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Geriatric Disorders (K Zdanys, Section Editor)

Treatment of Parkinson's Disease Psychosis

Leora L. Borek, MD[1,*]
Joseph H. Friedman, MD[2]

Address
[*,1]Department of Psychiatry, NewBridge on the Charles, Harvard Medical School, 46 McLean street, Wellesley, MA, 02481, USA
Email: Leolisa@yahoo.com
[2]Movement Disorders Program, Butler Hospital Department of Neurology, Warren Alpert Medical School of Brown University, Providence, RI, USA

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Abstract

Purpose Psychotic symptoms in Parkinson's disease are relatively common and include hallucinations, illusions, and delusions. Psychosis is a major cause of disability and is one of the most distressing symptoms for both patients and caregivers. The management of psychosis is often complex and challenging and involves determining the degree and severity of psychotic symptoms and whether intervention is required. In this review, the authors describe the phenomenology and risk factors of Parkinson's disease psychosis (PDP) and current evidence-based treatment options.
Recent findings In randomized, double-blind, placebo-controlled trials, pimavanserin was found to be effective and well-tolerated in PDP but its onset of benefit takes 4–6 weeks. Present reviews of evidence-based medicine suggest that low doses of clozapine can provide benefit without worsening PD motor symptoms. While quetiapine is frequently used, its efficacy is not supported by randomized, double-blind, placebo-controlled trials.
Summary Clozapine and pimavanserin have proven efficacy in the treatment of PDP, without impairing motor function. Therefore, these agents should be considered first-line treatment of PDP at this time. Although quetiapine did not show efficacy in PDP, many PD experts use it as it does not worsen motor function and lacks the blood monitoring requirement of clozapine.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is clinically defined by its motor signs including resting tremor, rigidity, bradykinesia, and postural instability coupled with the absence of atypical features such as eye movement abnormalities, ataxia, or corticospinal signs [1, 2]. PD is diagnosed clinically with definitive diagnosis obtained at autopsy. PD involves the loss of pigmented, dopaminergic neurons in the substantia nigra and locus coeruleus and the presence of Lewy body neuronal inclusions. However, these criteria are under review with the identification of patients who met clinical criteria for PD but lacked Lewy bodies at autopsy.

PD is more common in the elderly and there is usually no family history. Although PD is a movement disorder, psychiatric disturbances are prevalent, including depression, anxiety, apathy, psychosis, and dementia, and are often under-recognized and undertreated [3•]. Effective treatment of psychosis in PD improves quality of life for patients and may reduce the need for institutionalization [4].

The first formal description of PD was in "An Essay of the Shaking Palsy" by James Parkinson in 1817 [5]. Psychotic symptoms and dementia were not present in James Parkinson's patients, "the senses and intellects being uninjured", as psychosis is rare in patients who are not on PD medications. It has only been in the past 50 years, with the introduction of levodopa and other PD medications, that neuropsychiatric disorders have gained recognition as being common and as disabling as the motor symptoms of PD.

Phenomenology and risk factors of Parkinson's disease psychosis

Parkinson's disease psychosis (PDP) has a lifetime prevalence of up to 60% [4, 6]. It is a major cause of disability and reduces quality of life for both patients and their caregivers [4]. The pathophysiology of PDP is unknown although theories abound.

Psychotic symptoms in PD are primarily comprised of hallucinations, illusions, and delusions [3•, 7•]. Hallucinations occur in approximately 30% of medication treated patients. The hallucinations consist of "minor hallucinations," "presence hallucinations," and illusions." Minor hallucinations" are fleeting images in the peripheral visual field that disappear when looked upon and often precede the development of hallucinations that are easy to see. In "presence hallucinations," there is a perception that something is present when it is not, such as when patients "feel" there is someone behind them whom they cannot see or hear. Patients may also experience illusions, which are distorted interpretations of real images.

Hallucinations are primarily visual, with auditory being half as common [7•]. This is in contrast to psychotic symptoms in primary psychiatric disorders, in which hallucinations are primarily auditory and often have emotional content, such as hearing negative or derogatory voices [8, 9]. In PD, the visual hallucinations are usually of people, and sometimes animals, who ignore the patient. They are generally devoid of emotional content and the patient may retain insight into the unreality of the image. They often occur in low stimulus environments, such as in the evening, and may last a few seconds or hours. When the patient talks to the hallucinations, they usually do not respond and may disappear. The hallucinated figures may recur a few times per week in the same clothing and may perform the same activities, such as playing cards, watching television, or reading books. Auditory hallucinations may accompany

the visual, with patients having conversations with the images, but more often auditory hallucinations are unrelated, such as hearing a radio in another room or conversations in which the words are not understood.

Delusions occur in approximately 5–10% of medication-treated patients and are often a hallmark of a more advanced disease and comorbid dementia. Delusions are defined as irrational beliefs that are not based on facts. In PDP, delusions most often develop in the setting of hallucinations. They are primarily paranoid in nature [7•] and are often distressing to the patient. The most common delusions have jealous themes, such as believing the spouse is having an affair and delusions that someone is taking their belongings. Capgras syndrome, in which the patient believes a closely related person has been replaced by an imposter, can also occur but is less common. Since vivid dreams are often present in levodopa (L-Dopa)-treated patients, it is important to distinguish these from delusions. For example, a patient may inquire about an event that took place in a dream as if it occurred in real life but the family believes it to be a delusion.

Risk factors for developing PDP include anti-PD medications, dementia, REM sleep behavior disorder, visual impairment, and longer disease duration [10]. PD patients often develop psychosis after many years on stable doses of medications. This likely occurs because PD is progressive and psychotic symptoms increase with dementia, which increases with disease duration.

Approach to treatment

Managing PDP is often complex and challenging, in part because most antipsychotic medications adversely affect motor function, while dopaminergic medications used to treat PD can worsen psychosis. Treatment of PD involves determining the degree and severity of psychotic symptoms and whether intervention is required. Most patients are not bothered by hallucinations and do not require treatment. However, hallucinations may worsen and warrant treatment, particularly if the patient requires an increase in medication to treat motor dysfunction.

Management of PDP involves a stepwise process, summarized in Table 1:

1. Exclude medical illnesses, such as infections and metabolic disturbances, as these can cause delirium with psychosis.

Table 1. Algorithm for the management of PD psychosis

1. Exclude medical causes.
2. Review and modify non-PD medications.
3. Modify and reduce PD medications.
4. Treat with cholinesterase inhibitors.
5. Initiate pimavanserin.
6. Consider ECT.

2. Review medication regimen. It is important to note that many patients develop psychosis without a change in medication due to the disease progression.
3. Discontinue any nonessential, non-PD psychoactive medications. Psychotic symptoms are generally medication related, such as from the introduction of a new drug or an increase in drug dose. Anticholinergic medications (such as medications to treat overactive bladder), anxiolytics, antidepressants, and narcotic pain medications may play a role in PDP and should be simplified or discontinued.
4. Modify and reduce PD medications to the lowest tolerable dose without exacerbating motor symptoms. The recommendations are to reduce or stop anticholinergic drugs, amantadine, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors in that order and then consider reduction in L-Dopa.
5. Treat psychosis with cholinesterase inhibitors or antipsychotic medications.
6. If there is no improvement in psychosis or if patients cannot tolerate medications, then consider electroconvulsive therapy (ECT).

Medications

Not all antipsychotic medications are used to treat PDP, and most are off-label. All antipsychotic drugs carry a black box warning issued by the United States Food and Drug Administration (US FDA) due to an increased risk of death, and this warning includes pimavanserin despite the absence of data for this drug.

Clozapine

Clozapine was the first drug studied for the treatment of PDP. The initial studies demonstrating its efficacy in treating PDP involved case reports [11, 12] followed by an open-label series [13]. In a chart review from four large PD clinics, the majority of PD patients had a complete resolution of psychosis and an improvement in depression, anxiety, and sleep on clozapine [14]. In a review article summarizing open-label reports of clozapine treatment in over 400 PDP patients, clozapine was effective in treating psychosis, and motor function was not compromised [15]. In addition, clozapine improved tremor in PD patients [14, 16, 17•].

The first double-blind, placebo-controlled trial (DBPCT) of clozapine involved large doses [16], similar to those used in the treatment of patients with schizophrenia. Patients were started on 25 mg/day and increased by 25 mg/day, and this produced intolerable sedation [16]. Two multicenter DBPCT demonstrated that low-dose clozapine was effective in PDP, did not worsen motor function, and improved tremor [17•, 18]. In the first study, the mean effective clozapine dose was 24.7 mg/day [17•], and in the second study, the mean effective clozapine dose was 35.8 mg/day [18]. Both studies measured efficacy with positive symptom scales validated only in schizophrenia, not in PD, and used more than one outcome scale. The studies concluded that treatment with clozapine at low doses ameliorates psychosis, improves tremor, and does not

affect mobility [17•, 18].

It is recommended that clozapine be instituted at 6.25 mg/day, but 12.5 mg or 25 mg may be used to improve sleep or behavior at night. The most common adverse side effects of clozapine are sedation and orthostatic hypotension and in some cases, hypersalivation. Increased sedation may worsen confusion in patients with dementia. The risk of clozapine-induced agranulocytosis is 1–2% and is thought to be unrelated to dose. Patients treated with clozapine must be closely followed with blood monitoring protocols. In the USA, weekly testing is required for 6 months, followed by biweekly for 6 months, followed by every 4 weeks testing. Data do not exist to assess whether low doses of clozapine are associated with the same or lessened risk as higher doses. In one report, granulocytopenia occurred in PD patients on low doses of clozapine, even after more than a year into treatment [19]. Clozapine is also associated with myocarditis and the metabolic syndrome, but these rarely occur at the low doses used in PDP treatment.

Quetiapine

Quetiapine is often used in the treatment of PDP because it lacks parkinsonian side effects and has no blood monitoring requirement. Of the four randomized, placebo-controlled trials of quetiapine [20–23], three did not report significant improvement of psychosis with quetiapine [20–22] and the fourth had too few subjects to conclude benefit [23]. The studies suggest that quetiapine is not effective in treating PDP, although it did not worsen motor function. Although quetiapine did not show efficacy in PDP, many PD experts use it as it does not worsen motor function and lacks the blood monitoring requirement of clozapine [24]. Quetiapine should be started at a low dose of 12.5 mg or 25 mg/day in order to reduce adverse side effects. The main adverse side effects of quetiapine in PD patients are sedation and orthostatic hypotension.

Olanzapine

Olanzapine was found to be poorly tolerated in PDP patients. Four DBPCT demonstrated harmful motor effects of olanzapine in this population [25–28]. One study was closed prematurely by the safety monitoring committee and advised against its use in PD patients [25]. The target doses used in these trials were similar to those used in schizophrenia. The studies failed to show significant efficacy in treating PDP and were associated with an increased prevalence of adverse effects [25–28].

Melperone

A multicenter DBPCT demonstrated that melperone was not effective in the treatment of PD psychosis [29]. Similar to clozapine and quetiapine, melperone did not worsen motor function in PD patients [29].

Other atypical antipsychotic drugs

Risperidone was found to worsen motor function in patients with PDP [30–32]. Open-label studies of aripiprazole and ziprasidone did not support efficacy for use in PDP [33, 34]. To date, there are no reports on the efficacy of iloperidone, paliperidone, or lurasidone in the treatment of PDP, but as these medications

may cause parkinsonism in healthy adults, they may not be well-tolerated in PD.

Pimavanserin

Pimavanserin is a selective serotonin 5-HT2A inverse agonist and is the first antipsychotic drug without dopaminergic, adrenergic, histaminergic, or muscarinic affinity. In PD, visual hallucinations are associated with an increased number of 5-HT2A receptors in visual processing areas [35]. With its receptor selectivity, pimavanserin has been developed to provide antipsychotic benefit without the adverse effects of current antipsychotics. Pimavanserin is the only US FDA-approved drug for the treatment of PDP.

Pimavanserin has been found to be effective in PDP [36, 37•]. In a randomized, double-blind, placebo-controlled 4-week trial, patients receiving pimavanserin demonstrated significant improvement in psychosis without worsening of motor function [36]. In a larger, multicenter DBPCT, 95 subjects received pimavanserin and 90 subjects received placebo [37•]. The benefit of pimavanserin was seen at 4 weeks and increased further by the endpoint of 6 weeks [37•]. There was a greater than twofold benefit of drug over placebo with the primary outcome (Survey Assessment of Psychotic Symptoms) improving by 37% in the active arm versus 14% in the placebo. There was also significant improvement in the secondary outcomes of caregiver burden, nighttime sleep, and daytime wakefulness [37•]. Pimavanserin is administered as a single dose of 34 mg/day. Pimavanserin was well-tolerated with few side effects and was not associated with exacerbation of motor disability, sedation, or other safety concerns [37•].

In a retrospective study of pimavanserin in a movement disorders clinic, pimavanserin was well tolerated, with no adverse effects reported [38]. Pimavanserin improved psychosis in 10/15 subjects, including 10 with idiopathic PD, 4 with dementia with Lewy bodies, and 1 with multiple-system atrophy [38]. In a second chart review of 26 parkinsonian patients with psychosis treated with pimavanserin, 50% of patients found pimavanserin to be useful and continued to take it for at least 6 weeks [39]. In another retrospective chart review, pimavanserin was well-tolerated and effective in 17 parkinsonian patients as both monotherapy and adjuvant treatment and facilitated the reduction and cessation of dopamine receptor blockers used to treat PDP [40].

Cholinesterase inhibitors

Cholinesterase inhibitors are used to treat dementia. There are few data on cholinesterase inhibitors in PDP. Two open-label trials of donepezil, one with 10mg [41] and one with 5 mg [42], reported improvement in psychotic symptoms and a deterioration in motor disability was present in 2/8 subjects in the 5 mg trial [42]. Rivastigmine has been reported to be helpful in a small open trial [43]. One large multicenter DBPCT of rivastigmine for dementia included patients with psychosis [44]. The study reported improvement in visual hallucinations in dementia associated with PD, but adverse effects were reported more frequently by

rivastigmine-treated patients [44]. The most common adverse side effects of cholinesterase inhibitors are loose stools, diarrhea, and indigestion.

Electroconvulsive therapy

In isolated case reports, ECT improved psychosis in patients who failed to respond to antipsychotic medications [45–47]. Combined ECT and clozapine improved drug-induced psychosis in PD patients who did not respond to clozapine monotherapy [45]. ECT often produces beneficial motor responses which may be sustained for a few weeks but are never long-lasting [46, 47].

Conclusion

PD is increasingly being recognized as a neuropsychiatric disease with significant behavioral symptoms. Psychotic symptoms are common and are associated with significant distress to the patient and caregiver. Effective treatment of psychosis in PD improves quality of life for patients and may reduce the need for institutionalization. The initial management of PDP is to exclude medical causes of delirium, such as infections. This is followed by modification of drugs that may be contributing to the psychosis, particularly psychoactive medications used to treat bladder symptoms, sedation, and pain. If the patient remains psychotic, medications to treat PDP may be indicated.

In placebo-controlled trials, clozapine and pimavanserin demonstrated significant efficacy in treating PDP and are considered first-line treatment of PDP at this time, although quetiapine may be considered. As of January 2018, the International Parkinson's Disease and Movement Disorders Society endorsed recommendations published in 2013, recommending that clozapine and not quetiapine be used in the treatment of PD [48]. It is not yet updated to include the study results of pimavanserin.

Pimavanserin does not produce clinical improvement until 4 to 6 weeks whereas the response of clozapine and quetiapine is evident within 1 week. In cases in which the psychotic symptoms are tolerated and a response lag of 4–6 weeks is acceptable, pimavanserin should be instituted. When a rapid reduction in psychotic symptoms is required, it is recommended that quetiapine or clozapine be initiated.

Olanzapine, risperidone, and ziprasidone did not demonstrate clear benefit in PD and were associated with an increase in adverse effects. Thus, these drugs should be avoided in the treatment of PDP. Cholinesterase inhibitors may be considered in PDP if the psychotic symptoms are minor and the patient has mild to moderate dementia. It is unclear how effective these drugs are or how quickly they work, but a rapid response is unlikely. If patients are unable to tolerate antipsychotic medications, ECT should be considered.

Future studies should focus on measuring long-term outcomes of pimavanserin (beyond 6 weeks) related to efficacy and safety. Such studies would ensure effects are maintained over longer periods of time. In addition, head-to-head comparisons with other agents, such as

clozapine, will further clarify the role of pimavanserin in the treatment of PDP.

Compliance with ethical standards

Conflict of interest
Dr. Joseph H. Friedman declares honoraria from Springer Press, Cambridge University Press, and Medlink as well as research support from the NIH and MJ Fox Foundation. Dr. Leora L. Borek declares no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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