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Parkinson's Psychosis

Laura B. Zahodne, MS[1] and **Hubert H. Fernandez, MD**[*]

Hubert H. Fernandez: fernandez@neurology.ufl.edu

[*]Department of Neurology, University of Florida, P.O. Box 100236, Gainesville, FL 32610-0236, USA

[1]Department of Clinical & Health Psychology, University of Florida, P.O. Box 100165, Gainesville, FL 32610-0165, USA

Opinion statement

Psychosis is a leading reason for nursing home placement of patients with Parkinson's disease (PD). It may also be the single greatest stressor for caregivers of PD patients, it is generally persistent, and its presence markedly increases the risk of mortality. For these reasons, it is essential to recognize and appropriately treat psychosis in PD. Treatment of psychotic symptoms should be initiated after potential medical and environmental causes of delirium (eg, infection) have been eliminated or addressed. Initial pharmacologic changes should include limiting the patient's anti-PD medications to those that are necessary to preserve motor function (ie, eliminating adjunctive agents). Should that fail, an atypical antipsychotic agent is the treatment of choice. Clozapine is presently the gold standard, and quetiapine represents another option because of its ease of use and good tolerability profile. Emerging treatment options include the use of acetylcholinesterase inhibitors, antidepressants, and cognitive behavioral therapy. This article reviews what is currently known about treatment strategies in PD psychosis.

Introduction

Psychotic symptoms have long been recognized as possible side effects of dopaminergic medication for the treatment of the motor features of Parkinson's disease (PD), but more recently they have been linked to processes inherent in the disease itself [1•]. Approximately 20% to 40% of PD patients will develop psychosis [2], and management presents a unique clinical challenge, as many antipsychotic agents are known to induce parkinsonism in individuals without PD and to exacerbate parkinsonism in many PD patients. Thus, management must be considered within the context of an individual patient's unique profile of motor and nonmotor symptoms.

In PD, psychotic features typically arise late in the disease course (10 or more years after initial diagnosis) and usually present first in the context of a clear sensorium and retained insight [3]. PD psychosis most commonly takes the form of visual hallucinations and minor sensory disturbances such as illusions or "passage" and "sense of presence" hallucinations, but it also may be characterized by paranoid delusions. Symptoms tend to recur and worsen over time, and insight is ultimately lost. Indeed, psychosis can be prognostic of cognitive decline in PD [4]. Some researchers previously conceptualized a continuum of PD psychosis

Correspondence to: Hubert H. Fernandez, fernandez@neurology.ufl.edu.

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marked first by minor experiences such as vivid dreaming and misperceptions, followed by more frank hallucinations and delusions, and ultimately florid psychosis and dementia [5]. However, more recent evidence does not support such a chronology [6]. Despite our lack of a clear understanding of its natural course, we know that psychotic features in PD, once present, are persistent and distressing. Psychosis in PD has been independently linked with negative outcome variables such as caregiver distress, nursing home placement, and mortality [7,8].

Use of dopaminergic medication was the first risk factor considered to be implicated in the development of PD psychosis, and many authors have indicated that dopamine agonists put patients at higher risk than levodopa [9]. However, there are reports of hallucinations in PD patients prior to the introduction of levodopa [10], and it is now generally accepted that dopaminergic medications are neither necessary nor sufficient to account for psychosis. Indeed, there is no clear relationship between medication dosage and occurrence or severity of psychosis in PD, and nondopaminergic agents such as anticholinergics and amantadine have also been linked with psychotic symptoms [1•]. Thus, it is likely that intrinsic processes combined with iatrogenic variables produce psychotic symptoms. Important areas of contemporary research on the complex pathophysiology of PD psychosis include visual processing abnormalities, sleep dysfunction, and specific neurochemical changes (involving, for example, dopamine, serotonin, and acetylcholine [ACh]).

The most appropriate first-line treatment for PD psychosis involves simplification of the patient's anti-PD medication regimen. However, if distressing symptoms persist despite reduction of PD medications to the lowest tolerable dosages, addition of a pharmacologic agent should be considered. Choice of an atypical antipsychotic (AA) is based largely on each drug's unique side effect profile. Currently, clozapine and quetiapine are the most commonly used AAs. Fueled in part by the black box warning issued by the US Food and Drug Administration (FDA) regarding higher mortality risk with AAs in elderly patients with dementia, recent clinical studies have turned to alternative agents for the treatment of PD psychosis, including cholinesterase inhibitors (eg, rivastigmine) and memantine.

Because antipsychotic medications can worsen motor functioning and psychotic symptoms tend to persist in PD despite aggressive pharmacologic treatment, behavioral intervention represents an important, albeit understudied, strategy for optimizing psychosis management. Although most studies of cognitive behavioral therapy for psychosis have been conducted in the schizophrenia population, PD patients have been reported to benefit from self-driven coping strategies to manage psychotic symptoms. Thus, structured psychological interventions may be a valid avenue for new research.

Treatment

Pharmacologic treatment

- Drug therapy for the treatment of PD psychosis aims to reduce the frequency and severity of psychotic symptoms with minimal worsening of PD motor symptoms.
- Early treatment with antipsychotic medications may also reduce the risk of later deterioration to psychosis without insight [11].
- However, psychosis in PD tends to persist despite aggressive pharmacologic treatments. In many cases, adequate pharmacologic treatment may be precluded by a patient's motor profile.
- Thus, adding a pharmacologic agent should be considered only after other efforts have proven ineffective and should follow patient preferences.

Atypical antipsychotics

Clozapine

Standard dosage: 6.25 to 800 mg/d (in PD psychosis, typically 12.5–100 mg/d).

Contraindications: Avoid with epilepsy, myeloproliferative disease, agranulocytosis with prior clozapine treatment use with caution in elderly patients and those with cardiac disease, dementia, renal impairment, hepatic impairment, diabetes mellitus, suicide risk.

Main drug interactions: Avoid with cisapride, dronedarone, potassium salts.

Main side effects: Agranulocytosis (1%), seizures, myocarditis, gastrointestinal hypomotility, weight gain, diabetes mellitus or hyperglycemia, hypercholesterolemia, orthostatic hypotension, sedation, sialorrhea. Clozapine bears a “black box” warning of potential for increased mortality risk in elderly dementia patients on conventional or atypical antipsychotics. (Most deaths are due to cardiovascular or infectious events it remains unclear if the deaths are due to antipsychotics or to patient characteristics or the patient population.)

Special points: Weekly monitoring of white blood cell (WBC) count during the first 6 months and biweekly monitoring thereafter is required because of agranulocytosis risk. Clozapine is the only AA fully recommended for the treatment of PD psychosis because of its demonstrated efficacy and tolerability in well-designed randomized controlled trials [12,13, Class I]. Longitudinal studies have shown clozapine to be well tolerated and effective in the long term [14]. Despite its effectiveness, clozapine is often avoided because of its cumbersome monitoring requirements.

Cost: The brand-name drug costs about $240 for 100 tablets of 25 mg. Generic clozapine is available.

Quetiapine

Standard dosage: 25 to 800 mg/d (in PD psychosis, typically 25–200 mg/d).

Contraindications: Use with caution in elderly patients and those with seizure history, cardiovascular disease, dementia, diabetes mellitus, hepatic impairment, suicide risk.

Main drug interactions: Avoid with cisapride, dronedarone, phenothiazines, triptorelin.

Main side effects: Gastrointestinal hypomotility, weight gain, hypercholesterolemia, diabetes mellitus, or hyperglycemia. Quetiapine bears a black box warning of potential for increased mortality risk in elderly dementia patients taking conventional antipsychotics or AAs. (Most deaths are due to cardiovascular or infectious events it remains unclear whether the deaths are due to antipsychotics or to patient characteristics or the patient population.)

Special points: Quetiapine is the AA most chemically similar to clozapine, but it does not show a risk of agranulocytosis. Numerous open-label studies involving more than 400 patients have shown quetiapine to be well tolerated and efficacious [15,16, Class II]. However, two double-blind trials documented no significant improvements in PD psychosis, and a third showed no difference in the efficacy of quetiapine versus clozapine [17–19, Class I]. A recent double-blind, placebo-controlled trial demonstrated the efficacy of quetiapine over placebo in improving visual hallucinations in PD [20••, Class I]. Because of its relatively mild extrapyramidal side effect profile and the lack of a monitoring requirement, quetiapine is a common first choice in treating PD psychosis.

Cost: About $160 for 25 mg (60 tablets), $290 for 100 mg (60 tablets), $538 for 200 mg (60 tablets).

Risperidone

Standard dosage: 1 to 3 mg/d.

Contraindications: Use with caution in elderly patients and those with seizure history, cardiovascular disease, dementia, diabetes mellitus, hepatic impairment, or suicide risk.

Main drug interactions: Avoid with triptorelin, haloperidol, sodium oxybate, or ziprasidone.

Main side effects: Extrapyramidal symptoms, including neuroleptic malignant-like syndrome and tardive syndromes, hyperprolactinemia, gastrointestinal hypomotility, weight gain, diabetes mellitus or hyperglycemia. Risperidone bears a black box warning of potential for increased mortality risk in elderly dementia patients taking conventional or atypical antipsychotics. (Most deaths are due to cardiovascular or infectious events it remains unclear if the deaths are due to antipsychotics or to patient characteristics or patient population.)

Special points: Risperidone should be avoided by clinicians treating PD psychosis because of numerous reports of motor worsening. Risperidone appears to more closely resemble first-generation typical neuroleptics, with a dose-dependent incidence of extrapyramidal side effects and prolactin elevation. Open-label studies have demonstrated improvement in PD psychosis with significant motor side effects [21–26, Class II]. The only double-blind study in PD reported no differences between groups treated with risperidone or clozapine, but slight motor worsening was unique to the risperidone-treated group [27, Class I].

Cost: Available in generic form cost for brand name is about $124 for 0.25 mg (30 tablets), $135 for 0.5 mg (30 tablets), and $159 for 1.0 mg (30 tablets).

Olanzapine

Standard dosage: 5 to 20 mg/d.

Contraindications: Use with caution in elderly patients and those with seizure history, cardiovascular disease, dementia, diabetes mellitus, hepatic impairment, or angle-closure glaucoma.

Main drug interactions: Avoid with potassium salts, triptorelin.

Main side effects: Extrapyramidal symptoms, including neuroleptic malignant-like syndrome and tardive syndromes, hyperprolactinemia, gastrointestinal hypomotility, weight gain, diabetes mellitus or hyperglycemia. Olanzapine bears a black box warning of potential for increased mortality risk in elderly dementia patients taking conventional or atypical antipsychotics. (Most deaths were due to cardiovascular or infectious events it remains unclear whether the deaths are due to antipsychotics or due to patient characteristics or patient population.)

Special points: A 2003 review estimated that olanzapine led to motor worsening in 40% of PD patients this agent should be avoided in the treatment of PD psychosis [28]. An early open-label trial demonstrated improved psychosis without motor worsening [29, Class II]. However, subsequent controlled and open trials documented both lack of improvement in psychosis and motor deterioration [30,31, Class I]. One particular study was discontinued

after six of seven olanzapine-treated subjects experienced significant motor decline [32, Class I].

Cost: About $229 for 2.5 mg (30 tablets), $277 for 5 mg (30 tablets), $336 for 7.5 mg (30 tablets), and $412 for 10 mg (30 tablets).

Aripiprazole

Standard dosage: 2 to 15 mg/d.

Contraindications: Use with caution in elderly patients and those with a seizure history, cardiovascular disease, dementia, diabetes mellitus, or suicide risk.

Main drug interactions: Avoid with sodium oxybate.

Main side effects: Extrapyramidal symptoms, including neuroleptic malignant-like syndrome and tardive syndromes, dizziness and hypotension, weight gain, diabetes mellitus or hyperglycemia. Aripiprazole bears a black box warning of potential for increased mortality risk in elderly dementia patients taking conventional or atypical antipsychotics. (Most deaths are due to cardiovascular or infectious events it remains unclear if the deaths are due to antipsychotics or due to patient characteristics or patient population.)

Special points: Several case reports and two open-label trials on aripiprazole in PD suggest that its efficacy and tolerability is drastically variable but there is clear worsening of motor symptoms [33–37, Class IV]. Though aripiprazole may be efficacious for some patients, it should not be used until further controlled trials are carried out in the PD population. Aripiprazole is a partial agonist at both D_2 and 5-HT_1 receptors.

Cost: About $445 for 30 tablets of 2, 5, 10, or 15 mg.

Ziprasidone

Standard dosage: 10 to 40 mg/d.

Contraindications: Use with caution in elderly patients and patients with seizure history, cardiovascular disease (especially arrhythmia and prolonged QT interval), dementia, diabetes mellitus, hepatic or renal impairment, or angle-closure glaucoma.

Main drug interactions: Avoid with amiodarone, antiarrhythmics (class 1A), apomorphine, arsenic trioxide, cisapride, dofetilide, dolasetron, dronedarone, droperidol, ibutilide, lopinavir/ritonavir, mefloquine, methadone, nilotinib, paliperidone, pentamidine, phenothiazines, pimozide, quinolones, QT prolongers, sotalol, tacrolimus, telithromycin, tetrabenazine, or triptorelin.

Main side effects: Prolongation of the QT interval, priapism, serotonin syndrome, extrapyramidal symptoms (including neuroleptic malignant-like syndrome and tar-dive syndromes), weight gain, diabetes mellitus or hyperglycemia, syncope. Ziprasidone bears a black box warning of potential for increased mortality risk in elderly dementia patients on conventional or atypical antipsychotics. (Most deaths are due to cardiovascular or infectious events it remains unclear if the deaths are due to antipsychotics or due to patient characteristics or patient population.)

Special points: Case reports and case series have suggested that ziprasidone may be a relatively safe treatment for PD psychosis, particularly when other AAs have proven

ineffective or have caused intolerable side effects [38–40, Class IV]. However, the use of ziprasidone has been limited because of its cardiac side effects. A review of its use in schizophrenia concluded that the extrapyramidal side effect profile of ziprasidone is "better than risperidone, the same as olanzapine, but not quite as good as quetiapine or clozapine" [41]. This would suggest that it should be avoided in PD.

Cost: About $427 for 20 mg (60 capsules), $433 for 40 mg (60 capsules), $514 for 60 mg (60 capsules).

Acetylcholinesterase inhibitors

Rivastigmine

Standard dosage: 1 to 6 mg/d.

Contraindications: Use caution in patients with cardiac conduction defects, asthma, chronic obstructive pulmonary disease (COPD), history of gastrointestinal (GI) bleeding or seizure, and in patients using NSAIDs.

Main drug interactions: Avoid with cholinergic agents, succinylcholine.

Main side effects: Seizures, urinary obstruction, bradycardia, hypotension, GI bleeding, nausea and vomiting, diarrhea.

Special points: Rivastigmine is the only cholinesterase inhibitor FDA-approved for the treatment of PD dementia. A large, double-blind, placebo-controlled trial using rivastigmine to treat visual hallucinations in PD patients with dementia documented significant improvements in neuropsychiatric symptoms [42, Class I]. Case series and one open-label study have also supported its efficacy and tolerability in PD psychosis [43,44, Class II–IV]. It inhibits both acetylcholinesterase and butyrylcholinesterase.

Cost: About $225 for 1.5, 3, 4.5, or 6 mg (60 capsules).

Donepezil

Standard dosage: 5 to 10 mg/d.

Contraindications: Avoid in patients with cardiac conduction defects, seizure disorder, asthma, COPD, ulcer history, or patients using NSAIDs.

Main drug interactions: Avoid with cholinergic agents, succinylcholine.

Main side effects: Seizures, urinary obstruction, bradycardia, hypotension or syncope, nausea and vomiting, diarrhea.

Special points: Donepezil is not FDA-approved for dementia in PD. It has the advantage of once-daily dosing. Several open-label studies in PD have shown improvements in psychosis, but motor side effects are variable [45–47, Class II]. Two placebo-controlled trials have not shown significant improvements in psychosis these results may reflect small sample sizes and/or low baseline symptom severity [48,49, Class I].

Cost: About $215 for 5 or 10 mg (30 tablets).

Tacrine

Standard dosage: 20 to 40 mg/d.

Contraindications: Avoid in patients with hepatic impairment, cardiac conduction defects, asthma, COPD, ulcer history.

Main drug interactions: Avoid with cholinergic agents, cimetidine, duloxetine, fluvoxamine, pimozide, succinylcholine, tizanidine.

Main side effects: Hepatic toxicity, seizures, bradycardia or heart block, nausea, vomiting, diarrhea, dizziness.

Special points: Tacrine is rarely used for the treatment of PD psychosis because of a high risk of hepatic toxicity. Alanine aminotransferase (ALT) needs to be measured every 2 weeks from week 4 to week 16, then every 3 months watch for GI bleeding. An early open-label trial showed complete resolution of psychotic symptoms in five of seven demented PD patients and improvement in the other two [50, Class II]. Exacerbation of parkinsonism has been reported in at least one PD patient treated with tacrine [51, Class IV].

Cost: About $310 for 10, 20, or 40 mg (120 tablets).

Galantamine

Standard dosage: 8 to 24 mg/d.

Contraindications: Avoid in patients with cardiac conduction defects, seizure disorder, asthma, COPD, hepatic or renal impairment, ulcer history.

Main drug interactions: Avoid with cholinergic agents, succinylcholine.

Main side effects: Seizures, urinary obstruction, bradycardia, hypotension or syncope, nausea and vomiting, diarrhea, GI bleeding, urinary obstruction, renal impairment, anemia.

Special points: Active at nicotinic ACh receptors. It has been suggested that galantamine's actions at nicotinic ACh receptors may prevent the downregulation of ACh that accompanies treatment with other cholinesterase inhibitors. Action at presynaptic nicotinic receptors on dopamine neurons may facilitate the release of dopamine and improve motor symptoms. A study using galantamine in nine PD patients with psychosis reported complete resolution of hallucinations in three patients and improvement in four others. Additionally, parkinsonism improved in six of the patients, but tremor worsened in the other three patients [52, Class III]. A recent open-label, randomized controlled trial of galantamine for PD dementia reported significant improvements in hallucinations with tremor worsening in 2 of 21 treated patients [53, Class II].

Cost: The brand name drug costs about $100 for 4, 8, or 12 mg (30 tablets). Available in generic form.

Other pharmacologic agents

Ondansetron

Standard dosage: 8 to 32 mg/d.

Contraindications: Use caution in patients with hepatic impairment or recent abdominal surgery.

Main drug interactions: Avoid with apomorphine, dronedarone.

Main side effects: Hypersensitivity reaction, bronchospasm, transient blindness, QT prolongation, headache, constipation, fatigue, diarrhea, dizziness, urinary retention.

Special points: This antinausea medication has been reported to possibly improve hallucinations in PD. Several early reports suggest that ondansetron may be useful in treating PD psychosis without motor worsening, presumably owing to its high selectivity for 5-HT_3 receptors. Two open-label trials conducted by the same group reported improved psychosis with limited side effects [54,55, Class II]. Positive results have not been reproduced by others [56], and the cost of the drug has prevented its being tested further in the PD population.

Cost: Expensive brand-name drug costs about $244 for 4 mg (10 tablets) and $1169 for 8 mg (30 tablets). Available in generic form.

Memantine

Standard dosage: 10 to 20 mg/d.

Contraindications: Use with caution in elderly patients and those with renal or hepatic impairment or a history of seizures.

Main drug interactions: Avoid with pemetrexed.

Main side effects: May cause Stevens-Johnson syndrome, seizures, dizziness, confusion, headache, constipation.

Special points: Memantine is FDA-approved for the treatment of moderate to severe Alzheimer's disease (AD). It has been suggested that memantine may exhibit neuroprotective effects in PD through NMDA antagonist effects, which prevent glutamatergic overstimulation and resultant cell death and disruption. Most clinical trials with memantine in PD have not been specifically designed to show changes in neuropsychiatric symptoms. However, limited data suggest that memantine may indeed have positive effects on agitation/aggression, appetite, and irritability/lability [57–59]. A case study in AD reported an antipsychotic dose-sparing effect [60, Class IV]. However, memantine has caused worsening psychotic symptoms and confusion in some patients who have dementia with Lewy bodies, PD, or AD [61,62].

Cost: About $180 for 5 or 10 mg (60 tablets).

Antidepressants

Standard dosage: Depends on the antidepressant.

Contraindications: Use with caution in elderly patients and those with hepatic impairment, seizure disorder, mania or hypomania, alcohol use, or age less than 25 years.

Main drug interactions: Avoid with linezolid, pimozide, thioridazine use with caution with a monoamine oxidase (MAO) inhibitor.

Main side effects: Worsening of depression, serotonin syndrome, neuroleptic malignant-like syndrome, withdrawal syndrome, mania, seizures, hyponatremia commonly nausea, headache, insomnia, diarrhea, dry mouth, erectile dysfunction, somnolence, tremor. Antidepressants bear a black box warning regarding their potential to increase the risk of suicidality in children, adolescents, and young adults with major depressive or other psychiatric disorders, especially during the first months of treatment.

Special points: Certain antidepressants (eg, clomipramine and citalopram) may improve psychotic symptoms in PD, especially in patients with concurrent depression [63,64, Class IV]. However, many antidepressants have been shown to induce or exacerbate psychotic symptoms [65,66]. The literature on antidepressants for the treatment of PD psychosis comprises only case reports controlled trials are needed. Based on this limitation, they should not be used as antipsychotic therapy.

Cost: Depends on the drug several drugs are available in generic form.

Other treatments

Reduction of anti-PD medication regimen

Standard procedure: Gradual removal of anti-PD medications in the following order: anticholinergics, amantadine, MAO-B inhibitors, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, levodopa.

Complications: Worsening motor symptoms abrupt withdrawal of medications may cause neuroleptic malignant-like syndrome.

Special points: Use of the short-acting formulation of levodopa, as compared with the controlled-release form, may reduce the risk of accumulating adverse effects. Withdrawal of amantadine after chronic use can lead to acute delirium [67].

Cost: Inexpensive.

Psychological interventions

Standard procedure: Cognitive behavioral therapy (CBT) involves modifying maladaptive thoughts and teaching coping strategies to reduce distress in a highly individualized, supportive setting.

Special points: Psychosis may lead to or exacerbate disturbing emotional problems such as depression and anxiety. Self-management skills and structured psychological interventions may be beneficial for management of PD psychosis early on, when insight is intact. One study reported that many PD patients use self-driven coping strategies to manage hallucinations and that these patients are less bothered by their symptoms [68]. CBT for psychosis has been shown to be effective [69,70, Class I], but the literature is limited to schizophrenia. Thus, there is a need for studies addressing this promising area of research in the PD population.

Cost: Variable short-term CBT can be carried out in 8 to 24 sessions.

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