medications.[8] Unlike other AP medications, there was no increase in sedation, parkinsonism, stroke, rapid cognitive decline, hematological disease, cardiovascular events, or other important safety issues such as sudden death.[4] It is the only AP specifically licensed in the United States to treat hallucinations and delusions related to PD psychosis (PDP), and a randomized controlled study showed that it was effective.[21,22] When evaluating novel and experimental pharmacological therapies for psychosis, a recent international consensus panel gave pimavanserin its unanimous support.[19,23] This early favorable assessment is based on data showing the medication's effectiveness and tolerability in PDP patients with cognitive impairment,[1,22] as well as pertinent findings from Phase II clinical research done on 181 AD patients who were psychotic.[24] The effectiveness results for pimavanserin in the PDP and AD psychosis populations suggest that pimavanserin may have a beneficial therapeutic effect on psychotic symptoms across various neurodegenerative dementing disorders.[1] This comprehensive analysis sheds light on the potential use of pimavanserin in treating psychosis that arises in the most prevalent dementia-related diseases.

METHODS

This systematic review seeks to learn more about and assess the use of pimavanserin in the treatment of DRP. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[25] were followed in the conduct of this systematic review. The study was registered in the International Database to Register your Systematic Reviews with the number INPLASY202430089.

Search strategy

Databases such as PubMed, Google Scholar, and the Cochrane Library were thoroughly searched for relevant literature. The keywords "Pimavanserin," "Dementia," and "Psychosis" were used to construct the search, which was then combined using the BOOLEAN operators "AND" and "OR." The published articles were reduced using a mesh technique. Following the application of the proper filters, Table 1 lists the number of articles produced in each of the databases.

Eligibility requirements

The studies were picked for inclusion based on the participant, intervention, and result characteristics listed below:

Participants

For the investigations, populations of all racial and gender identities with dementia-related psychotic symptoms were selected.

Intervention

Use of pimavanserin in the aforementioned population.

Results

Patients who are suffering from psychosis owing to dementia seem to benefit symptomatically from taking pimavanserin.

Inclusion and exclusion criteria

Papers were only considered if they were written entirely in English, free full-text articles published within the previous

Table 1: Databases used for literature search

Database	Search strategy	Filters	Number of articles
PubMed	Pimavanserin AND Dementia OR ("Dementia/etiology"[Mesh] OR "Dementia/pathology"[Mesh] OR "Dementia/physiopathology"[Mesh] OR "Dementia/prevention and control"[Mesh] OR "Dementia/psychology"[Mesh] OR "Dementia/therapy"[Mesh]) AND Psychosis ("Psychotic Disorders/etiology"[Mesh] OR "Psychotic Disorders/pathology"[Mesh] OR "Psychotic Disorders/physiopathology"[Mesh] OR "Psychotic Disorders/prevention and control"[Mesh] OR "Psychotic Disorders/psychology"[Mesh] OR "Psychotic Disorders/therapy"[Mesh])	Free full text; past 10 years; Humans; English	120
Google Scholar	allintitle: Pimavanserin AND Dementia AND Psychosis	Last 10 years	9
Cochrane library	Pimavanserin AND Dementia AND Psychosis in Title Abstract Keyword	Last 10 years	28

10 years, randomized control trials (RCTs), non-RCTs, case series, and case reports; cohort studies; case–control studies; systematic reviews; literature reviews; and meta-analyses. This systematic review did not take animal research into account.

RESULTS

A total of 157 articles were found in the databases indicated above within the past 10 years (January 1, 2013–July 12, 2023) using the search techniques and suitable filters. After duplicates and irrelevant records were eliminated from the screened articles, the quality of the articles was evaluated using tools such as AMSTAR-2 (for systematic reviews and meta-analyses),[26] the Jadad scale (for RCTs and non-RCTs),[27] SANRA (for narrative review articles),[28] the JBI quality appraisal checklist (for case series and case reports),[29] and the Newcastle–Ottawa checklist (for case–control and cohort studies).[27] The PRISMA chart, as shown in Figure 1, provides an overview of the screening procedure.

The studies included in this systematic review are presented in Table 2.

DISCUSSION

In neurodegenerative diseases such as PD and DLB, psychosis is a prevalent symptom that frequently coexists with other nonmotor symptoms, including cognitive impairment and sleep problems.[1] The overall prevalence of psychosis in various dementia-related disorders is demonstrated in Figure 2.

PD is a progressive neurodegenerative condition marked by resting tremor, stiffness, bradykinesia/akinesia, and postural instability. It is linked to a decline in the neurotransmitter dopamine. Psychosis, dementia, restlessness, autonomic dysfunction, and altered sensory perception are nonmotor characteristics of PD.[30] Common neuropsychiatric features of PD are represented in Figure 3.

PDP has a considerable negative impact on QoL, increased placement in nursing homes, morbidity, and mortality. PDP's complicated pathophysiology is still unknown; however, it may involve impairments in visual processing, sleep problems, and specific dopamine, serotonin, and acetylcholine neurochemical alterations.[30] The majority of AP used off-label exhibit antagonistic action toward the dopamine D2 receptor, which may intensify the motor symptoms linked to PD.[31] When administered in older dementia patients, these drugs are linked to an increased death rate.[30] The only atypical AP drug that the FDA has presently licensed for treating hallucinations and delusions associated with PDP without impairing motor skills is pimavanserin. With a high binding affinity for serotonin 5-HT2A receptors and a decreased binding affinity for serotonin 5-HT2C receptors, it functions as an inverse agonist/antagonist. Pimavanserin does not exhibit any significant affinity for dopaminergic (including D2) receptors when tested *in vitro*.[30] Pimavanserin has only a weak affinity for dopaminergic, muscarinic, histaminergic, or adrenergic receptors and was created in response to the finding that most effective and licensed AP share the ability to antagonize the 5-HT2A receptor.[1] In PDD patients, including PDD patients with psychosis from the HARMONY trial, pimavanserin was well tolerated.[8,31] Various atypical AP used in PDP are summarized in Table 3.

Individuals with multiple dementia diagnoses were included in the HARMONY study because most AP block the 5-HT2A receptor independent of neuropathology, and individuals with dementia subtypes frequently have many underlying neuropathologies.[2] HARMONY was a Phase 3 randomized, double-blind discontinuation trial of pimavanserin in DRP. In that experiment, the effectiveness of pimavanserin for avoiding the recurrence of psychosis in patients who responded to pimavanserin during 12 weeks of open-label therapy, followed by randomized discontinuation of treatment or continuing pimavanserin for up to 26 weeks, was assessed.[2,8] Following randomization, there was an estimated 16% point difference in the proportion of patients who experienced a psychotic relapse in those who continued to take pimavanserin (13%), compared to 28% in those who were transferred to a placebo. With pimavanserin compared to a placebo, the likelihood of a study ending early for any reason was reduced.[8] In PDP patients receiving pimavanserin for up to 9 months, analyses from HARMONY reveal no adverse effects on motor or cognition-related function.[31]

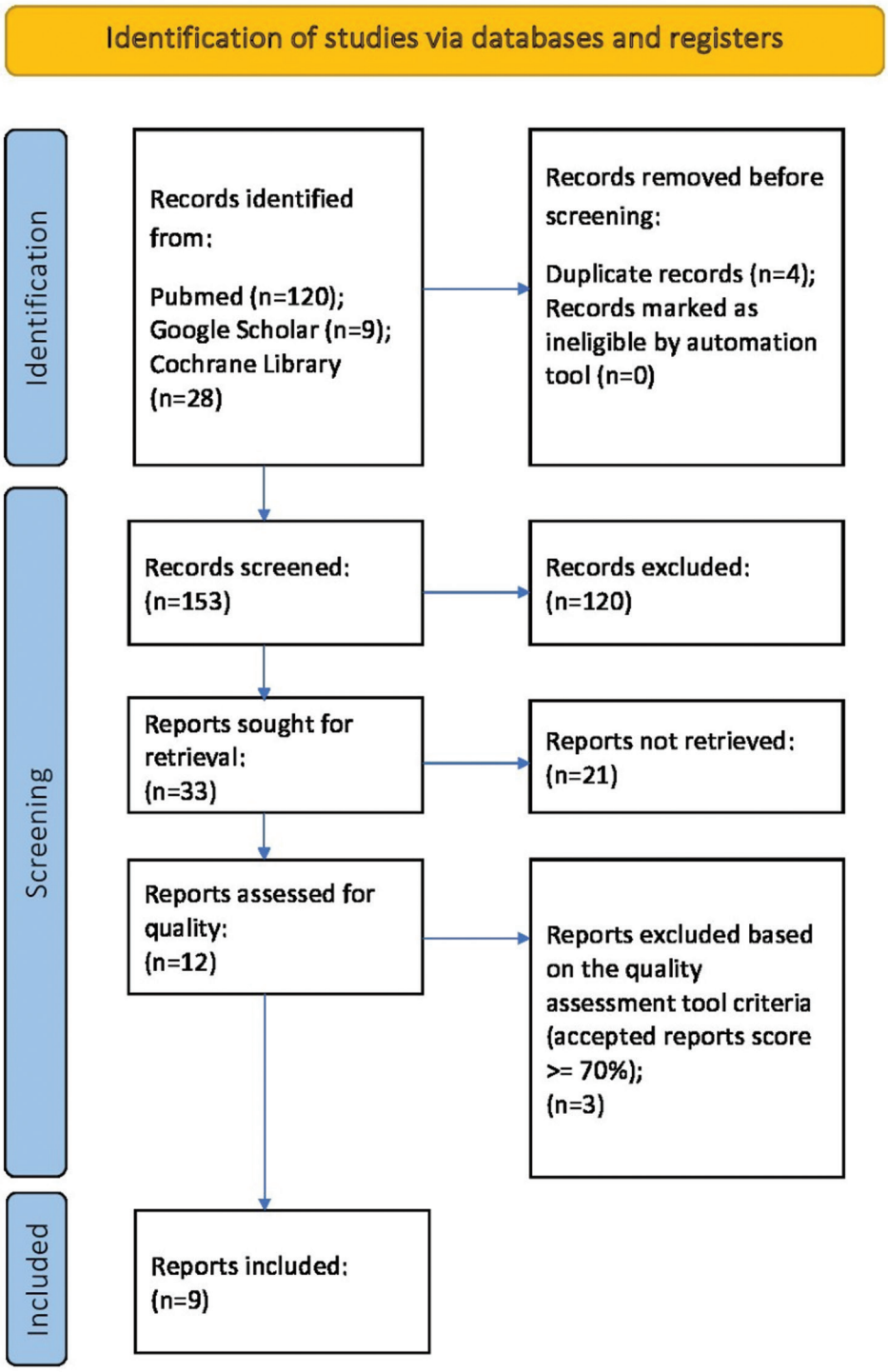

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Chart

In a study by Espay *et al*.,[21] pimavanserin showed a significant improvement in clinical global impression-improvement scores and the Scale for the Assessment of Positive Symptoms adapted for PD (SAPS-PD; scores 0–45, higher scores indicating greater severity of psychosis) scores[32] among patients with PDP regardless of baseline cognition, but with larger responses in patients with impaired baseline cognitive performance.[21] There was also a numerical SAPS-PD effect

Table 2: Studies included in the systematic review

Author	Year of publication	Type of study	Conclusions
Cummings *et al.*[1]	2018	Review article	Pimavanserin has shown considerable effectiveness greater than that reported with existing off-label therapies in two distinct models of dementia-related psychosis (PD and AD)
Sellers *et al.*[3]	2019	Retrospective cohort	In this large cohort of patients, pimavanserin significantly reduced psychosis in 67% of cases, whereas adverse effects were recorded in 22% of cases
Ballard *et al.*[4]	2020	Review article	Although there is a critical information vacuum about psychological therapy, there is intriguing evidence for novel pharmacological treatments. Precision medicine and novel therapy targets will be possible, thanks to genetics
Caraci *et al.*[18]	2020	Review article	Market authorization has been granted for the 5-HT2A and 5-HT2C serotonin receptor antagonist pimavanserin for the treatment of psychosis in PDP. In AD patients with more severe psychosis, recent phase II studies support the effectiveness of this medication
Tariot *et al.*[8]	2021	Randomized Control Trial	Patients in this efficacy-only study with dementia-related psychosis who responded to pimavanserin had a decreased risk of recurrence with continued use of the medication compared to stopping treatment
Fredericks *et al.*[30]	2017	Review article	Pimavanserin has been demonstrated to be effective in treating the hallucinations and delusions connected with PDP; it has no noticeable impact on motor function, blood counts, or metabolic indicators
Espay *et al.*[21]	2018	Research article	Pimavanserin has a potent antipsychotic effect in PD patients with cognitive impairment, which may be boosted by concurrent administration of a cognitive-improving drug
Abler *et al.*[31]	2022	Meta-analysis	In individuals with PD psychosis, pimavanserin 34 mg was well tolerated and had no detrimental effects on motor or cognitive performance
Tariot *et al.*[2]	2022	Correspondence report	The entire pimavanserin development program influences the therapeutic treatment of dementia-related psychosis

PD=Parkinson's disease; AD=Alzheimer's disease; PDP=PD psychosis

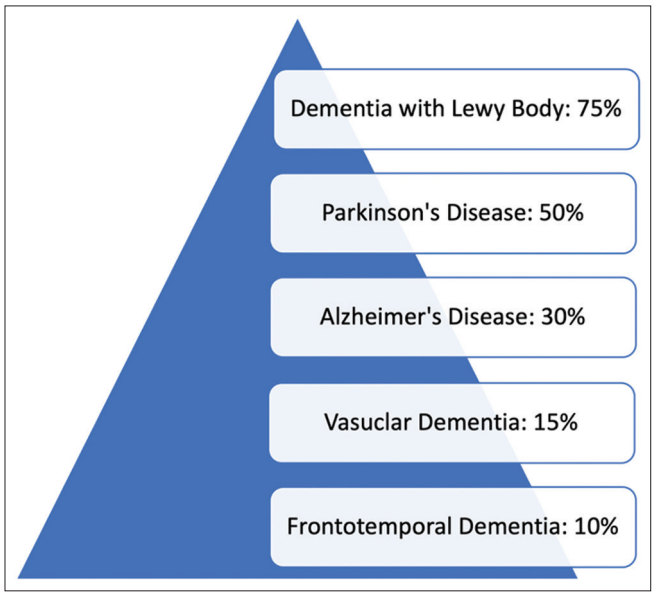

Figure 2: Prevalence of psychosis across various dementia-related disorders. Modified from Cummings *et al.*[1]

Figure 3: Neuropsychiatric symptoms of Parkinson's disease. Modified from Fredericks *et al.*[30]

that was greater in participants taking concurrent cognitive enhancers compared to those who were not. However, this effect was not statistically significant given the limited power of this *post hoc* analysis.[21] In conclusion, this study revealed that pimavanserin may be a safe and effective therapy alternative for PDP patients with cognitive impairment as well as those on cognitive-boosting drugs.[21] In a different trial by Sellers *et al.*, 69 of the 91 patients (76%) experienced a reduction in psychotic symptoms following the initiation of pimavanserin medication.[3] Pimavanserin may be an effective treatment for

Table 3: Atypical antipsychotics in treatment of Parkinson's disease psychosis

Antipsychotic	Salient features
Clozapine	There is sufficient evidence to justify the use of low-dose clozapine in PDP
	At minimum dosages, little likelihood of extrapyramidal adverse effects
	Use with prudence in individuals with heart illness, dementia, hepatic, renal, or diabetes mellitus, as well as those who are at risk of suicide
	FDA enclosed alert (boxed warning) of elevated risks of syncope, bradycardia, orthostatic hypotension, seizure, myocarditis, and cardiomyopathy
Quetiapine	The most often recommended antipsychotic medication for PDP patients
	When dealing with older patients or those who have a history of seizures, cardiovascular illness, dementia, diabetes mellitus, hepatic impairment, or a suicide risk, use caution
	FDA boxed warning: General rise in the frequency of suicide ideation and actions
Pimavanserin	Accredited for the management of PDP-related hallucinations and delusions
	Treatment effectiveness demonstrated for PDP-related delusions and hallucinations
	FDA class warning: Higher mortality in older adults with psychosis associated with dementia

Modified from Fredericks *et al*.[30] FDA=Food and Drug Administration; PDP=Parkinson's disease psychosis

psychosis in patients with DLB and PDD, according to this study, which found equal efficacy for improvement in psychosis independent of the existence and severity of dementia.[3]

The behavioral and psychological symptoms of dementia (BPSD) are almost ubiquitous in patients with AD, even though it is typically thought of as a memory impairment. During their illness, more than half of AD sufferers will show signs of psychosis.[4] BPSD is characterized by persistently altered perception, mood, behavior, and thinking content. Apathy, despair, anxiety, psychosis, agitation, and violence are just a few of the symptoms that can be used as early clinical diagnostic markers for AD and are frequently what leads to institutional care.[18] Psychotic symptoms are typically upsetting for the person experiencing them as well as their caretakers, and they are also linked to worse disease outcomes.[4] Pimavanserin was singled out by the most recent Delphi consensus as one of the most promising prospective treatments for individuals with AD who experience psychosis.[18,23] Results from a Phase II trial including 181 patients with AD psychosis were recently released, and they revealed that 55% of patients in the treatment arm had improved symptoms at the primary endpoint at 6 weeks (compared to 37% in the placebo group).[4] Pimavanserin appeared to be more beneficial for those with more severe symptoms, according to a subgroup analysis.[4]

But like any other medication, pimavanserin is also associated with some side effects that are worth mentioning. A black-boxed warning on the pimavanserin medicine label mentions an elevated mortality risk in older DRP patients.[31] Headache, constipation, and urinary tract infection were typical side effects that pimavanserin patients experienced more frequently than those who received a placebo in the HARMONY trial. In the open-label phase, individuals who received pimavanserin experienced a mean QTcF change of 5.4 ms, and there were five documented adverse events involving asymptomatic QT prolongation.[8] Patients with preexisting QT prolongation or a history of arrhythmias should not take it since it can cause electrocardiographic QT interval prolongation.[19] In the trial by Sellers *et al*., 22% of patients receiving pimavanserin reported side symptoms including increased gait instability, somnolence, minor lower extremity edema, nausea, and nightmares.[3] When pimavanserin is taken alongside an atypical AP, there is also the possibility of increased mortality risk to consider. The only published data on this topic comes from a long-term open-label safety trial in PDP, where 18.5 deaths per 100 patient-years occurred in the group that added another AP, compared to 4.5 deaths per 100 patient-years in the group that continued to take pimavanserin alone.[4,33] Therefore, the combination of pimavanserin and an atypical AP is a significant concern for PDP patients, but it might also be a problem for patients with AD psychosis if the drug is approved for it.[4]

Limitations

This systematic review faces some limitations. Most of the data gathered for this review has been extracted only from the studies, research, and clinical trials that were published in the past 10 years. In addition, only the free full-text publications that are accessible across different databases have been used for this study. During the screening procedure, publications that were not in English were discarded. The evaluation has disregarded studies that tested the effectiveness and safety of pimavanserin using animal models. The majority of the studies included in this review consist of a small cohort. Apart from PD and AD, this review does not talk much about the use of pimavanserin in psychosis across other dementia-related disorders. The review's limited generalizability also stems from the fact that it only includes information from three databases.

CONCLUSION

It is promising to see the development of novel pharmaceutical therapies for DRP, with pimavanserin, a serotonin receptor antagonist, garnering the greatest traction. Pimavanserin is superior to other atypical AP in treating DRP

as it has the least number of side effects associated with the use of other AP because of its minimal activity on other receptors, such as muscarinic, histaminic, or adrenergic. This study has effectively demonstrated that pimavanserin is a potential treatment option for Parkinson's and Alzheimer's patients who exhibit indicators of psychosis. Potential research for the future includes studies with a larger cohort to increase their power; a Phase III double-blinded, RCT for pimavanserin in patients with AD psychosis; and clinical trials to assess the use of pimavanserin across other spectrums of dementia-related disorders such as DLBs, VaD, and FTD.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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