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Review

Clearing the Fog: A Review of Antipsychotics for Parkinson's-Related Hallucinations: A Focus on Pimavanserin, Quetiapine and Clozapine

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Abstract

Parkinson's disease is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, including hallucinations. The use of antipsychotic medications is a common strategy to manage hallucinations associated with Parkinson's disease psychosis (PDP). However, careful consideration is necessary when selecting the most appropriate drug due to the potential risks associated with the available treatment options. Atypical antipsychotics (AAPs), such as Pimavanserin and Clozapine, have effectively controlled PDP symptoms. On the contrary, the support for utilizing quetiapine is not as substantial as other antipsychotics because research studies specifically investigating its application are still emerging and relatively recent. The broad mechanisms of action of AAPs, involving dopamine and serotonin receptors, provide improved outcomes and fewer side effects than typical antipsychotics. Conversely, other antipsychotics, including risperidone, olanzapine, aripiprazole, ziprasidone, and lurasidone, have been found to worsen motor symptoms and are generally not recommended for PDP. While AAPs offer favorable benefits, they are associated with specific adverse effects. Extrapyramidal symptoms, somnolence, hypotension, constipation, and cognitive impairment are commonly observed with AAP use. Clozapine, in particular, carries a risk of agranulocytosis, necessitating close monitoring of blood counts. Pimavanserin, a selective serotonin inverse agonist, avoids receptor-related side effects but has been linked to corrected QT (QTc) interval prolongation, while quetiapine has been reported to be associated with an increased risk of mortality. This review aims to analyze the benefits, risks, and mechanisms of action of antipsychotic medications to assist clinicians in making informed decisions and enhance patient care.

Keywords: neurodegenerative disorders; Parkinson's disease; antipsychotics; hallucinations

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting primarily individuals over the age of 65 [1]. This condition is characterized by the loss of neurons in the substantia nigra, which leads to a dopamine deficiency in the striatum. Additionally, it is marked by the presence of abnormal intracellular structures known as Lewy bodies, primarily composed of aggregated alpha-synuclein protein, in various brain regions. These Lewy bodies are a defining pathological feature of the disease and contribute to its neurodegenerative progression and clinical manifestations [1–3]. PD presents motor symptoms such as bradykinesia, resting tremor, rigidity, and postural instability [4–6]. Nevertheless, non-motor symptoms are common but often overlooked, including autonomic dysfunction, fluctuations, dyskinesias, cog-

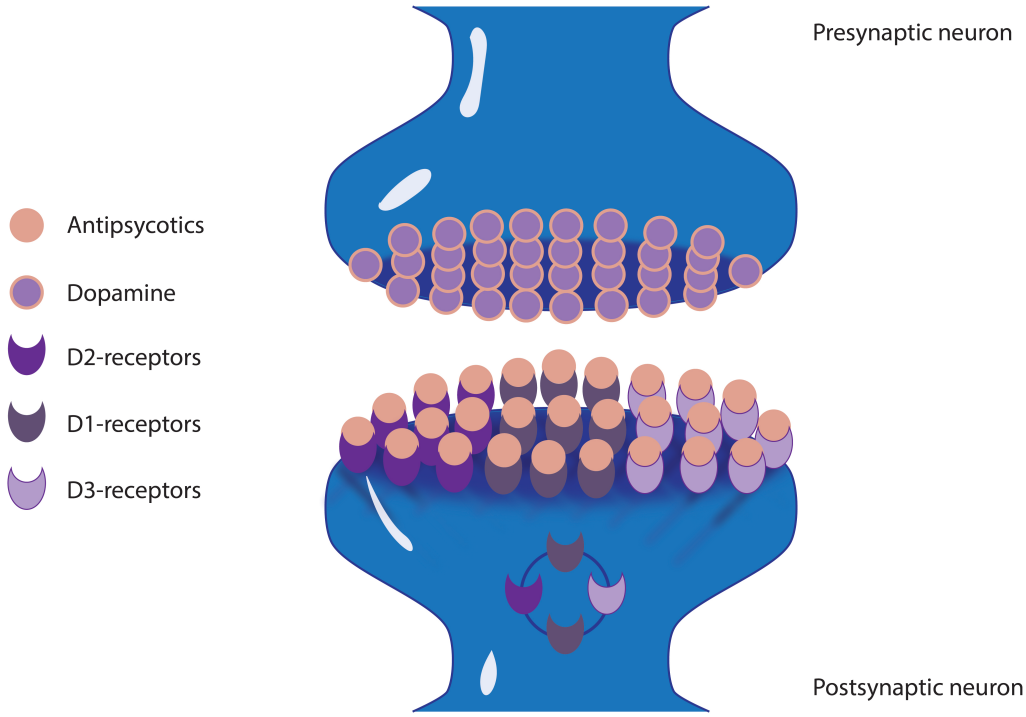

Fig. 1. General mechanism of action of antipsychotics. Caption: The general mechanism of action of Antipsychotics involves the inhibition of dopaminergic neurotransmission by blockage of dopamine receptors in the brain. Abbreviations: D1, Dopamine 1; D2, Dopamine 2; D3, Dopamine 3.

nitive/neurobehavioral disorders, sensory perception, and sleep abnormalities [1,7]. The incidence of PD ranges from 5 to >35 new cases per 100,000 individuals annually, with higher rates observed in older age groups [8–10]. The global prevalence of the disease is estimated to be 0.3%, rising to 3% in individuals over 80 years old [11]. Genetic mutations account for only a small percentage of PD cases, with the most common genetic mutations associated with PD found in the *PARK* genes [12]. In addition, environmental factors, including exposure to pesticides or consumption of dairy products and a history of traumatic brain injury or melanoma, have been associated with an increased risk [12,13]. Conversely, certain lifestyle factors, for example physical activity, may decrease the risk [13]. Molecular causes of PD involve various pathways and mechanisms, like α-synuclein processing problems, mitochondrial dysfunction, oxidative stress, calcium imbalance, axonal transport issues, and neuroinflammation [1].

Among the non-motor symptoms of PD is Parkinson's disease psychosis (PDP), characterized by hallucinations [14]. These encompass a range of sensory experiences, including visual, auditory, olfactory, tactile, and gustatory phenomena [15,16]. To meet diagnostic criteria, hallucinations should occur after the onset of PD and persist for at least one month, while other potential causes must be ruled out [17]. Visual hallucinations (vHs) and illusions are commonly encountered forms. The prevalence rates of vHs in PD vary depending on the study design and population. In clinic-based samples, the prevalence ranges from 22% to 38%, while community-based samples have lower figures of 16% to 23% [15]. Considering "minor forms" of hallucinations, such as passage hallucination and sense of presence, the prevalence increases up to 75% [18,19]. The prevalence of vHs in PD patients with associated dementia exceeds 50% [15]. Longitudinal studies indicate that the point prevalence of vHs increases over time, reaching 74% in a 20-year follow-up period [20–22]. Auditory hallucinations prevalence data is also diverse; some studies reported ranges from 22% to 48% [23]. However, a more recent analysis identified a prevalence of 8.9% for auditory hallucinations and 28.2% for vHs [24]. Olfactory hallucinations are less studied but can occur alongside vHs [25]. Tactile hallucinations involving sensations of insects or small animals are also reported, albeit less frequently [26]. Gustatory hallucinations in PD have been reported in a few case reports [27]. Overall, hallucinations in PD have significant psychosocial effects and have been a major factor contributing to the placement of patients in nursing homes [1,23,28].

The management of PDP is challenging due to the lack of prospective studies examining its long-term benefits and concerns about the increased risk of morbidity and mortality associated with antipsychotic use. Because of this, treatment for hallucinations is typically reserved until symptoms become bothersome or pose a safety concern [16]. The in-

troduction of atypical antipsychotics (AAPs), with the discovery of Clozapine, has revolutionized the treatment of psychotic patients. AAPs not only reduce hospitalization rates and symptom severity but also enhance safety, socialization, and rehabilitation [29,30]. Unlike typical antipsychotics, AAPs have a broader mechanism of action, targeting not only dopamine dopamine type 2 (D2) receptors but also other receptor systems involved in regulating neurotransmitters, such as serotonin type 2A (5-HT2A) serotonin receptors (Fig. 1) [30]. Antipsychotic options for hallucinations in PD that may be considered include Clozapine, Pimavanserin, and quetiapine, as they do not significantly worsen motor symptoms [16,31]. However, each of them has different safety and efficacy concerns.

This review aims to thoroughly analyze and compare the commonly used antipsychotic treatment options in PDP patients presenting hallucinations, focusing on evaluating their efficacy and safety based on available evidence.

2. Antipsychotics for Treating Hallucinations in PD

2.1 Commonly Used Antipsychotics in PD

The management of PDP requires careful consideration due to the potential risks associated with available treatment options. Hallucinations in PD can be attributed to disease progression or medications used to treat motor dysfunction [14]. Managing these symptoms is challenging; the first option is reducing PD medications, but it may worsen motor function, necessitating alternative treatment strategies [32]. AAPs have revolutionized the treatment of psychotic patients, offering improved outcomes compared to typical antipsychotics [33]. AAPs exhibit a weak antagonistic effect on dopamine D2 receptors while targeting other receptor systems involved in regulating dopamine and other neurotransmitters [30]. This broader mechanism of action reduces side effects like Parkinsonism and hyperprolactinemia associated with strong D2 receptor blockade [30,34]. The approved medications for PDP in the United States and European Union are Pimavanserin and Clozapine, respectively, while quetiapine is commonly used off-label [35]. Other AAPs, such as risperidone, olanzapine, aripiprazole, ziprasidone, and lurasidone, worsen motor symptoms and should be avoided in PDP patients [33,36–41].

2.2 Efficacy of Antipsychotics in Reducing Hallucinations

Effective treatment options for hallucinations are crucial in managing PDP. As mentioned, AAPs such as Pimavanserin and Clozapine have effectively controlled hallucinations and delusions associated with PDP. Their mechanisms of action, which involve modulation of dopamine and serotonin receptors, contribute to their therapeutic effectiveness and reduced side effects compared to other atypical and typical antipsychotics [30]. Clozapine, despite the risk of agranulocytosis, has shown effectiveness in clinical trials [14,42–44]. Pimavanserin has shown effectiveness and exhibits long-term safety [44–47]. On the other hand, quetiapine, although commonly used, lacks strong evidence supporting its efficacy in PDP patients [48–51].

2.3 Safety Concerns with Antipsychotics in PD

Treating hallucinations presents considerable difficulties when it comes to the use of antipsychotic medications, primarily due to safety concerns and potential adverse effects, especially in older patients. Even though AAPs are considered safer than typical antipsychotics, they can still cause extrapyramidal symptoms [52,53]. Also, safety concerns with antipsychotics extend beyond their primary pharmacological targets. AAPs can antagonize various off-target receptors, including histaminergic, adrenergic, and cholinergic receptors, leading to adverse effects in PD patients with compromised brain circuitry [35]. Histaminergic blockade, primarily associated with Clozapine and quetiapine, commonly results in somnolence [35]. Blocking adrenergic receptors, as observed with Clozapine and quetiapine, can cause orthostatic hypotension [35,54]. Cholinergic receptor blockade, prevalent with Clozapine and quetiapine, can increase nonmotor symptoms such as constipation, excessive saliva production (sialorrhea), and cognitive impairment [35]. Moreover, the risk of agranulocytosis (severe neutropenia) associated with Clozapine limits its widespread use [53]. Pimavanserin lacks activity in histaminergic, adrenergic, and cholinergic receptors, avoiding these side effects [55]. Nevertheless, like other AAPs, Pimavanserin can prolong the corrected QT (QTc) interval and is contraindicated in patients with known QT prolongation or when used with other drugs that prolong the QT interval [53]. Furthermore, antipsychotics in PDP have been associated with a higher mortality risk [56]. A systematic review revealed a 1.5-fold increase in all-cause mortality with antipsychotic use, particularly in PD patients and those over 65 [57]. Because of that, caution is advised when considering their administration to PD patients,

3. Clozapine in PD

3.1 Mechanism of Action of Clozapine

In recent years, Clozapine has received considerable attention in treating PD owing to its prospective therapeutic benefits [58]. Despite the extensive research conducted thus far, the precise mechanisms underlying the therapeutic action of Clozapine in PD remain incompletely elucidated [58]. Clozapine, an AAP, may reduce levodopa-induced dyskinesia (LIDs) and improve motor symptoms in PD patients [59]. It modulates neurotransmitter systems to treat several conditions. Originally licensed to treat schizophrenia, Clozapine has drawn interest for its ability to treat motor symptoms, psychosis, and cognitive deficits in PD. While its actual mechanism of action is unknown [60], numerous possibilities have been presented to explain its therapeutic benefits.

Table 1. Comprehensive analysis of the included studies, outlining their respective characteristics and summarizing the outcomes of treatment with Clozapine.

CLOZAPINE				
Author	Year	No. of Studies	Outcome	Study design
Ellis T, *et al.* [38]	2000	10	Effective	Clinical trial
Pollak P, *et al.* [54]	2004	60	Effective	Clinical trial
Factor SA, *et al.* [67]	2001	53	Effective	Clinical trial
Merims D, *et al.* [68]	2006	27	Effective	Clinical trial
Pintor L, *et al.* [69]	2012	16	Effective	Clinical trial
Mentzel TQ, *et al.* [70]	2018	16	Effective	Meta-Analysis
Durif F, *et al.* [71]	2004	50	Effective	Clinical trial
Yaw TK, *et al.* [72]	2015	1	Effective	Case Report

The table provides information on whether the use of Clozapine was determined to be effective, ineffective, or showed no significant difference when compared to a placebo.

3.1.1 Dopaminergic Modulation

Dopamine and other neurotransmitter systems are modulated by Clozapine. Clozapine may affect dopamine receptor expression and signaling in PD, although its specific mechanism of action is uncertain [60]. Clozapine reduces dopamine release inhibition by antagonistically binding to dopamine D2 receptors [61]. It also enhances basal ganglia dopaminergic transmission as a partial agonist at dopamine D1 receptors [61]. Levodopa-induced dyskinesia and motor symptoms may be reduced by this dual action [59]. Dopamine D4 receptors are extensively expressed in the prefrontal cortex and limbic regions, and Clozapine inhibits them [62]. Glutamate and γ-aminobutyric acid (GABA) release may decrease and rise, improving motor symptoms. Clozapine may also improve cognitive performance and reduce psychosis in PD patients due to its affinity for the D4 receptor [62].

3.1.2 Serotonin Receptor Modulation

Clozapine exhibits a notable binding affinity towards serotonin 5-HT2A receptors and functions as an antagonist [63]. The amelioration of motor symptoms in PD may be attributed to the modulation of 5-HT2A receptors [63]. Additionally, the enhancement of cognitive functions and reduction of depression and anxiety, commonly observed in PD, may be facilitated through interactions with 5-HT6 and 5-HT7 receptors [64].

3.1.3 Glutamate Modulation

PD pathogenesis may include aberrant glutamatergic signaling. N-methyl-D-aspartate (NMDA) receptor inhibition by Clozapine affects glutamatergic transmission [65]. Excitotoxicity, neuroinflammation, and dopaminergic neuron degeneration may be reduced by this regulation. Clozapine may potentially treat PD by activating the glutamate NMDA receptor [65]. Moreover, Clozapine increases the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which may improve synaptic plasticity and glutamatergic transmission in PD.

3.1.4 Anti-inflammatory and Neuroprotective Effects

Clozapine reduces pro-inflammatory cytokine levels, potentially by acting on brain immune cells called microglia [66]. Microglia activation contributes to PD's inflammatory response. This indicates that it may protect neurons in PD. By increasing neurogenesis, neuronal survival, and apoptotic pathways, it may decrease PD degeneration.

3.2 Clinical Trials and Effectiveness of Clozapine in PD

Numerous clinical trials have investigated the potential application of Clozapine in PD, specifically to manage psychosis (Table 1, Ref. [38,54,67–72]). Psychosis is a prevalent non-motor manifestation in advanced PD linked to augmented caregiver burden and functional deterioration [73]. Numerous randomized controlled trials 15 (RCTs) have provided evidence for the effectiveness of Clozapine in mitigating psychosis in PD, which is frequently unresponsive to alternative antipsychotic medications [38,54,67–69]. The aforementioned studies have consistently demonstrated noteworthy enhancements in scores related to hallucinations and delusions in comparison to placebo or alternative antipsychotic medications [54,67–69]. The effectiveness of Clozapine in managing psychotic symptoms in PD is attributed to its distinct pharmacological profile, which involves potent antagonism of serotonin 5-HT2A receptors [63].

Clozapine has had variable effects on motor symptoms in PD clinical studies. Motor symptoms, including dyskinesias and Parkinsonian motor signs, worsened in certain trials. A meta-analysis of Clinical studies on Clozapine Monotherapy as a Treatment for Antipsychotic-Induced Tardive Dyskinesia revealed worsening of dyskinesia in patients with minimal to mild Tardive Dyskinesia [70]. However, it was recommended that Clozapine should be considered for patients with significant discomfort following dyskinesia. Clinical studies have shown that Clozapine improves motor symptoms such as tremors, stiffness, and bradykinesia [67,71]. This impact may be caused by modifying dopamine receptors, enhancing cholinergic activity, and decreasing glutamate excitotoxicity [61,63,65]. The data demonstrates that although Clozapine may aggravate motor symptoms in certain people, its effect on motor symptoms varies and needs close monitoring. More well-designed RCTs are required to determine Clozapine's appropriate dose, duration, and long-term effects on PD motor symptoms. Clozapine may interact with dopaminergic PD medicines and affect motor symptoms.

The effect of Clozapine on the overall quality of life among individuals with PD is a subject of continued interest [72]. Enhanced quality of life in patients with PD has been

linked to improvement in non-motor symptoms, specifically psychosis [72]. The concept of quality of life encompasses multiple dimensions, such as physical, psychological, and social well-being. While specific research has documented enhancements in quality-of-life metrics, alternative studies have suggested restricted advantages. The need for cautious deliberation arises from the possibility of a trade-off between enhancements in psychiatric symptoms and the potential for motor deterioration.

3.3 Adverse Effects of Clozapine

Although Clozapine is an effective treatment option, it is associated with several adverse effects that must be monitored to ensure patient safety and well-being. Agranulocytosis, a condition that significantly reduces white blood cell count, is one of the most severe adverse effects of Clozapine [74]. This increases the risk of infection and may be lethal. Blood cell counts, especially neutrophils, must be monitored to identify and prevent agranulocytosis. Leukopenia, neutropenia, and thrombocytopenia are other hematological side effects [74]. Cardiovascular adverse effects of Clozapine include Orthostatic hypotension and myocarditis [75]. This may cause irregular heartbeat, chest discomfort, and shortness of breath. In the first few months of clozapine therapy, patients should be monitored for myocarditis symptoms.

Weight gain, hyperglycemia, dyslipidemia, and insulin resistance are metabolic adverse effects of Clozapine [76]. These impacts may raise the risk of cardiovascular disease and other health issues [75]. To identify and control these side effects, weight, blood sugar, and cholesterol levels must be monitored regularly [76]. Clozapine usage may cause drowsiness, hypersalivation, and seizures [77]. Seizures need cautious observation and, in certain situations, the addition of antiepileptic therapy [77]. Clozapine may cause tardive dyskinesia; however, it has a reduced risk of extrapyramidal symptoms than other antipsychotics.

The administration of Clozapine has been associated with gastrointestinal complications such as constipation and sialorrhea, characterized by excessive saliva production [77]. The aforementioned effects have the potential to exert an influence on patient compliance and overall well-being. Implementing assessment and management strategies, including dietary and pharmacological interventions aimed at enhancing gastrointestinal motility, holds significant importance. Clozapine has been linked to various adverse outcomes, such as urinary incontinence, respiratory complications, and ocular adverse effects [78–80].

4. Quetiapine in PD

Quetiapine, a dibenzothiazepine derivative, is a pharmacologic agent with demonstrated efficacy in treating various psychiatric disorders, including bipolar disorder, schizophrenia, and depression [81]. Its precise mode of action is still unspecified. However, it is thought to work as an antagonist for the dopamine D1 and D2 receptors and the serotonin 5-HT2 receptor [82]. It also demonstrates an affinity for muscarinic M1, M3, M5, histamine H1, and 1-adrenergic receptors [83]. The anticholinergic effects of quetiapine may be attributed to its metabolite, norquetiapine, which has an affinity for several muscarinic receptors [83]. Quetiapine's antidepressant effect is postulated to result from antagonism of the 5-HT2 and α2 receptors, as well as noradrenaline transporter inhibition by norquetiapine [84]. Norquetiapine, the active metabolite of quetiapine, has been shown to bind to several receptors, including the serotonergic 5-HT1E, 5-HT2A, 5-HT2B, and 5-HT7 receptors, as well as the muscarinic M1, M3, and M5 receptors and the 1-adrenergic receptors [85]. This broad range of receptor affinity may contribute to the multifaceted pharmacologic effects of quetiapine. Although quetiapine is typically prescribed to treat schizophrenia and bipolar disorder, it is occasionally used off-label to treat psychosis in Parkinson's patients [86].

Treating psychosis in PD patients presents significant challenges. While quetiapine has been given a level C rating for probable efficacy in treating PD psychosis by the American Academy of Neurology's evidence-based practice criteria, there is still insufficient data to conclude its effectiveness [87]. A recent study by the US Department of Veterans Affairs reported an increased risk of mortality associated with quetiapine and other antipsychotic use in Parkinsonism patients, with a hazard ratio of 2.16 for quetiapine compared to non-use [88]. These findings highlight the need for caution when prescribing quetiapine to PD patients with psychosis. Given these concerns, Pimavanserin, a newly authorized molecular entity, is clinically useful for treating PD psychosis. Unlike traditional antipsychotics, Pimavanserin does not block dopamine receptors and is less likely to worsen motor symptoms [89].

In PD, vHs can be a distressing and challenging symptom to manage. Two randomized, double-anonymized, placebo-controlled studies were conducted to probe the efficacy of quetiapine in treating vHs in PD patients. Fernandez *et al*. [48] found that quetiapine effectively reduced the severity of hallucinations compared to a placebo, although the study had a high dropout rate due to inefficacy and drowsiness. Meanwhile, Kurlan *et al*. [90] did not find substantial discrepancies in the effectiveness or adverse events between the quetiapine and placebo groups in treating psychosis and agitation.

It should be noted that although the American Academy of Neurology has given quetiapine a level C rating for probable efficacy in treating PD psychosis, other organizations have stated that more data is needed to draw a firm conclusion on its effectiveness. Additionally, a recent study has reported an increased risk of mortality associated with quetiapine and other antipsychotic use in Parkinsonism patients, highlighting the importance of cautious prescribing practices [53]. Thus, while quetiapine may be a poten-

Table 2. Comprehensive analysis of the included studies, outlining their respective characteristics and summarizing the outcomes of treatment with quetiapine.

QUETIAPINE				
Author	Year	No. of Studies	Outcome	Study design
Miyasaki J.M, *et al*. [87]	2006	4	Effective	Systematic review
Fernandez H.H, *et al*. [48]	2009	16	Effective	Clinical trial
Kurlan R, *et al*. [90]	2007	40	No significant difference	Clinical trial
Ondo W.G, *et al*. [49]	2005	31	Ineffective	Clinical trial
Rabey J.M, *et al*. [50]	2007	58	No significant difference	Clinical trial
Shotbolt P, *et al*. [51]	2009	24	No significant difference	Clinical trial
Merims D, *et al*. [68]	2006	27	Effective	Clinical trial
Chen J.J, *et al*. [91]	2019	7	Ineffective	Systematic review

The table provides information on whether the use of quetiapine was determined to be effective, ineffective, or showed no significant difference when compared to a placebo.

tial treatment option for vHs in PD, its benefits and risks should be carefully weighed by healthcare professionals on a case-by-case basis.

Ondo *et al*. [49] and Rabey *et al*. [50] found no substantial distinctions in outcomes between the quetiapine and placebo groups for hallucinations and drug-induced psychosis (Table 2, Ref. [48–51,68,87,90,91]), with somnolence being the most common adverse event reported and dropout rates being high. Shotbolt *et al*. [51] also conducted an RCT and reported no considerable disparities in outcomes between the quetiapine and placebo groups. In a comparative study, Merims *et al*. [68] found that both quetiapine and Clozapine reduced hallucination frequency, but only Clozapine significantly reduced delusion frequency. However, both groups had high dropout rates due to low efficacy and adverse effects. Chen *et al*.'s systematic review [91] found that quetiapine's efficacy in treating psychosis in Parkinsonism is not superior to placebo or Clozapine, and RCT completion rates among quetiapine-treated patients are low.

Despite having a lower risk of extrapyramidal symptoms drawn a parallel between other AAPs, quetiapine has been linked to a higher death rate in older patients with dementia-related psychosis [81]. Its D2 receptor blockage can cause neuroleptic malignant syndrome, while its use in people with major depressive disorder may raise the risk of suicidal thoughts and actions. The most commonly reported side effects of quetiapine include somnolence, orthostatic hypotension, and dizziness, which are caused by antagonistic interactions with the H1 receptor and the alpha-1 receptor [81].

One of the most significant risks of quetiapine use is a high mortality risk in aged individuals with dementia-related psychosis [92]. This risk is shared with other AAPs, and caution should be exercised when prescribing these medications to this patient population. Another risk associated with quetiapine use is the potential for prolongation of the QT interval. This risk is heightened in patients with preexisting cardiac arrhythmia, hypokalemia, or hypomagnesemia, and clinicians should carefully monitor these patients for signs of cardiac dysfunction. Metabolic panels should be assessed before initiating quetiapine treatment to identify patients at increased risk of adverse events. Additionally, careful consideration should be given to medications that may prolong the QT interval or interact with quetiapine, such as fluoxetine or ciprofloxacin.

5. Pimavanserin in PD

Pimavanserin, a selective serotonergic 5-HT2a receptor targeting drug, is a promising medication for treating PD psychosis. The drug's ability to specifically target the 5-HT2a receptor has been demonstrated in studies, showing higher affinity than other receptors such as 5-HT2b, 5-HT2c, and D3 [93]. Furthermore, Pimavanserin possesses a unique D2-blocking activity, setting it apart from other antipsychotics like Clozapine and quetiapine.

In 2016, the US Food and Drug Administration (FDA) authorized Pimavanserin for treating hallucinations and delusions in PD based on a randomized placebo-controlled trial involving 185 patients [94]. However, the FDA's approval for Pimavanserin raised concerns as two positive trials are typically necessary for drug approval. The boxed warning for Pimavanserin highlights the increased risk of mortality associated with the drug, which is also seen with other antipsychotics. In addition, the warning cautions against QT interval prolongation, a property shared by many psychotropic drugs and other agents, which can lead to fatal cardiac arrhythmias. Given these potential risks, caution should be exercised when prescribing Pimavanserin.

Mosholder *et al*. [95] investigated the use of Pimavanserin in Medicare beneficiaries with PDP. They found that the drug had a lower mortality rate than other atypical antipsychotics, particularly quetiapine, during the initial six-month follow-up period. However, the study found no significant benefit for short-term or long-term use of Pimavanserin in nursing home patients [95].

A clinical trial evaluated the efficacy and safety of Pimavanserin over six weeks in patients with PDP [47]. The study found a statistically significant reduction in Scale for the Assessment of Positive Symptoms-PD (SAPS-PD) scores of participants who received Pimavanserin compared to those who received the placebo. Patients well-tolerated Pimavanserin, but peripheral edema and confusion were reported as adverse events. Nonetheless, adverse effects leading to treatment discontinuation were rare.

The durability of Pimavanserin's response was investigated in a study involving 424 patients who had completed one of three double-anonymized, placebo-controlled core studies [96]. The subsequent open-label extension study administered pimavanserin 34 mg once daily to all patients for an additional four weeks. The study's results demonstrated that patients who had previously taken Pimavanserin 34 mg during the core studies showed sustained efficacy during the subsequent four-week open-label extension SAPS-PD assessment. After four weeks of taking open-label Pimavanserin, individuals who had previously taken a placebo also improved. The findings provide further evidence of Pimavanserin's effectiveness in treating PDP.

A meta-analysis examined the efficacy of 5HT2A antagonists and inverse agonists, including Pimavanserin, in treating PDP [97]. The analysis included four randomized controlled studies that compared Pimavanserin versus a placebo. The findings showed that patients who received Pimavanserin had significantly lower Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions (SAPS-H+D), SAPS-H, and SAPS-D scores than those in the placebo group. Discontinuation and adverse event rates were comparable between both groups. Pimavanserin has also been researched in combination with other antipsychotic drugs, and the results are encouraging, showing fewer side effects.

6. Comparison of Antipsychotics in PD

People who suffer from PD often experience psychotic symptoms, leading to adverse health consequences, including higher mortality rates, increased likelihood of being placed in a nursing home, and more stress for caregivers [98]. In 2016, US FDA approved Pimavanserin as the first antipsychotic drug specifically designed to treat PDP [47]. The use of second-generation or atypical Antipsychotics (APs), such as Clozapine, quetiapine, risperidone, olanzapine, and aripiprazole, for PDP has nevertheless long been done off-label [99]. Additionally, these drugs have been used to treat adult patients with neurodegenerative illnesses' behavioral or mood problems. Clinical safety recommendations, however, do not support their use for such reasons or in populations of older adults [99].

It is commonly believed that the use of AP in patients with PD could worsen their symptoms of Parkinsonism because of its ability to block dopamine receptors, potentially harming their safety and tolerance towards the treatment [100]. Currently, there is not a clear understanding of the exact process that leads to the decreased occurrence of Parkinsonism observed with atypical APs [100]. Several theories have been proposed to explain why atypical APs may lead to a lower incidence of Parkinsonism compared to typical APs, including the blocking of 5-HT2A receptors, the balance between 5-HT2A and D2 receptor blocking, as well as the speed at which atypical APs bind and unbind to D2 receptors in comparison to typical APs [100]. Aripiprazole, for instance, is believed to have a lower incidence of extrapyramidal side effects (EPS) because it partially antagonists the D2 receptor and the 5-HT2A receptor [101]. On the other hand, Pimavanserin is a specific 5-HT2A inverse agonist that does not have a strong affinity for most of the other receptors that atypical APs typically target [30]. As a result, it is used to treat the psychotic symptoms present in PD without aggravating the motor symptoms.

Typically, second-generation antipsychotics (SGAs) are considered a safer treatment option for individuals with PD, as they tend to exhibit less D2 antagonism than other antipsychotics [7]. However, compared to first-generation antipsychotics (FGAs), they still have a decreased propensity to cause extrapyramidal symptoms [102]. According to retrospective cohort research, 61.4% of PD patients maintained receiving overall treatment within six months after starting antipsychotic medicine, while 38.6% stopped after receiving the first prescription [103]. In contrast to the serotonin receptor-targeting medication pimavanserin, drugs that have established dopamine receptor-blocking effects, such as quetiapine, aripiprazole, risperidone, and olanzapine, were found to have a higher likelihood of leading to the discontinuation of therapy. Increased dopamine-receptor-blocking activity drug use was also linked to the termination of the first antipsychotic therapy. To ensure proper antipsychotic use in this population, the study stresses the need to understand antipsychotic cessation in PD better.

In early reports and subsequent randomized, placebo-controlled trials, Clozapine was the foremost AAP reported to reduce psychotic symptoms in patients with PDP without worsening motor symptoms [104]. According to a meta-analysis, the effectiveness of Clozapine was demonstrated by a significant effect size difference for treating psychotic symptoms against a placebo [44]. Although the empiric use of antidepressants and acetylcholinesterase inhibitors has been suggested for PDP, there is only anecdotal proof of their effectiveness and tolerability. Additionally, decreasing dopaminergic medications for motor symptoms can make psychosis worse and is ineffective in treating it in some cases. A significant decrease in the frequency and severity of hallucinations and delusions in PDP patients was observed without a decline in motor function in a critical six-week clinical trial. This study employed a placebo-controlled, randomized approach and utilized Pimavanserin, an antipsychotic with a unique pharmacological profile as a serotonin 5HT-2a receptor inverse agonist

Table 3. Comparison between Clozapine, quetiapine, and Pimavanserin according to their average effectiveness and adverse effects.

Author	Year	Study Type	No. of Studies	Outcome	AE
Merims D, *et al*. [68]	2006	Rater-blinded, prospective comparison	27	Clozapine and Quetiapine drugs were equally effective	Leukopenia in the clozapine arm
Morgante L, *et al*. [105]	2004	Randomized, open-label, blinded-rater, parallel-group trial	45	No differences were found between Clozapine and quetiapine	-
Horn S, *et al*. [106]	2019	Retrospective cohort study	47 in the quetiapine cohort and 45 in the pimavanserin cohort	Quetiapine was more effective than Pimavanserin	Orthostatic hypertension in the quetiapine cohort
Alipour-Haris G, *et al*. [107]	2023	Retrospective cohort study	844 pimavanserin users and 2505 quetiapine users	No significant difference in effectiveness	Hospitalizations for heart-related issues were higher with Pimavanserin

AE, Adverse Effects.

and antagonist, which does not exhibit dopaminergic antagonism [48]. Additionally, many patients receiving Pimavanserin showed complete remission, and the long-term investigations revealed no unanticipated adverse events or fresh safety concerns. However, when motor symptoms appeared unchanged, data from the four double-blind, randomized clinical studies of quetiapine for PDP have not typically supported using this medication [49–51,68].

The efficacy of quetiapine and Clozapine in treating psychosis and PD was evaluated in two randomized studies by researchers. In one of these studies, conducted by Merims *et al*. [68], the efficacy of quetiapine and Clozapine was compared by analyzing the delusion and hallucination items of the Neuropsychiatric Inventory (NPI) and the Clinician Global Improvement-Change Scale (CGI-C) [105]. Despite decreased hallucination frequency in both treatment groups, only the clozapine group showed a statistically significant difference between the baseline and final assessment. Delusions were statistically significantly less frequent among participants in the clozapine group, while they were more frequent, albeit inconsistently, among those taking quetiapine. Between the two groups, there was a relative change in CGI-C scores. The motor score was absent, but the Unified Parkinson's Disease Rating Scale (UPDRS) total score was given. No treatment group saw an increase in Parkinsonian symptoms as judged by the UPDRS. However, the completion rate of the study was only 59.26%, with lower leukocyte count being the most commonly reported reason for discontinuation in the quetiapine group and a lack of treatment effectiveness being the most frequent reason for discontinuation in the placebo group.

Morgante *et al*. [105] conducted a randomized controlled study to compare the effectiveness of quetiapine and Clozapine in treating psychosis and PD [106]. Seventy-five participants were randomly assigned to either quetiapine or Clozapine. Their hallucinations, suspicion, and anger were assessed using various tools, such as the brief psychiatric rating scale (BPRS), Clinician Global Improvement-Severity Scale, Abnormal Involuntary Movement Scale, and UPDRS. The participants were aware of the medication they received, while the assessors were blinded to the treatment assignments. After treatment, the BPRS, Clinician Global Improvement-Severity Scale, and Abnormal Involuntary Movement Scale scores were higher for both groups than the baseline. Three individuals receiving more than 100 mg of quetiapine daily experienced a moderate deterioration of Parkinsonism, but the overall UPDRS scores remained stable. There was no significant difference in efficacy between quetiapine and Clozapine. Both medications had few adverse effects, and there was no significant statistical difference between them. In the quetiapine group, sedation was the primary reason for dropout, while sedation, dizziness, and severe hypotension caused dropout in the clozapine group. Most participants completed the 12-week study.

In a retrospective cohort study, researchers assessed the effectiveness of quetiapine and Pimavanserin in treating psychosis in patients with PD or dementia with Lewy bodies (DLB) [107]. The study included 92 patients diagnosed with psychosis with no severe mental illness or missing follow-up data. Of those patients, 47 were treated with quetiapine and 45 with Pimavanserin. The researchers used Kaplan-Meier survival analysis to determine the duration until the antipsychotic therapy was discontinued, assuming that the discontinuation rate would be lower in the pimavanserin group. The results indicated that patients in the pimavanserin group were likelier to have DLB and a history of antipsychotic use. The time-to-discontinuation analysis showed that the pimavanserin group had a lower rate of early discontinuation and a higher rate of late discontinuation. There was no significant difference in mortality between the two groups. Quetiapine was more often prescribed for non-primary purposes than Pimavanserin. Considering the efficacy, safety, and tolerability factors, Pima-

vanserin might be a more suitable option for rapidly treating psychosis in PD and DLB patients. At the same time, quetiapine could provide additional secondary benefits in the long run.

In a recent study, the relative safety of Pimavanserin and quetiapine for treating PD psychosis in medicare patients was evaluated concerning the risk of hospitalization and mortality [108]. Eight hundred forty-four new pimavanserin users and 2505 new quetiapine users were enrolled in the trial. The results showed that pimavanserin users had a decreased chance of hospitalization than quetiapine users, but no discernible difference was found between the two groups' mortality rates (Table 3, Ref. [68,105–107]). These findings shed significant light on the safety profile of Pimavanserin and quetiapine in treating PD psychosis in elderly patients.

Additionally, the doses that resulted in dopamine blocking and sedation, as well as the effectiveness of Pimavanserin, Clozapine, and quetiapine for the treatment of PDP in an animal model, were identified. Rats with bilateral substantia nigra lesions underwent increased amphetamine-induced locomotion tests to evaluate the effectiveness of antipsychotic drugs. In rats with unilateral 6-hydroxydopamine lesions, inhibition of apomorphine-induced rotations was used to assess the antidopaminergic activity. Sedation was evaluated by looking at the amount of spontaneous movement. A selective 5-HT2A inverse agonist/antagonist, pimavanserin, may be preferable to quetiapine or Clozapine as a PDP treatment because it has a therapeutic ratio of at least 170. Therefore, Pimavanserin might be a suitable PDP medication because it can reduce psychotic symptoms at levels that do not cause drowsiness or impair motor skills.

7. Discussion of Factors to Consider when Choosing an Antipsychotic for PD

The selection of antipsychotics for individuals with PD demands meticulous consideration of various factors, given the intricate interplay between the neurodegenerative process and psychiatric symptoms. Psychosis, hallucinations, and delusions often manifest alongside PD, necessitating a cautious approach to minimize potential adverse effects of modulating dopamine levels. Prioritizing medications with diminished affinity for dopamine D2 receptors is advised to mitigate the risk of exacerbating motor symptoms already compromised in this patient population [108].

The administration of antipsychotics may give rise to EPS, including Parkinsonism, dystonia, and akathisia. Considering the inherent susceptibility of PD patients to motor complications, careful deliberation is necessary while choosing antipsychotics with a favorable side effect profile, thereby minimizing the probability of inducing or worsening motor symptoms. Moreover, specific antipsychotics can potentially prolong the QT interval, thereby elevating the risk of life-threatening cardiac arrhythmias [109]. Given the presence of cardiac autonomic dysfunction in PD, a comprehensive assessment of the cardiac safety profile of antipsychotics assumes paramount significance [110]. It is recommended to prioritize agents with a lower inclination toward QT interval prolongation to ensure the well-being of patients [111].

PD's management, which often entails intricate medication regimens, a comprehensive evaluation of potential drug interactions between antipsychotics and other medications is pivotal. Particular attention should be devoted to the concurrent use of dopaminergic agents to circumvent compromised efficacy or adversities stemming from drug interactions [108]. When selecting antipsychotics, individual patient characteristics exert considerable influence. Factors such as age, overall health, comorbidities, and previous medication responses should be thoughtfully considered [112]. Elderly patients may exhibit heightened vulnerability to side effects, necessitating personalized approaches, while patients with specific comorbidities may require alternative antipsychotic choices or closer monitoring.

8. Conclusions

Due to the potential risks associated with available treatments, it is essential to manage hallucinations related to PD carefully. This review analyzed the effectiveness of AAPs such as Pimavanserin and Clozapine in controlling hallucinations. However, there is limited evidence supporting the effectiveness of quetiapine in this regard. AAPs function through broad mechanisms of action involving dopamine and serotonin receptors, leading to improved outcomes and fewer side effects. Conversely, other antipsychotics like risperidone, olanzapine, aripiprazole, ziprasidone, and lurasidone can exacerbate motor symptoms and are generally not recommended.

Although AAPs have revolutionized the treatment of hallucinations related to PD, they may give rise to extrapyramidal symptoms, somnolence, hypotension, constipation, and cognitive impairment. Clozapine poses a risk of agranulocytosis, while Pimavanserin may prolong the QTc interval. It is crucial to acknowledge that the use of antipsychotics in PD is associated with increased mortality, necessitating caution. While AAPs have demonstrated significant improvements compared to typical antipsychotics, further prospective studies are recommended to evaluate their long-term benefits and risks. These studies provide evidence that could help clinicians select and prescribe antipsychotics for hallucinations associated with PD, thereby enhancing the patients' care.

Abbreviations

PD, Parkinson's disease; PDP, Parkinson's disease psychosis; vHs, Visual hallucinations; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; RCTs, Random-

ized controlled trials; 5-HT2A, serotonin type 2A; D2, Dopamine type 2; EPS, Extrapyramidal side effects; SGAs, second-generation antipsychotics; FGAs, first-generation antipsychotics; NPI, Neuropsychiatric Inventory; CGI-C, Clinician Global Improvement-Change Scale; DLB, Dementia with Lewy bodies; UPDRS, Unified Parkinson's disease rating scale.

Author Contributions

Conceptualization of Ideas: GMA, AA, TA-R, AAW. Sort out references: TA-R, AAW, FTA, NIM, AA, MNA, AP, GMA, LL. Create tables and figure: REH-C, NA, MK, OE, LL. Supervision: AA, GMA. Visualization: TA-R, AAW, FTA, LL. Writing Original Draft: TA-R, REH-C, NA, MK, AAW, FTA, OE, LL, NIM, AA, MNA, AP, GMA. Writing – review & editing: TA-R, REH-C, NA, MK, AAW, FTA, OE, LL, NIM, AA, MNA, AP, GMA. Funding acquisition: MNA. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Athanasios Alexiou and Ghulam Md Ashraf are serving as the Guest editors of this journal. We declare that Athanasios Alexiou and Ghulam Md Ashraf had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel. Additionally Athanasios Alexiou is employed by AFNP Med Austria but he declares no conflict of interest with this work.

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