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An update expert opinion on management and research strategies in Parkinson's disease psychosis

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Abstract

Introduction—Psychosis, a frequent complication in Parkinson's disease (PD), contributes significantly to morbidity, mortality, nursing home placement, and quality of life. Medication side effects, issues of trial design, and negative outcomes have limited clinical advances of new treatments for PD psychosis. Evidence-based medicine maintains clozapine as the most effective antipsychotic in PD without motor worsening, despite risk of agranulocytosis. Safe, effective treatments that improve psychosis without exacerbating parkinsonism are greatly needed.

Areas covered—This article reviews: 1) the phenomenology of PD psychosis, 2) pharmacological rationale for antipsychotics in PD, 3) clinical trials of antipsychotics in PD, 4) novel research strategies such as neuroimaging, genetics, and animal models, and 5) associated challenges in studying and treating PD psychosis. Preparation of this review included an extensive literature search using PubMed.

Expert Opinion—Management of PD psychosis is complex. Challenges pertaining to study design, rating scales, subject recruitment, and completion have limited PD psychosis treatment trials. Novel research strategies focus on non-dopaminergic systems and incorporate neuroimaging, genetic associations, and animal models. These strategies also have challenges but have the potential to enhance our understanding of PD psychosis and advance the development of agents that can ultimately be tested in well-designed, randomized, controlled trials.

Keywords

Antipsychotic; cholinesterase inhibitors; delusions; dopamine; hallucinations; neuroleptic; Parkinson's disease; psychosis

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the well-known motor hallmarks of rest tremor, bradykinesia, rigidity, and gait impairment but

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also non-motor features related to the disease and its treatment including psychosis, dementia, sleep disturbances, autonomic dysfunction, and sensory abnormalities. Many of these non-motor symptoms affect both patient and caregiver and to date, lack optimal treatments¹. PD psychosis is frequent, affecting about one-third of patients treated with chronic dopaminergic therapy,² and is often associated with increased morbidity, mortality³, nursing home placement⁴, caregiver stress⁵, and worsened quality of life⁶. Treatment of PD psychosis poses special challenges as antipsychotic (or neuroleptic) medications may worsen motor symptoms of PD by virtue of their dopamine-blocking pharmacological properties.

2. Phenomenology and definitions of PD psychosis

The clinical spectrum of PD psychosis ranges from mild illusions to formed hallucinations to frank delusions^{7–11} (Table 1). On the milder end of the spectrum are illusions, passage hallucinations, and presence hallucinations, sometimes grouped together as “minor” hallucinations. Most hallucinations in PD are visual, though they can occur in all sensory modalities. Hallucinations in PD tend to be non-threatening, consist of familiar humans or animals, and occur with a clear sensorium. They are typically brief (seconds to minutes) and may increase at night or in instances of compromised vision. Some hallucinations are simple and “benign,” but others can be elaborate or frightening. Hallucinations may occur alongside delusions, particularly in settings of delirium or advanced disease. Visual hallucinations are more common in PD, whereas auditory hallucinations are more common in schizophrenia. Hallucinations in non-visual modalities also occur in PD but are generally accompanied by visual hallucinations⁷. Auditory hallucinations in PD are often vague, and in contrast to schizophrenia, not usually threatening. Less frequent in PD are tactile or olfactory hallucinations^{12, 13}.

Delusions are less common than hallucinations in PD psychosis and affect about 5–10% of drug-treated PD patients². In PD, delusions often consist of well-systematized ideas focused on a single theme. While persecutory delusions are common in both schizophrenia and PD, delusions in schizophrenia more frequently encompass themes of grandiosity, reference, and bizarre beliefs¹⁴. Misidentification syndromes, a specific type of delusion, can create challenging situations since the patient’s behavioral changes often are directed toward family members. Capgras¹⁵ and Fregoli syndromes¹⁶ have been reported in PD, especially with dementia.

As definitions of PD psychosis have differed over the years, a National Institutes of Health NINDS-NIMH sponsored working group recently reviewed and proposed diagnostic criteria for PD psychosis¹⁷. According to these criteria, the diagnosis of PD psychosis requires at least one of the following: illusions, false sense of presence, hallucinations, or delusions. These features should occur after the onset of PD and be present for at least one month, either as recurrent or continuous symptoms; other medical, neurological, or psychiatric causes and acute delirium should be excluded. Associated features for assessment include the presence or absence of insight, dementia, or treatment for PD. Not surprisingly, the prevalence of PD psychosis depends, in part, on operational definitions used. When NINDS-NIMH criteria were applied to a cross-sectional PD cohort, the prevalence of PD psychosis was 60%, compared to 43% when defined by only the presence of hallucinations and/or delusions¹⁸. Minor psychotic phenomena and non-visual hallucinations, features not often included in older epidemiological studies, represent an important part of the PD psychosis spectrum.

3. Pharmacological rationale for PD psychosis treatments

The pathophysiology of PD psychosis and pharmacological rationale for treatment are linked to three main neurotransmitter systems: dopamine, acetylcholine, and serotonin. These neurotransmitter systems underscore interactions among psychosis, cognition, sleep, and mood. While dopaminergic medications can induce PD psychosis by stimulating or inducing hypersensitivity of mesocorticolimbic dopamine receptors and are almost always being used at the time PD patients develop hallucinations, the pathophysiology of PD psychosis extends beyond the dopaminergic system. This section explores these three neurotransmitter systems and their relationship to PD psychosis management.

3.1 Dopaminergic system

The frequent occurrence of PD psychosis in association with chronic dopaminergic treatment prompted the hypothesis that psychosis represents a medication-induced syndrome due to overstimulation of mesolimbic D3 and D4 dopaminergic receptors. A proposed pharmacological kindling model suggested enhanced sensitivity of dopaminergic receptors after chronic treatment¹⁹. In this model, dopamine is no longer adequately stored at the presynaptic level, leading to overflow onto supersensitive receptors and thus, clinically evident psychotic features. Moreover, all dopaminergic drug classes (i.e., levodopa, dopamine agonists, monoamine oxidase (MAO) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors added to levodopa) are associated with psychosis induction or exacerbation.²⁰

Several observations, however, challenge the hypothesis of PD psychosis as simply dopaminergic intoxication. The daily levodopa dose may not differ between PD hallucinators and non-hallucinators^{7,9}, and high-dose intravenous levodopa does not provoke hallucinations in predisposed patients²¹. In a study of over 400 PD patients, the time to onset of hallucinations was only weakly linked with use of other dopaminergic drugs, specifically selegiline or dopamine agonists²². Furthermore, intrinsic factors of PD such as older age, advanced disease, cognitive decline, depression, visual impairment, and perhaps genetic susceptibility are important contributors to PD-related psychosis.

Despite these data, reducing dopamine by decreasing dopaminergic drug doses or using antipsychotics with dopamine blocking actions remains a practical management tool of PD psychosis. A “drug holiday” from dopaminergic drugs was one of the earliest therapeutic interventions for psychosis²³; although “drug holidays” are seldom practiced today, reduction or elimination of dopaminergic PD medications is commonly done. Current treatment of PD psychosis usually involves the use of antipsychotic medications that carry some degree of dopamine receptor site antagonism. Use of antipsychotic agents necessitates monitoring patients for worsened motor function as a side effect from dopamine blockade. Atypical antipsychotic agents such as clozapine have greater affinity to 5-HT₂ receptors than to mesolimbic D3 and D4 receptors, which accounts for their efficacy in treating PD psychosis without exacerbating parkinsonism.

2.2 Cholinergic system

Compensatory overactivity of acetylcholine function occurring in the dopaminergically-deprived striatum of PD suggests an imbalance of cholinergic and dopaminergic systems. This imbalance has been advocated as an explanation for psychosis because hallucinations can be triggered by anticholinergic as well as dopaminergic treatments²⁰. Anticholinergic-induced hallucinations, however, frequently occur in the context of delirium, whereas PD-related hallucinations may occur with a clear sensorium²⁴. A revival of the cholinergic-dopaminergic theory has been prompted by quantitative post-mortem neurochemical findings

in PD dementia (PDD) and dementia with Lewy bodies (DLB), two disorders frequently associated with hallucinations. In PDD and DLB, profound neocortical loss of cholinergic neurons and decreased choline acetyltransferase activity occur; these changes are more pronounced in PDD and DLB than in PD without dementia^{25, 26}. Marked frontal cortical denervation results from disruption of the ascending cholinergic transmitter system and degeneration of central cholinergic structures such as the nucleus basalis of Meynert and pedunculopontine nucleus, which are involved in attention, cognition, and REM sleep^{27, 28}. Cortical acetylcholine normally enhances the neuronal signal to noise ratio; when levels are reduced, irrelevant intrinsic and sensory information, that is normally processed in parallel at a subconscious level, may enter conscious awareness as hallucinations²⁷.

The cholinergic system also plays a role in pharmacologic strategies for PD psychosis. Cessation of anticholinergic medication reduces hallucinations, and these medications are typically among the first to be discontinued in the setting of PD psychosis. Clinicians should be mindful of non-PD medications such as bladder agents that also have anticholinergic properties. Several reports suggest that cholinesterase inhibitors improve neuropsychiatric features associated with PDD and DLB^{29, 30}. Subanalyses of a double-blind, placebo-controlled study in PDD³¹ suggested that rivastigmine, a dual butyrylcholinesterase and acetylcholinesterase inhibitor, was mildly more effective in selected cognitive and behavioral measures in PD hallucinators compared to non-hallucinators³⁰. Cholinesterase inhibitors may provide a treatment option for chronic psychosis in demented PD patients but are less likely useful in acute psychotic or emergency settings. At present, evidence for treating psychosis in non-demented PD is lacking.

2.3 Serotonergic system

The pharmacology of the serotonergic (5HT) system is particularly complex, and several lines of evidence link the serotonergic system to PD psychosis, mood disorders, and sleep disturbances. Early autopsy studies showed that PD patients with psychosis had lower cerebral serotonin levels than those without³². Dopaminergic drug treatment reduces already low cerebral serotonin levels, with reports of dopamine-serotonin ratios reduced to about 20% of normal values³³. Dopamine administration also may lead to hyperstimulation of 5-HT_{2A} receptors, which affects glutamatergic-modulated activity of dopamine neurons in the ventral tegmental area; this may lead to excitation of the limbic system and inhibition of the prefrontal cortex, areas important in cognitive and behavioral processes. Recent post-mortem studies demonstrate abnormalities in brain 5-HT_{2A} receptors; increased [³H]-ketanserin binding was found in the inferolateral temporal cortex of PD patients who had visual hallucinations, compared to those who did not³⁴. In addition, PD hallucinators demonstrated increased 5-HT_{2A} receptor binding in multiple brain regions including the ventral visual pathway, dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula on a positron emission tomography study using a selective 5-HT_{2A} receptor ligand, [¹⁸F]-setoperone. These findings suggest alterations in pathways mediating visual and cognitive processing and a role for 5-HT_{2A} receptor pharmacology in PD hallucinations³⁵.

In PD, there is extensive loss of serotonergic raphe neurons and reduction of serotonergic projections to the frontal cortex, temporal cortex, and putamen. These neurochemical and neuroanatomical changes suggest shared substrates for hallucinations, sleep disturbances, and mood disorders. Hallucinations in PD patients have been hypothesized to occur as daytime REM intrusions, and hallucinating PD patients have altered sleep-wake patterns^{36, 37}. In cats, lesioning raphe neurons or depleting serotonin induces disinhibition of phasic REM processes during sleep and behaviors suggestive of hallucinations³⁸. The frequent association of depression and hallucinations also may be consistent with hypotheses of serotonin dysregulation. Therapeutically, serotonin augmentation in PD patients with hallucinations would seem to be a logical treatment approach. Early open-label trials with

tryptophan yielded conflicting results³⁹. Several case reports and series suggest beneficial effects of serotonin or serotonin-norepinephrine reuptake inhibitor antidepressants in PD psychosis, particularly those patients with co-existing mood disorders^{40,41}, though further study is needed.

Other evidence for serotonergic involvement comes from the development of antipsychotics such as clozapine, quetiapine, and pimavanserin that demonstrate greater 5-HT₂ affinity than dopamine antagonism (see Section 3).

3. Review of PD psychosis treatment trials

Treatment trials of PD psychosis have been the focus of evidence-based medical reviews by the Movement Disorder Society (MDS) and American Academy of Neurology (AAN). The MDS program involves a systematic critique of published reports based on pre-specified criteria. Treatments are ranked as: Efficacious, Likely Efficacious, Unlikely Efficacious, Non-efficacious and Insufficient data, and safety conclusions are drawn from review of adverse effects. Based on efficacy and safety conclusions, each treatment receives a designation regarding Implications for Clinical Practice: Clinically useful, Possibly useful, Unlikely useful, Not useful or Investigational. Treatments for PD psychosis were reviewed in 2002 and 2011 reports^{42,43}. Also using Evidence-Based Medical Review methodology, the AAN Quality Standards Subcommittee published a Practice Parameter report on the evaluation and treatment of depression, psychosis, and dementia in PD in 2006⁴⁴. With our focus on evidence-based medicine in this section, randomized controlled trials for PD psychosis and conclusions from the evidence-based reviews will be emphasized (Tables 2 and 3).

3.1. Clozapine

Clozapine is a dibenzodiazepine that binds to D₁ mesolimbic receptors with relative sparing of striatal dopamine receptors. It has prominent activity at D₄ dopamine receptors and is an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors. In the 2002 MDS review, clozapine was the only antipsychotic agent with consistent evidence from randomized controlled trials to be rated as Efficacious⁴². Clozapine had an acceptable risk but requires specialized monitoring due to risk of agranulocytosis, a rare (0.38%) but potentially life-threatening occurrence. As a result, clozapine was designated as Clinically Useful. Since 2002, three new clozapine studies have been published and the 2011 MDS report supports the same conclusions⁴³. The AAN Practice Parameter recommendations were that clozapine should be considered (Level B) with white blood count monitoring⁴⁴, based on one Class I study^{45,46} and one Class II study⁴⁶.

Two multicenter, double-blind, placebo-controlled trials were considered for the 2002 MDS review^{45,47}. In both the Parkinson Study Group and the French Clozapine Parkinson Study Group trials, clozapine doses were relatively low (6.25–25 mg/d; 6.25–50 mg/d, respectively), and clozapine-treated patients had significant improvement on psychosis outcome measures compared to placebo, without motor worsening. Both studies lasted 4-weeks and were followed by 12-week open label extensions; the French study included a one-month post-study washout with continued observation. In the US-based study, efficacy was maintained among survivors, but an unexpectedly high death rate occurred during the 12-week period (6/53 patients died)⁴⁸. Mortality was related to advanced PD rather than clozapine exposure. In the French follow-up study, 25/53 had resolution of psychosis on clozapine, but of these, 19 relapsed within the one-month washout⁴⁹. This observation underscores the chronic nature of PD psychosis and the need of continued therapy in most patients.

Because clozapine requires blood count monitoring, comparison studies have focused on whether safer antipsychotics are equally efficacious. Two single-blind randomized trials have compared clozapine and quetiapine^{50, 51}. Morgante et al conducted a 12-week randomized, rater-blinded trial of clozapine and quetiapine in 45 hallucinating PD patients⁵⁰. On either drug, patients improved about 25–30% on the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) Scale without motor worsening on the Unified Parkinson's Disease Rating Scale (UPDRS) motor section. There were no significant differences in psychosis or motor scores between the two groups. In a 22-week study, Merims et al randomized 27 PD patients with psychosis to receive either clozapine or quetiapine⁵¹. During the first month of treatment, both groups showed a significant improvement in the CGI, with no difference between treatments. Differences in Neuropsychiatric Inventory (NPI) scores for hallucination and delusion frequency were seen in the clozapine group over time, but neither group demonstrated significant differences in severity scores on these items. Only 7/14 clozapine-treated patients and 9/13 quetiapine-treated patients completed the study. There was no motor worsening in either group, but neutropenia occurred in 3 clozapine-treated patients. Clozapine, like other atypical antipsychotics, also has been associated with an increased risk for all-cause mortality and cerebrovascular events in elderly patients with dementia⁵².

3.2 Quetiapine

Quetiapine is an atypical dibenzothiazepine structurally similar to clozapine. Data from randomized clinical trials, however, are less consistent for quetiapine than for clozapine. Comparator studies of quetiapine and clozapine suggest equivalent efficacy, but quetiapine has failed to show a consistent efficacy profile when compared with placebo. Four randomized controlled trials have studied quetiapine vs. placebo in PD psychosis^{53–56}; another randomized trial included patients with PDD, DLB, and Alzheimer's dementia and parkinsonism⁵⁷. Of these five trials, only one has been positive regarding psychosis outcome.

Ondo et al conducted a double-blind, placebo-controlled study of quetiapine in 31 PD patients with clinically problematic hallucinations⁵³. No significant differences were seen on psychosis (BPRS and Baylor PD Hallucination Questionnaire) or motor (UPDRS) assessments. There were no dropouts related to quetiapine adverse events. The study, however, may have been underpowered (power of 22%, effect size of 35%). In a double-blind, placebo-controlled study, Rabey et al investigated quetiapine in 58 psychotic PD patients, 29 with dementia, using the BPRS and CGI as primary outcome measures⁵⁴. A high drop-out rate (26/58, 45%) occurred, primarily due to lack of efficacy in both groups. Compared to placebo, quetiapine had no effect on the CGI, BPRS, or UPDRS scores.

Two double-blind, placebo-controlled studies with quetiapine evaluated primary outcomes other than psychosis rating scales. Shotbolt et al evaluated the time to dropout due to lack of improvement of psychosis using survival analysis⁵⁵. In this study of 24 PD patients with psychosis, 13 patients completed 6 weeks (quetiapine n = 4; placebo n = 9) and 8 completed the 12-week double-blind phase (four from each group). There was no significant difference in time to drop out between the groups. Due to the high drop-out rate, secondary outcome measures (BPRS, NPI, Baylor PD Hallucination Questionnaire, UPDRS) were only analyzed at 6 weeks by intention to treat and missing value imputation, and no significant changes were found. Another study examined quetiapine's effect on sleep including REM sleep architecture as measured by pre- and post-treatment polysomnography⁵⁶. In this pilot study, 16 PD patients with predominantly nocturnal visual hallucinations were randomized to receive quetiapine or placebo. Compared to placebo, quetiapine led to significant improvement on the BPRS hallucination item ($p=0.02$), although the change in total BPRS was not significant between the two treatment arms. No difference was noted in UPDRS

motor scores. No significant differences in REM duration were found in either treatment group, although the sample size was small and study completion rate was low. This study, designed specifically to study sleep architecture, is the only placebo-controlled trial to show a significant anti-hallucinatory effect of quetiapine.

In a double-blind, placebo-controlled study, Kurlan et al investigated quetiapine for agitation or psychosis in patients with dementia and parkinsonism⁵⁷. Not all patients had PD, and diagnoses included: PDD (n=9), DLB (n=23), and Alzheimer's disease with parkinsonism (n=8). Recruitment problems led to modification of the trial design to include patients taking cholinesterase inhibitors. There were no significant differences in the primary outcome (BPRS) or UPDRS in the treatment groups. Quetiapine was well-tolerated, but conclusions about efficacy were limited and concerns raised regarding adequate doses and large placebo effects.

Given the conflicting data regarding efficacy and methodological concerns of studies, the MDS report concluded that there is Insufficient Evidence to establish a role of quetiapine for treating PD psychosis⁴³. It carried acceptable safety without specialized monitoring, but for Practice Implications was rated as Investigational. Like clozapine, quetiapine has a "black box" warning for elderly patients with dementia⁵². On the basis of one Class II study comparing quetiapine and clozapine⁵⁰, the AAN Practice Parameters concluded that quetiapine may be considered (Level C)⁴⁴.

3.3 Olanzapine

Olanzapine, a thienobenzodiazepine of similar structure to clozapine, has affinity for 5HT receptors but also prominent D2 receptor blockade. It may have additional actions on alpha-1 adrenergic, histamine H1, and cholinergic muscarinic receptors. There have been four randomized trials of olanzapine for PD psychosis. The earliest was a comparator trial between olanzapine and clozapine, which was stopped due to severe exacerbation of parkinsonism in the olanzapine group⁵⁸. Two placebo-controlled studies, reported in one publication, examined low dose olanzapine (maximum 15 mg/d) and found significant improvement in hallucinations as measured by the BPRS, NPI, and CGI in placebo-treated and olanzapine-treated patients⁵⁹. In both studies, there was no significant difference between treatment groups for hallucinations. Motor function worsened significantly in the olanzapine group compared to placebo. Another trial corroborated these findings with no difference between olanzapine and placebo for efficacy and significant worsening in motor measures⁶⁰.

Olanzapine was rated in the MDS 2011 report as Not Efficacious, with an Unacceptable risk of exacerbating parkinsonism, and Clinically Not Useful⁴³. Olanzapine also is associated with an increased risk for all-cause mortality and cerebrovascular events in elderly patients with dementia⁵². The AAN Practice Parameter concluded that olanzapine should not be considered (Level B), as based on the 2 Class II studies described above⁴⁴.

3.4. Pimavanserin

Pimavanserin (ACP-103) acts as an inverse agonist on 5-HT_{2A} receptors, with 10-fold selectivity over 5-HT_{2C} receptors. It has no significant affinity or activity at 5-HT_{2B} or dopamine receptors, making it a novel agent for PD psychosis treatment⁶¹. A double-blind, placebo-controlled, multicenter study investigated its tolerability, safety, and efficacy in the treatment of psychotic symptoms in non-demented PD patients. Sixty PD patients with hallucinations or delusions were randomized to receive pimavanserin or placebo. The primary outcome measure, the Scale for the Assessment of Positive Symptoms (SAPS), showed a trend for improvement (p=0.09, effect size=0.52), but the change was not

statistically significant in comparison to placebo. The study, powered for differences in UPDRS activities of daily living and motor section scores, had favorable results regarding motor function. A recently completed double-blind, placebo-controlled, randomized, multicenter Phase III trial with a larger sample of PD patients did not demonstrate statistically significant benefit for psychosis measures, though the drug was tolerated in terms of parkinsonism and side effects⁶². Pimavanserin also has been studied in primate models of levodopa-induced dyskinesias, schizophrenia-related psychosis, and insomnia⁶³. Since serotonin may influence sleep architecture, pimavanserin and similar compounds could play a role in sleep and hallucinations.

3.5. Antipsychotic and other agents reported only in open-label trials, case series or reports

3.5.1. Risperidone—Risperidone, a benzisoxazole atypical antipsychotic, has mixed serotonin-dopamine antagonist activity with high affinity binding to 5-HT₂ receptors and lower affinity binding to D₂ receptors. Similar to clozapine, risperidone has been used for psychosis in PD, but unlike clozapine, has been associated with dose-dependent motor side effects and prolactin release. There have been no double-blind, placebo-controlled studies of risperidone in PD psychosis, and data remains inconsistent. Although some reports show the drug to be well tolerated without worsening mobility^{64, 65}, most others reveal profound exacerbation of parkinsonism^{66, 67}.

3.5.2. Aripiprazole—Aripiprazole, an atypical antipsychotic, has a unique pharmacology with combined dopaminergic and serotonergic properties. Aripiprazole demonstrates partial agonism (agonism/antagonism) at D₂ and 5-HT_{1A} receptors and antagonism at 5-HT₂ receptors. Its use in PD psychosis treatment, however, has been disappointing given its promising pharmacological profile. Two small open-label series in PD patients with psychosis revealed worsened parkinsonism and only modest improvement in psychosis. In one open-label trial, only 2/8 PD patients showed near complete resolution of psychosis; the other 6 patients discontinued aripiprazole within 40 days, with increased parkinsonism in 2 patients⁶⁸. An open-label, multicenter study of 14 PD patients demonstrated that while some patients had a favorable response, motor symptoms worsened⁶⁹. Case reports reveal variable efficacy with frequent motor worsening⁷⁰.

3.5.3. Ziprasidone—Ziprasidone is a second-generation antipsychotic with combined dopamine, serotonin, and histaminergic receptor antagonist activity; because of the high 5-HT_{2A} to D₂ ratio, it is thought to have a low propensity for extrapyramidal adverse effects. Studies with ziprasidone are few, and none is a double-blind, placebo-controlled trial. In an open-label trial, 10/12 PD patients reported significant improvement in psychiatric symptoms without motor deterioration⁷¹. In a case series, 3/4 ziprasidone-treated PD patients had improved psychosis; however, 1 patient developed worsened off-periods, and 2 patients had pathological laughing⁷². Concern has been raised regarding cardiac side effects including QT prolongation.

3.5.4. Melperone—Melperone has been available in some European countries and used as an antipsychotic for schizophrenia for over 10 years. Although a butyrophenone, melperone has been considered “atypical” due to its low extrapyramidal symptoms and lack of increase in plasma prolactin⁷³. Similar to clozapine, it has high 5-HT_{2A} affinity relative to D₂ receptor binding affinities. In an open-label trial, Barbato et al assessed the efficacy and safety of melperone in 30 PD psychotic patients over 24 months⁷⁴. In 28/30 PD patients, BPRS scores improved without worsening motor scores. Doses (mean 37.5 mg/d) were lower than those utilized in schizophrenia, similar to the low clozapine and quetiapine doses used in PD psychosis. Side effects included hypotension, dizziness, and sedation (leading to

discontinuation by 2 patients). A 10-week, double-blind, placebo-controlled, multicenter Phase II trial evaluating the safety and efficacy of melperone in PD psychosis was recently finished in the US, but no results have been published in scientific journals.

3.5.5. Cholinesterase inhibitors—Although not antipsychotic agents per se, cholinesterase inhibitors have been reported to improve hallucinations and cognitive measures in PDD and DLB. To date, these medications have not been studied in PD psychosis with double-blind, placebo-controlled trials. In a large double-blind, placebo-controlled study in PDD, rivastigmine was mildly more effective in improving cognition in PD dementia patients with visual hallucinations, but the drug did not significantly reduce the hallucinations³¹. Other studies follow similar patterns but provide only indirect information on hallucinations because the study group and primary outcomes focus on dementia⁷⁵, though motor worsening did not occur.

4. Novel methods for studying PD psychosis

In order to further elucidate the pharmacology and pathophysiology of PD psychosis, novel research strategies have incorporated neuroimaging, genetics, and animal models. Focusing on neurotransmitters besides the dopamine system may foster development of novel therapeutic agents. Furthermore, the development of rating scales specifically for PD psychosis is a critical element in studying PD psychosis and measuring effects of interventions. Challenges associated with these research strategies and treatments for PD psychosis will be discussed in the Expert Opinion section.

4.1. Neuroimaging and PD psychosis

Neuroimaging studies permit *in vivo* investigations of anatomical substrates and brain alterations associated with PD hallucinations. Techniques utilized include structural magnetic resonance imaging (MRI) to assess gray matter atrophy, functional MRI to examine activation patterns, and perfusion scans to investigate changes in regional cerebral blood flow or glucose metabolism.

Structural MRI studies in PD hallucinators have examined regional and global brain atrophy patterns using manual volumetry or semi-automated, whole-brain voxel-based morphometry (VBM). Compared to non-hallucinating PD patients, PD hallucinators exhibit reduced gray matter volume in the lingual gyrus and superior parietal lobe, regions associated with higher-order visual processing⁷⁶, and in the hippocampus, an area invoked in memory function⁷⁷. Non-demented PD hallucinators also demonstrated hippocampal atrophy⁷⁷. Ibarretxe-Bilbao et al followed 12 non-demented, hallucinating PD patients, 14 PD patients without hallucinations, and 12 healthy controls for a mean 29.91 $\pm$ 5.74 months with MRI and neuropsychological tests⁷⁸. At follow-up, 75% of the hallucinating PD patients had developed dementia. The PD hallucinators demonstrated widespread limbic, paralimbic and neocortical gray matter loss, regions also abnormal in PD dementia.

Functional MRI (fMRI) studies demonstrate altered cortical activation patterns in PD hallucinators compared to non-hallucinators. Stebbins et al studied 12 PD patients with chronic visual hallucinations, matched for age, disease duration, and dopaminergic drug exposure to PD patients who had never hallucinated, using stroboscopic and kinematic visual stimulation fMRI paradigms. PD hallucinators had significantly greater frontal and subcortical activation and decreased cerebral activation in occipital, parietal, and temporal-parietal regions to both visual stimulation paradigms, compared to non-hallucinators⁷⁹. When faced with complex visual stimuli (e.g., a face recognition task), PD hallucinators had significantly reduced activation in right prefrontal areas and anterior cingulate gyrus, compared to non-hallucinating PD and healthy controls⁸⁰. Meppelink et al reported that

non-demented, hallucinating PD patients showed reduced activation of the lateral occipital cortex and extrastriate temporal visual cortices, compared to non-hallucinating PD and healthy controls, during the several seconds prior to an image recognition task⁸¹. These studies suggest disruption of normal visual processing mechanisms in PD hallucinators, with abnormal activation in anterior (e.g., frontal) and posterior (e.g., parietal, temporal, occipital) regions and impairment in distinguishing relevant from irrelevant visual information.

Decreased perfusion or glucose metabolism in predominantly posterior brain regions has been reported in PD hallucinators using single photon emission computed tomography (SPECT) or positron emission tomography (PET). Although imaging modalities differ, regions of decreased cerebral blood flow or metabolism in PD hallucinators, compared to non-hallucinators, have included temporal-occipital lobes⁸², bilateral inferior parietal lobules, inferior temporal gyrus, precuneus gyrus, and occipital cortex⁸³, and temporal-occipital-parietal regions⁸⁴. The temporal-occipital-parietal region abnormalities complement the functional and structural imaging findings. Greater regional cerebral glucose metabolic rates have been detected in frontal regions in PD hallucinators, compared to non-hallucinating PD and healthy controls, using [¹⁸F] FDG-PET⁸⁵, further suggesting disruption in frontal and posterior activation patterns. Overall, the neuroimaging studies emphasize relationships between frontal and posterior brain regions, visual and cognitive processing, and pathogenesis of PD hallucinations.

4.2. Genetic risk factors for PD psychosis

Besides clinical risk factors such as age, PD duration, motor severity, depression, dementia, and sleep disturbances, genetic factors may influence the development of PD psychosis. Genetic polymorphisms affecting dopaminergic medication metabolism may influence PD-related motor complications such as dyskinesias or fluctuations^{86, 87}. With the growth of pharmacogenetics, inter-individual differences in medication responses due to genetic polymorphisms may become increasingly important in drug development, evaluation of drug efficacy and toxicity, and individualized patient care. Genetic polymorphisms studied regarding increased risk of PD psychosis include those in dopamine, serotonin, and cholecystokinin systems as well as apolipoprotein E (APOE) 4 allele status. Some studies, however, have yielded conflicting or negative results, and the relationship between genetic inter-individual variability and PD-related complications awaits further exploration. Differences in study methodologies and subjects' racial backgrounds may account for some of the negative or conflicting results.

4.2.1. Dopaminergic system—Investigations of the dopaminergic system have included D1 receptors (DRD1, DRD5), D2 receptors (DRD2, DRD3, DRD4), and the dopamine transporter gene (DAT), which controls presynaptic reuptake of dopamine. DRD2 (−141C/del in the promoter region and TaqIA restriction fragment length polymorphism C>T) or DRD3 (Ser9Gly) polymorphisms did not differ significantly in white PD hallucinators matched to non-hallucinating PD controls on disease duration, age at disease onset, duration of dopaminergic therapy, and gender⁸⁸. An association, however, was found with late-onset hallucinators (i.e., PD patients who developed hallucinations after 5 years of disease) and the C allele of the TaqIA polymorphism to DRD2. In a case-control study of 44 matched pairs of white PD patients with and without chronic hallucinations, Goetz et al found a borderline increased frequency of the DRD3 2 allele in hallucinators ($p=0.047$)⁸⁹. A case-control study of Chinese PD patients with and without hallucinations did not find associations at DRD2 (TaqIA, 32806 C>T), DRD3 (Ser9Gly and Msp1), or DRD5 (978 T>C)⁹⁰. Positive associations of the DRD2 polymorphism with dyskinesias and wearing off but not with hallucinations suggest differences in pathogenic mechanisms. A 40-bp variable

number of tandem repeat (VNTR) polymorphism in the DAT gene has been associated with attention-deficit hyperactivity disorder, alcoholism, and schizophrenia. In white PD patients, Kaiser et al found that the 9×40 bp VNTR allele of the DAT gene was more frequently present in levodopa-treated PD patients with psychosis or dyskinesias, compared to non-affected patients⁹¹. Differences in the 9-copy allele of the DAT VNTR, however, were not confirmed in two case-control studies of PD hallucinators and non-hallucinators, one in Chinese patients⁹⁰ and the other in whites⁹².

4.2.2. Serotonergic system—Polymorphisms in the 5HT transporter (5HTT) gene have been thought to influence anxiety and depression by altering serotonergic tone⁹³. Two functional polymorphisms in the 5HTT gene, a promoter VNTR (short, long alleles) and intron 2 VNTR (9, 10, 11, 12 alleles), contribute to protein expression; less efficient transcription and decreased reuptake results from a deletion (short [s] allele compared to long [l] allele) or presence of 10-copy allele in intron 2 VNTR in the transporter gene. In a case-control study of 44 matched pairs of white PD patients with and without hallucinations, however, no significant differences in allelic or genotypic frequencies of short or long alleles or intron sequences of the VNTR element were found⁹⁴. Since the serotonin system encompasses many receptor subtypes, individual receptors rather than the transporter itself may be associated with psychosis, as suggested by atypical antipsychotic pharmacology. Kiferle et al examined polymorphisms in the 5-HT_{2A} gene (T102C) as well as the 5HTT gene (short, long alleles)⁹⁵. In their non-demented, white PD group, no significant differences between PD patients with and without hallucinations were found for either polymorphism. Serotonin polymorphisms may have greater association with anxiety and affective disorders rather than psychosis, although further study is needed.

4.3. Animal models of PD psychosis

Animal models such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primates and 6-hydroxydopamine (6-OHDA)-lesioned rodents have been influential in studying parkinsonism and levodopa-induced dyskinesias. Hallucinations and other psychotic behavior, however, have been more difficult to study in animals given the subjective nature of hallucinations and the challenge of inferring meaning from an animal's behavior. Amphetamine, ketamine and phencyclidine have been used in rodent and primate models of psychosis or positive symptoms of schizophrenia since they stimulate or induce locomotor activity, stereotypies, and striatal dopamine release⁹⁶. In primates treated with chronic amphetamine, stereotypies, hyperactivity, and behaviors such as hypervigilance, checking, grasping, and staring may occur.

MPTP-lesioned primates have been noted to experience abnormal psychomimetic behaviors reminiscent of “psychosis-like” behaviors in amphetamine-sensitized animals, and these behaviors may have utility in studying PD psychosis^{97, 98}. Fox et al examined these phenomena in MPTP-treated marmosets exposed, after a stable parkinsonian period, to several different dopaminergic and antipsychotic medications. Psychosis-like behaviors, rated by a blinded observer, were quantified as: 1) agitation, 2) hallucinatory-like response to apparent non-stimuli, 3) obsessive grooming, and 4) stereotypies and summed for a total psychosis-like behavior score.

Both levodopa and dopamine receptor agonists (pergolide, pramipexole, and ropinirole) induced peak-dose psychosis-like behavior in the MPTP-lesioned primates as well as reversed parkinsonian disability, compared to vehicle⁹⁷. No difference in psychosis-like behavior was observed among the dopaminergic agents. In a companion study, levodopa produced psychosis-like behavior in the 7 marmosets studied⁹⁸. Of the psychosis-like behaviors exhibited, stereotypies were the most common, and all animals exhibited

“hallucinatory-like” (staring and tracking) behavior. There was no correlation between severity of dyskinesias and psychosis-like behavior in individual animals with levodopa. Psychosis-like behaviors, particularly stereotypies, and dyskinesias decreased with haloperidol, but parkinsonism worsened. Quetiapine effects differed based on dose; significant reduction in the total psychosis-like score was seen in the 1.5 mg/kg group but not the 0.5 mg/kg or 4.5 mg/kg doses, compared to vehicle. Clozapine reduced psychosis-like behaviors, compared to vehicle, with a decrease in hallucinatory-like behavior. Neither quetiapine nor clozapine worsened parkinsonism or produced somnolence.

4.4. Development of rating scales for PD psychosis

Psychotic symptoms are inherently difficult to rate since they may not occur in the presence of physicians. Hallucinations and delusions, by virtue of their bizarre nature, are frequently underreported, and caregivers are often unaware of them until they become problematic. Several scales have been developed for rating PD psychosis, but most have been borrowed or adapted from assessment tools used in other psychotic disorders such as schizophrenia. Psychosis in schizophrenia and PD, however, differ phenomenologically. As a result, rating scales that specifically address hallucinations, delusions, and other psychotic phenomena in PD are needed.

To address this issue, the Movement Disorder Society Task Force on Rating Scales for Parkinson’s Disease systematically critiqued scales used for assessing PD psychosis⁹⁹. The Task Force designated scales as Recommended if they had been used specifically in PD studies, used by multiple authors or groups other than the people who developed the scale, and had clinimetric testing of the scale. A total of 12 psychosis scales or questionnaires were reviewed, and 4 scales met the Recommended criteria: the NPI, BPRS, Positive and Negative Syndrome Scale (PANSS), and SAPS (Table 4). Each scale had different advantages and disadvantages. The NPI and SAPS follow a standardized method of administration for consistency, whereas the BPRS and PANSS are less structured. As such, in instances where the rater may be less trained or less familiar with PD psychosis, the NPI and SAPS may be more suitable, whereas raters experienced in evaluating the nuances of the behavioral repertoire of PD psychosis may favor the others. None of these scales was considered to be a definitive rating tool for the assessment of PD psychosis. The Task Force officially recommended the development of a new scale, and efforts are currently ongoing¹⁰⁰.

5. Conclusion

Although the dopaminergic system remains important in the pathogenesis of PD psychosis, other neurotransmitters such as cholinergic and serotonergic systems are integral to the neurobiology of PD psychosis. These neurochemical substrates underlie several related neuropsychiatric features of PD including psychosis, cognition, sleep, and mood. Potential therapeutics for PD psychosis may stem from examining shared neurochemical and neuroanatomical alterations in attention, cognition, sleep, and mood. Safe and effective treatment of PD psychosis remains a challenge, but integrating studies of neuroimaging and genetic susceptibility, and perhaps, animal models may advance drug development. While clozapine carries the most favorable evidence-based medicine review, improved therapeutics to treat psychosis without worsening motor symptoms are still needed.

6. Expert Opinion

PD psychosis is a frequent and troublesome complication that impacts both patient and caregiver and therefore, treatment interventions are often necessary. Management of PD psychosis starts with an evaluation for metabolic or infectious causes and the reduction or

elimination of centrally acting medications that are not absolutely required for treating PD-related symptoms and non-PD ailments. If psychosis does not improve, atypical antipsychotic medications are typically initiated. Treating PD psychosis, however, can be particularly challenging since antipsychotic agents may worsen motor symptoms. While clozapine has the most favorable profile by evidence-based medicine studies, its use is tempered by the risk of agranulocytosis and need for blood count monitoring, side effects of sedation or hypotension, and the “black box” warning for antipsychotic use in elderly patients with dementia. Quetiapine, despite its comparable efficacy to clozapine in comparison studies, ease of administration, and relatively low-risk side effect profile, has yet to demonstrate robust findings of psychosis reduction in double-blind, placebo-controlled randomized trials. It is, however, frequently used. Recent studies of aripiprazole and pimavanserin, atypical antipsychotic agents with novel pharmacological profiles, have yielded disappointing results. The predominance of failed treatment studies raises concerns regarding the study design or outcome measures to rate drug effects; efforts to develop new scales and novel approaches are currently active.

There are many challenges related to PD psychosis treatment trials including factors affecting study design, inclusion/exclusion criteria, subject recruitment, and study completion. Selection of the primary outcome measure is undoubtedly a critical step in trial design. For PD psychosis trials, this measure is often a rating scale of psychosis. Since efforts to develop a PD-specific psychosis scale are underway, several issues in designing optimal scales for screening and/or measuring PD psychosis are worthy of mention. The scale should focus on the primary form of hallucinations (visual), but be open to auditory, tactile, olfactory and “presence” hallucinations as well as delusions. Severity can be quantified by frequency, by the retention or loss of a clear sensorium or other features, but most importantly, how the hallucinations interfere with daily life and autonomy. These elements should be integrated into a final score that provides a meaningful number. Other important considerations relate to the information source (patient and/or caregiver), level of insight of the patient, and presence/absence of co-morbid dementia, mood disorders, sleep disturbances, and visual/hearing impairment. Distinguishing hallucinations from dreams must be emphasized, and while clinicians are generally aware of visual hallucinations, they should probe for hallucinations affecting other sensory domains. Furthermore, rating scales must be clinimetrically sensitive to treatment effects.

While double-blind, placebo-controlled trials are considered the most rigorous of study designs, there are challenges in performing these studies. The randomized controlled studies in PD psychosis reviewed in previous sections have included small sample sizes, ranging from 6 to 83 patients. Recruitment for PD psychosis trials can be difficult and may be influenced by patient and caregiver concerns about placebo assignment especially when hallucinations are frightening and delusions are present; risk of worsened motor function; “black box” warnings regarding antipsychotic use and increased risk of death in elderly patients with dementia; and widespread clinical use of quetiapine despite double-blind, placebo-controlled trial results. With small sample sizes, subanalyses of features such as psychosis duration, phenomenology, level of insight, or co-morbid neuropsychiatric impairment become difficult. Several of the PD psychosis trials discussed also had high drop-out rates, largely due to worsened motor symptoms, ineffectiveness of study medication, poor compliance, and various co-morbidities. Of the trials reviewed, the clozapine studies had highest rates of completion. Other methodological issues include the defined population (PD with or without dementia, DLB, and/or Alzheimer disease with parkinsonism), concomitant medications allowed (cholinesterase inhibitors), and antipsychotic doses used. These issues should be considered in trials for PD psychosis.

Research studies incorporating neuroimaging, genetics, and animal models may provide new avenues for understanding and treating PD psychosis, but also have challenges and limitations. Acquiring neuroimaging studies in PD patients can be difficult due to motor fluctuations, tremor or dyskinesias, impaired attention, dementia, and active psychosis. Moreover, fMRI studies can be affected by factors such as impaired attention, motivation, and cognition; medication effects including antipsychotics; and visual acuity deficits. Imaging PD patients while they are actively hallucinating or delusional could pose certain difficulties. The majority of the neuroimaging studies, to date, have focused on chronic visual hallucinations, and thus, whether findings reflect the pathogenesis of delusions or hallucinations in other sensory modalities is not known. Additionally, co-morbid neuropsychiatric issues such as cognitive impairment, even mild, and depression may share neuroanatomical substrates (e.g., temporal lobe) and could influence interpretations of studies.

Methodological issues and conflicting results have complicated studies of genetic polymorphisms and PD hallucinations. Variables that may influence the genetic association studies include small sample sizes, methodological differences (case-control studies vs. larger population-wide studies), and differences in demographic or PD-related issues such as age, gender, disease duration, medications, cognitive and mood disorders. Moreover, genetic polymorphisms vary across different racial groups. As some non-hallucinating patients examined in cross-sectional studies might convert to hallucinators over time, longitudinal evaluation would be necessary to assess conversion risk and genetic predictors of hallucinations. Nevertheless, genetic association studies may prove to be informative and useful regarding genetic susceptibility, drug development, and potentially individualized treatment regimens.

Regarding animal models, one of the greatest challenges is whether one can infer that the primates' behaviors recapitulate the subjective human experiences of hallucinations and psychosis. Dopaminergic-stimulated abnormal behaviors in primates, as distinguished from dyskinesias, however, may represent a close approximation of PD neuropsychiatric disturbances and an opportunity to evaluate pathophysiology and therapeutics for psychosis and heightened dopaminergic states.

Despite these challenges, research studies applying neuroimaging modalities, genetic associations, and translational animal models, either individually or in combination, have the potential to enhance our understanding of PD psychosis and to advance the development of agents that can ultimately be tested in well-designed, randomized, controlled trials. The profound impact of PD psychosis reinforces the need to identify novel compounds that are safe and effective in reducing psychosis without compromising motor function.

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Article Highlights Box

- PD psychosis affects about 1/3rd of patients treated with chronic dopaminergic therapy, can occur with any antiparkinsonian medication, and significantly impacts both patient and caregiver.
- The phenomenology of PD psychosis encompasses illusions, hallucinations, and delusions, and recent diagnostic criteria for PD psychosis have been proposed.
- Hallucinations in PD are generally visual, but other sensory domains including auditory, tactile and olfactory domains are involved, especially in late PD.
- Neurotransmitters such as dopamine, acetylcholine, and serotonin underlie the pathophysiology of PD psychosis; associations with cognitive impairment, mood disorders, and sleep disturbances; and pharmacological rationale of antipsychotic agents in treating PD psychosis.
- Treatment of PD psychosis may be difficult due to modest efficacy of antipsychotics and risk for motor worsening though clozapine and quetiapine are frequently used.
- There is a need for improved antipsychotic medications for PD psychosis that are safe and effective; novel research strategies investigating associated neuropsychiatric co-morbidities, multiple neurotransmitter systems, and translational approaches may further advances in PD psychosis treatments.

Table 1

Clinical spectrum of PD psychosis

Phenomenology	Definition	Examples
Illusions	<ul style="list-style-type: none"> Misperception of real stimuli, type of minor hallucination 	<ul style="list-style-type: none"> Seeing inanimate objects as living beings - a chair mistaken for a dog, a bedpost mistake for a tree
Passage hallucinations	<ul style="list-style-type: none"> Sensation of a person or animal passing in one's peripheral visual field, type of minor hallucination 	<ul style="list-style-type: none"> Catching a glimpse or sensing that a dog, cat or person is passing sideways
Presence hallucinations	<ul style="list-style-type: none"> Sensation of someone's presence when nobody is really there, type of minor hallucination 	<ul style="list-style-type: none"> Feeling like there is someone standing by one's side – a patient's report of a "guardian angel" standing nearby
Formed (or complex) hallucinations	<ul style="list-style-type: none"> Spontaneously experienced false, sensory perceptions which seem real but occur without external stimulation Occur during wakefulness Tend to be recurrent and stereotyped Can occur in any sensory modality (visual, auditory, tactile, olfactory, gustatory); often increased in dim light or low vision conditions Can be pleasant or frightening 	<ul style="list-style-type: none"> Seeing children playing, small, furry animals scurrying, or distorted, bizarre figures Hearing indistinguishable sounds or music of various types Feeling of being touched by someone Smelling pleasant or unpleasant odors
Delusions	<ul style="list-style-type: none"> False and fixed beliefs that are not based in reality 	<ul style="list-style-type: none"> Jealousy or spousal infidelity Paranoia Stealing Abandonment
Misidentification syndromes	<ul style="list-style-type: none"> Specific type of delusion, occurs frequently in patients who also have dementia 	<ul style="list-style-type: none"> Capgras syndrome: patient thinks that his/her recognizable spouse is an imposter Fregoli syndrome: patient believes that familiar people are, often malevolently, disguised as strangers

Table 2

Randomized, double-blind, placebo-controlled studies in PD psychosis

Authors	Drug	Study duration (weeks)	Total n	Completion rate (%)	Mean (SD) drug dose, mg/d	Baseline MMSE, Mean (SD)	Psychosis rating scales	Psychosis outcome	Motor worsening in active drug group
Wolters et al., 1990	CLZ	5.7	6	50%	170.8	Dementia in 3 patients	BPRS, SAPS	Improved in the 3 completers	Yes in 3/6
PSG, 1999	CLZ	4	60 (30 d, 30 c)	90% d, 90% c	24.7	23.8 (4.8) d, 21.7 (5.2) c	CGI*, SAPS, BPRS	Significant improvement on CGI, BPRS, SAPS	None
French Clozapine PSG, 1999	CLZ	4	60 (32 d, 28 c)	84% d, 68% c	36 (14)	26.1 d, 24.1 c	CGI*, PANSS	Significant improvement on CGI and PANSS positive subscore	Mild or transient in 7 patients
Breier et al., 2002	OLZ	4	US study: 83 (41 d, 42 c)	61% d, 83% c	4.2 (2.6)	24 (3.8) d, 24.7 (3.9) c	BPRS with positive symptom cluster subscore*, CGI-S, NPI	Significant improvement in BPRS total, positive, and hallucinations, CGI-S, and NPI total, hallucinations vs. baseline; not significant vs. placebo	Significant worsening on UPDRS total, motor, and ADL scores vs. placebo
Breier et al., 2002	OLZ	4	Europe an study: 77 (49 d, 28 c)	75.5% d, 85.7% c	4.1 (2.0)	24.7 (4.8) d, 25.0 (3.8) c	BPRS with positive symptom cluster subscore*, CGI- S, NPI	Significant improvement in BPRS total, positive, and hallucinations, CGI-S, and NPI total, hallucinations, and delusions vs. baseline; not significant vs. placebo	Significant worsening on UPDRS total, motor, and ADL scores vs. placebo
Ondo et al., 2002	OLZ	9	30 (18 d, 12 c)	89% d, 92% c	4.6 (2.2)	26.8 (3.3)	Structured interview for hallucinations in PD, UPDRS thought disorder item	No significant improvement	Significant worsening on UPDRS motor subscale and timed tapping test
Ondo et al., 2005	QTP	12	31 (21 d, 10 c)	81% d, 80% c	169.1 (46.4)	26.1 (2.5) d, 27 (2.9) c	Baylor PD Hallucination Questionnaire*, BPRS	No significant	None
Rabey et al, 2007	QTP	12	58 (30 d, 28 c)	50% d, 61% c	119.2 (56.4)	22.2 (6) d, 21.7 (6) c	BPRS*, CGI*	No significant improvement	None
Kurlan et al., 2007	QTP	10	40 (9 with PD)	85% d, 65% c	120	19.2 (6.5) d, 17.2 (5.9) c	BPRS*, NPI, ADCS-CGIC	No significant improvement	Not significant
Shoibolt et al., 2009	QTP	12	24 (11 d, 13 c)	36% d, 31% c	72.7 (26.1)	24.6 (3.6) d, 20.8 (5.7) c	BPRS, NPI, Baylor PD Hallucination Questionnaire	No significant improvement	Not significant
Fernandez et al., 2009	QTP	4	16 (8 d, 8 c)	50% d, 87% c	58.3	()	BPRS, CGI	Significant improvement on CGI and BPRS hallucination subscale; not BPRS total	Not significant
Meltzer et al, 2010	ACP-103 (pima-vanserin)	4	60 (29 d, 31 c)	97% d, 90% c	44.8 (16)	()	SAPS*, PPRS, CGI-S	Significant improvement in SAPS global hallucination and delusion scores, but trend for SAPS total domain score	Not significant

CLZ: clozapine, OLZ: olanzapine, QTP: quetiapine, ACP-103: pimavanserin, PSG: Parkinson Study Group, MMSE: Mini Mental State Examination, CGI: Clinical Global Impression Scale, CGI-S: severity subscore, SAPS: Scale for the Assessment of Positive Symptoms, BPRS: Brief Psychiatric Rating Scale, PANSS: Positive and Negative Syndrome Scale, NPI: Neuropsychiatric Inventory, ADCS-CGIC: ADCS-Clinical Golbal Impression of Change, UPDRS: Unified Parkinson’s Disease Rating Scale, PPRS: Parkinson’s Psychosis Rating Scale, ADL: activities of daily living. Missing data: (), d: drug, c: control group, primary outcome *.

Table 3

Conclusions from evidence-based medicine reviews on antipsychotics in PD

Medication	MDS Ranking	MDS Safety risks	MDS Implications for Clinical Practice	AAN Recommendations
Clozapine	Efficacious	Acceptable safety with need for specialized monitoring	Clinically Useful	Should be considered, Level B
Quetiapine	Insufficient data	Acceptable safety without specialized monitoring	Investigational	May be considered, Level C
Olanzapine	Not Efficacious	Unacceptable risk	Clinically Not Useful	Should not be considered, Level B

Movement Disorder Society (MDS); American Academy of Neurology (AAN)

Table 4
Psychosis rating scales reviewed by the Movement Disorder Society Task Force on Rating Scales in Parkinson's Disease

Psychosis Scale	Applied in PD	Used in studies beyond original authors	Successful clinimetric testing	Structured format	Validated in PD	Final recommendation
Parkinson Psychosis Rating Scale	✓		✓		✓	Suggested
Parkinson Psychosis Questionnaire	✓		✓	✓	✓	Suggested
Rush Hallucination Inventory	✓			✓		Listed
Baylor Hallucination Questionnaire	✓			✓		Listed
Neuropsychiatric Inventory	✓	✓	✓	✓		Recommended
Behavioral Pathology in Alzheimer's Disease Rating Scale	✓	✓		✓		Suggested
Brief Psychiatric Rating Scale	✓	✓	✓			Recommended
Positive and Negative Syndrome Scale	✓	✓	✓			Recommended
Scale for Assessment of Positive Symptoms	✓	✓	✓	✓		Recommended
Nurses' Observation Scale for Inpatient Evaluation	✓			✓		Listed
Clinical Global Impression Scale	✓	✓				Suggested
Unified Parkinson Disease Rating Scale Part I	✓				✓	Listed

Modified from Goetz CG. Scales to evaluate psychosis in Parkinson's disease. Parkinsonism Relat Disord 2009 Dec;15 Suppl 3:S38-41.