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Treatment of psychotic symptoms in patients with Parkinson disease

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Abstract

Persistent psychotic symptoms will develop in up to 60% of patients with Parkinson disease (PD). The initial approach to the management of PD psychosis (PDP) begins with addressing concurrent systemic conditions associated with psychotic behavior, such as delirium, medical conditions (eg, infections), psychiatric disorders (eg, major depression with psychotic symptoms, mania, schizophrenia), and substance misuse or withdrawal. A review of current medications is recommended, and medications that may trigger psychotic symptoms should be eliminated. If possible, antiparkinson medications should be reduced to the minimum therapeutic dose or discontinued in a sequential manner. Generally, dose reduction or discontinuation of anticholinergics is attempted first, followed by that of monoamine oxidase B inhibitors, amantadine, dopamine agonists, catechol-*O*-methyltransferase inhibitors, and lastly carbidopa/levodopa. The aim of antiparkinson medication dose reduction is to achieve a balance between improving drug-related psychotic symptoms and not significantly worsening the motor symptoms of PD. If additional measures are needed for chronic PDP treatment, the use of second-generation antipsychotics, such as clozapine, pimavanserin, or quetiapine, must be considered. The first-generation antipsychotics (eg, fluphenazine, haloperidol) are not recommended. In the patient with comorbid dementia, the addition of a cholinesterase inhibitor might also be beneficial for PDP. The choice of agent is based on patient-specific parameters, potential benefit, and side effects.

Keywords: Parkinson disease, psychosis, movement disorders, nonmotor symptoms, pimavanserin, clozapine, quetiapine, antipsychotics

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Introduction

Parkinson disease (PD) is a neurodegenerative disorder mainly defined and diagnosed on the basis of motor impairment. However, it is understood that nonmotor symptoms, such as PD psychosis (PDP), are underrecognized and undertreated.[1,2] The underrecognition of PDP may be due to providers placing a greater emphasis on treating motor symptoms, a lower awareness among providers of PDP, underreporting or nonrecognition of PDP symptoms by patients, family members, or caregivers, or the lack of appealing treatment options for PDP. Until recently, treatment options for PDP were limited.

Considering the emergence of new developments in the treatment of PDP, it is imperative for pharmacists to remain current with advances in therapy to better provide care and services to this population.

Epidemiology and Impact

Persistent psychotic symptoms will develop in up to 60% of patients with PD and in up to 75% of patients with PD and concurrent dementia.[2,3] Health care costs are higher for patients with PDP compared with those with PD without psychosis. In a Medicare survey of claims data from 2000 to 2010, patients with PDP had higher all-cause costs and resource use.[2] The highest annual cost differentials were found in long-term care costs ($31 178 for PDP versus $14 461 for PD without psychosis), skilled nursing facility costs ($6601 for PDP versus $2067 for PD without psychosis), and inpatient costs ($10 125 for PDP versus $6024 for PD without psychosis). Longer stays in long-term care and the use of associated resources were major cost drivers. The presence of psychotic symptoms is not only an independent cost-driving factor, but also intrusive to the patient's daily life and a significant determinant of increased caregiver burden.[4] Additionally, the presence of hallucinations and psychotic symptoms is an independent risk factor for nursing home placement and mortality in patients with PD.[5,6]

Psychotic symptoms in PD traditionally include hallucinations and delusions. However, minor psychotic phenomena are also common and include sense of presence (a sensation that someone is nearby, including behind the person, when no one is there and no one is seen), passage hallucinations (brief vision of a person, animal, or other object that passes sideways in the peripheral visual fields), and illusions (a distorted sensory perception of a real stimulus). Even the presence of minor psychotic phenomena can have a negative impact. In a community-based PD sample, minor psychotic phenomena of PDP were associated with more depressive symptoms and worse quality of life compared with PD without current psychotic symptoms.[7] Parkinson disease psychosis is also a primary reason and predictor for hospitalization, admission to long-term residential care facilities, and increased mortality.[5,6,8] When patients with PDP are admitted to long-term residential care facilities, the associated behaviors can be disruptive and increase long-term residential care personnel caregiver burden.

Clinical Presentation and Cases

The National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS) sponsored a workshop on PDP, and provisional diagnostic criteria were published in 2007 (Table).[9] It is important for providers to recognize the clinical spectrum of symptoms associated with PDP. Symptoms will range from mild visual distortions (illusions) and the sense of a "presence" (eg, someone unseen in the house) to fully formed, complex hallucinations (eg, visual images of people) to delusions (fixed, false beliefs). The most

Take Home Points:

1. Risk factors and correlates for the development of Parkinson disease psychosis (PDP) include advanced age, comorbid medical conditions (eg, dementia, depression, REM sleep behavior disorder, visual disorders), dopaminergic medications, and PD severity and duration.

2. Symptoms of PDP include hallucinations and delusions. The presence of intermittent, nondisruptive hallucinations must be monitored, because they will likely increase in severity and evolve into other disruptive psychotic behavior over time.

3. Identification of medications that can potentially trigger psychotic symptoms is essential. These include medications with anticholinergic properties, antiparkinson agents, muscle relaxants, and sedative-hypnotics. Attempts to decrease or discontinue potentially offending medications are recommended (with a preferred priority on non-PD medications).

4. If the patient's psychosis does not sufficiently improve after treatment of underlying medical conditions, alteration of the medication regimen, or through the use of nonpharmacologic strategies, the use of second-generation antipsychotics, such as clozapine, pimavanserin, or quetiapine, should be considered. Other antipsychotics (eg, aripiprazole, olanzapine, risperidone) are not recommended because of insufficient evidence of efficacy along with risk of worsening parkinsonism.

5. Pimavanserin is the first and only US Food and Drug Administration–approved medication for the treatment of hallucinations and delusions associated with PDP, and studies have indicated it does not worsen motor function.

TABLE: National Institute of Neurological Disorders and Stroke–National Institute of Mental Health provisional diagnostic criteria for Parkinson disease psychosis[a]

Features

1. Occurs in patients with established diagnosis of Parkinson disease
2. At least 1 symptom of: hallucinations, illusions, false sense of presence, delusions
3. Symptoms present for at least 1 month
4. May occur with or without: dementia, insight, medications for Parkinson disease

Differential diagnoses

Psychosis due to delirium, dementias, depression, schizophrenia, other psychiatric disorders

[a]Adapted from Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord. 2007;22(8):1061-8.

common type of complex hallucinations is visual, although other sensory modalities may be affected. Auditory hallucinations have been reported in 8% of patients with PDP, but predominant auditory symptoms are uncommon.[10] Hallucinations may initially be nondisruptive, such as seeing ants on the floor or hearing music. Patients may report such hallucinations are not disturbing and may be interesting or even entertaining. Because these types of hallucinations are not disruptive, patients may not be as likely to report their occurrence to caregivers or clinicians. Over time, and with the progression of PD, the nondisruptive quality of hallucinations tends to diminish and is replaced by an alarming or more malignant quality that disrupts daily activities.[11]

Delusions are a more disruptive symptom and can affect approximately 25% of non-demented patients with PD and up to 50% of patients with PD and dementia.[4] Delusions often are characterized by paranoid thoughts (eg, themes of spousal infidelity or intent of harm by familiar people). The resulting feelings of distrust can rapidly result in accusatory and disruptive behavior by the patient and make caregiving difficult.

Some clinicians choose to postpone treatment if symptoms are infrequent and nonthreatening and if the patient retains insight. However, in 1 study, 96% of patients with PDP characterized as having nondisruptive hallucinations, at baseline, experienced progression of PDP to delusions and disruptive psychotic behavior.[11] Thus, the presence of intermittent "benign" hallucinations must be monitored, because they will likely increase in severity and evolve into other disruptive psychotic behavior over time.

Consider a Treatment Plan for the Following Cases

Case 1

A 73-year-old patient received a diagnosis of PD 10 years ago. The patient has a history of levodopa-induced dyskinesias, orthostatic hypotension, visual hallucinations, paranoid delusions, insomnia, and weight loss. Psychotic behavior was noticed more than a year ago, and within the past 2 months the spouse has reported increasing difficulty caring for the patient because the episodes of delusional behavior have worsened, and the patient is frequently argumentative and paranoid. The patient believes the spouse is having an affair with someone who lives somewhere in the house and that they spy on the patient. The patient believes the spouse is "hiding" the person. The patient also has visual hallucinations of men loitering on the patio and believes these "patio people" conspire with a television news anchor to spy on the patient. Medications include amantadine 100 mg 3

times daily, amitriptyline 25 mg at bedtime, carbidopa/levodopa 25/100 mg 4 times daily, pramipexole 1 mg 3 times daily, and rasagiline 1 mg daily. Laboratory and imaging studies are unremarkable. What are the plausible next steps for management of psychotic symptoms?

Case 2

A 62-year-old patient with PD is seen in the clinic for new-onset psychosis. Two months prior, the dose of carbidopa/levodopa was increased because of worsening motor symptoms. Within a month, the patient started having delusions, and 2 weeks before the clinic visit, the patient's mental state gradually worsened. The patient presents with paranoid delusions. The patient's only child has schizophrenia, but otherwise has no known family psychiatric history. A physical examination reveals normal vital signs, disorientation to time and place, motor symptoms of PD (ie, resting tremor, cog-wheel rigidity, bradykinesia). Laboratory and imaging studies are unremarkable. Current medications are carbidopa/levodopa, and hydrochlorothiazide for hypertension. Current diagnosis is acute dopamimetic-induced psychosis. Because of the severity of the PD motor symptoms, the dosage of carbidopa/levodopa was not reduced. Treatment with quetiapine 12.5 mg once daily with an increase to twice daily was initiated. Because of the lack of response, the dose was increased to 25 mg twice daily. The parkinsonism deteriorated significantly, and the quetiapine was discontinued. Given the patient's vulnerability to antipsychotic-induced worsening of parkinsonism, what are the plausible medications for the management of psychotic symptoms?

Etiology, Risk Factors, or Correlates

The exact pathoetiology of PDP has not been identified. Nonpharmacologic risk factors and correlates for the development of PDP include advanced age, comorbid medical conditions (eg, dementia, depression, REM sleep behavior disorder, visual disorders), and PD severity and duration.[12] The complexity of PDP pathoetiology is apparent from a number of recent reviews and studies suggesting multifactorial abnormalities, including metabolic, neurotransmitter, sensory pathway, and structural brain alterations, as well as changes in visual processing and sleep disorders.[12-14] Although exposure to PD medications is not a requirement for development of PDP, multiple medication classes, such as amantadine, anticholinergics, catechol-O-methyltransferase inhibitors, dopamine agonists, levodopa, and monoamine oxidase type B inhibitors, have all been associated with triggering PDP.[13] In particular, up to one third of patients exposed to chronic dopaminergic therapy will experience visual hallucinations.[15] Other pharmacy elements, such as

polypharmacy burden, levodopa-equivalent doses, and use of certain medications (eg, anticholinergics, antidepressants, anxiolytics, sedative hypnotics), are also associated with the development of PDP symptoms.

Multiple processes involving different neurotransmitters (dopamine, serotonin, and acetylcholine) have all been implicated in the development of PDP.[12] Traditionally, hypersensitivity of mesocortical and mesolimbic dopamine receptors (resulting in dopaminergic overstimulation) has been proposed to kindle psychotic behavior. This has been the long-standing neurotransmitter/pharmacologic rationale behind PDP.[16] However, more recent studies indicate the serotoninergic system plays a more substantive role in the development of PDP than previously thought.[14,17] In PD, degeneration of presynaptic serotonin neurons is accompanied by a presumably compensatory upregulation of postsynaptic serotonin (5-hydroxytryptamine [5-HT_{2A}]) receptors, resulting in psychotic symptoms. In 1 study using positron emission tomography brain imaging, 5-HT_{2A} receptor activity was increased in the ventral visual pathway of patients with PDP.[17] This study demonstrated that serotonin receptors may govern the emergence of visual hallucinations through increased binding (ie, increased serotoninergic activity) within the ventral visual pathway. An autopsy study using autoradiographic binding to define 5-HT_{2A} receptors found increased binding in the inferolateral temporal cortex for patients with PD and hallucinations compared with patients with PD without hallucinations.[14] Overall, recent investigations have revealed that overstimulation of postsynaptic 5-HT neurons (particularly at 5-HT_{2A} receptors) contributes to psychotic symptoms in PD.

Assessment and Treatment of PDP

The initial approaches to the management of patients with PDP begins with establishing the diagnosis of PDP and ruling out other conditions associated with psychotic behavior, such as delirium, psychiatric disorders, substance misuse or withdrawal (eg, alcohol, amphetamines, benzodiazepines, narcotic analgesics, cannabis), and drug adverse effects or toxicity.[9,12,13] A careful history taken from caregivers and family members can aid in the clarification of preexisting conditions and potential triggers. Delirium is common in PD, especially among those with comorbid cognitive impairment, and must be considered with any acute decline in cognition, function, or mental state.[9,12,13] Patient assessment for delirium includes a targeted physical examination, a review of the medication profile, and broad screening investigations (including electrolytes; renal, thyroid, and liver function; complete blood count; urinalysis; C-reactive protein; chest radiograph), as well as those specific to the patient's medical history (eg, electrocardiogram, electroencephalogram, neuroimaging).[9,12,13] Infections must be ruled out (eg, respiratory and urinary tract) and oxygenation assessed (particularly if the patient has an underlying pulmonary condition).[9,12,13] Additionally, an assessment for acute or chronic pain is recommended. Once the underlying cause is treated, the patient must be monitored over time to ensure resolution of the delirium.

Medication effects are remediable triggers of PDP.[9,12,13] For patients on medications (see Case 1), identification of medications that can potentially trigger psychotic symptoms is an essential step in designing a treatment approach. These include medications with anticholinergic properties (eg, benztropine, diphenhydramine, trihexyphenidyl, tricyclic antidepressants, medications for overactive bladder), antiparkinson agents, muscle relaxants, and sedative-hypnotics. Attempts to decrease or discontinue potentially offending medications are recommended (with a preferred priority on non-PD medications). If dose adjustment of non-PD medications is not viable, then antiparkinson medications should be reduced to the minimum therapeutic dose or discontinued in a sequential manner, starting with the highest risk-to-benefit ratio.[9,12,13] Generally, dose reduction or discontinuation of anticholinergics is attempted first, followed by monoamine oxidase B inhibitors (rasagiline, selegiline), then amantadine, dopamine agonists (eg, pramipexole, ropinirole, rotigotine), catechol-O-methyltransferase inhibitors (eg, entacapone, tolcapone), and lastly carbidopa/levodopa. The aim of antiparkinson medication dose reduction is to achieve a balance between improving drug-related psychotic symptoms and not significantly worsening the motor symptoms of PD. In 1 study, 60% of patients who had a dose reduction of antiparkinson medications experienced clear improvements in psychotic symptoms that obviated a need for antipsychotic treatment; however, 40% had a worsening of parkinsonism or dyskinesia.[18] Overall, addressing the underlying medication and/or systemic illness triggers resulted in sufficient resolution of psychotic symptoms in the short term. However, patients who are susceptible to psychosis triggered by medications or systemic illness may be at greater risk for developing persistent PDP in the long term. About 50% of patients with initial resolution of psychotic symptoms experienced recurrence within 2 years and required antipsychotic treatment.

Nonpharmacologic Approaches

Nonpharmacologic approaches for the management of PDP should be used along with pharmacotherapy. If hallucinations or illusions occur during low-light environments, the use of room lighting may help. Referral for an eye examination to identify vision deficits is recommend-

ed. Although PDP may occur in the absence of comorbid dementia, it is more likely to happen in those with cognitive impairment or dementia. In such cases, non-pharmacologic approaches that benefit behaviors associated with dementia may have benefits for psychosis. Such approaches include person-centered care; optimization of sensory, communication, and physical function (eg, occupational or activities programs, music and sensory therapies); optimization of the environment (eg, bright lights); and behavioral/psychosocial strategies (eg, brief psychosocial therapy).[19-22]

Pharmacologic Approaches

If the aforementioned measures are insufficient to provide adequate control of psychotic symptoms, then the use of antipsychotic therapy must be considered. Of note, first-generation antipsychotics (ie, those possessing strong dopamine receptor–blocking properties, such as fluphenazine or haloperidol) are not recommended because of the substantive risk of causing harm and worsening motor features of PD.[23] For example, haloperidol is associated with increased all-cause mortality in patients with PD (hazard ratio, 5.08; 95% confidence interval [95% CI], 3.16 to 8.16, over nonuse).[24]

US Food and Drug Administration–Approved Agents for PDP: Pimavanserin

Pimavanserin is a $5\text{-}HT_{2A}$ inverse agonist indicated for the treatment of hallucinations and delusions associated with PDP.[25] Pimavanserin binds preferentially to the $5\text{-}HT_{2A}$ receptor and, to a lesser extent, to the $5\text{-}HT_{2C}$ receptors, and has low binding affinity to alpha, dopamine D_2, histamine, muscarinic, and other serotonin receptors.[26] The pharmacologic rationale for the efficacy of pimavanserin in PDP is based on investigations demonstrating that overstimulation of postsynaptic 5-HT neurons (particularly at $5\text{-}HT_{2A}$ receptors) contributes to psychotic symptoms in PD. Serotonin $5\text{-}HT_{2A}$ receptors exhibit baseline (constitutive) activity.[27,28] In other words, $5\text{-}HT_{2A}$ receptors spontaneously signal to produce and regulate cellular postsynaptic activity. Pimavanserin binds to $5\text{-}HT_{2A}$ receptors and blocks the receptor (ie, is an antagonist) and reduces the spontaneous baseline activity.[28] This property of binding to the receptor and reducing spontaneous baseline activity is referred to as inverse agonism.

Studies related to the clinical development of pimavanserin for PDP include 4 placebo-controlled studies and 2 open-label extension studies.[25] In 1 placebo-controlled trial,[29] 199 patients with PDP were randomized to receive either pimavanserin once daily or placebo for 6 weeks. The pimavanserin-treated group demonstrated a statistically and clinically significant improvement in the 9-item Scale for Assessment of Positive Symptoms adapted for PD ($P = .001$, effect size, 0.50; difference of least squares mean versus placebo, -3.06 [95% CI, -4.91 to -1.20]). Additional benefits included statistically significant improvements in the Clinical Global Impression Scale improvement and Clinical Global Impression Scale severity scores compared with placebo, and statistically significant improvements in caregiver burden scores and sleep measures. Pimavanserin was well tolerated, and no safety concerns were raised. Importantly, there was no evidence of treatment-related impairment of motor function. For patients who are vulnerable to antipsychotic-induced worsening of parkinsonism (as in Case 2), pimavanserin should be considered. In a meta-analysis of 4 randomized, placebo-controlled trials of pimavanserin for PDP, the results confirmed pimavanserin is associated with a statistically significant improvement of psychotic symptoms.[30] Pimavanserin was associated with less orthostatic hypotension than placebo. Other than the difference in orthostatic hypotension, there were no significant differences in adverse events between pimavanserin and placebo groups.

Pimavanserin is available through a network of specialty pharmacies. The recommended dosage of pimavanserin is 34 mg, taken orally as two 17-mg tablets once daily.[31] Unlike other antipsychotics used in the management of PDP, pimavanserin initiation does not require titration. The average wholesale price for a 1-month supply of pimavanserin at the recommended daily dosage of 34 mg (as two 17-mg tablets) is $2560.[32] The elimination half-life of pimavanserin is approximately 55 to 57 hours, and steady state is achieved in 12 days (5 half-lives) in the setting of once-daily dosing.[31,33] In clinical studies, the mean onset of therapeutic benefit occurs after 2 weeks.[29] Thus, if immediate symptomatic control is desired, an alternative agent must be considered. When switching to pimavanserin from another antipsychotic, a 2-week therapeutic overlap or "bridging" of concurrent agents may be considered to mitigate symptom exacerbation.

Pimavanserin is extensively metabolized, predominantly in the liver. Because the metabolism of pimavanserin is affected by strong cytochrome P450 3A4 enzyme (CYP3A4) inhibitors, which results in an increase in maximum serum concentration (C_{max}) and area under the curve of approximately 3-fold, a dosage reduction to 17 mg once daily is recommended when coadministering pimavanserin with moderate to strong CYP3A4 inhibitors.[31] Strong CYP3A4 inhibitors include, but are not limited to, clarithromycin, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, itraconazole, and ketoconazole. Use of concurrent strong CYP3A4 inducers (such as carbamazepine, phenytoin, and rifampin) may result in lowering of pimavanserin C_{max} and

area under the curve. Pimavanserin prolongs the QT interval by 5 to 8 ms (similar to that observed for quetiapine).[31,34] Until postmarketing data are available, the clinical significance of this QT interval prolongation remains unknown, and pimavanserin should be avoided in patients with known QT prolongation or in combination with other medications known to prolong the QT interval.[31]

The US Food and Drug Administration–approved labels for pimavanserin and all antipsychotics contain a boxed warning stating elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.[31] However, it is important to note that if the psychotic symptoms are related to the underlying PD, pimavanserin can be used in patients with concurrent dementia.

Off-Label Agents Used for PDP

Aripiprazole

The European Federation of Neurological Societies (EFNS) and the Movement Disorder Society–European Section (MDS-ES) recommend aripiprazole not be used because of insufficient evidence of efficacy along with risk of worsening parkinsonism.[23] Neither the American Academy of Neurology (AAN) nor the International Parkinson and Movement Disorder Society (MDS) mentions aripiprazole in its treatment recommendations.[35,36]

Clozapine

Clozapine is an atypical second-generation antipsychotic with antagonist activity at alpha, dopamine D_2, histamine, muscarinic, and serotonin 5-HT_{2A} receptors.[26] Clozapine is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. However, clozapine is used off-label for management of PDP symptoms. In clinical practice, the onset of benefit can occur within days. In the AAN evidence-based practice parameter on the treatment of psychosis in PD, clozapine was classified as level B (ie, probably effective) for the management of PDP.[35] The MDS concluded in an evidence-based report[36] that clozapine is an efficacious and clinically useful medication for the treatment of PDP but requires specialized monitoring for the development of clozapine-induced neutropenia. The EFNS/MDS-ES recommends clozapine as useful for PDP and recommends monitoring for rare but serious adverse events, such as myocarditis and neutropenia, and common adverse effects, such as sedation, dizziness, drooling, and orthostatic hypotension.[23] The clozapine studies[37,38] included in evidence-based guidelines consist of 2 randomized, controlled trials. In a meta-analysis of these 2 trials, clozapine (mean daily dosage range of 25-36 mg) demonstrated superiority over placebo in alleviating psychotic symptoms.[39] The meta-analysis confirmed clozapine does not worsen PD motor scores. Thus, for patients who are vulnerable to antipsychotic-induced worsening of parkinsonism (as in Case 2), clozapine may be considered. Consistently reported adverse effects included sedation, drooling, and orthostatic hypotension or dizziness. Overall, 3% of the patients exposed to clozapine experienced severe neutropenia requiring study withdrawal.

Although small, the risk for development of clozapine-induced neutropenia is serious and necessitates regular monitoring of the absolute neutrophil count (ANC) with a Risk Evaluation and Mitigation Strategy (REMS) program.[40,41] Prescribers must be certified in the Clozapine REMS Program to prescribe clozapine. Patients need to have their blood drawn on a weekly basis for the first 6 months of therapy, with the interval extending to every 2 weeks for the following 6 months if no abnormalities are seen, and extending to every month thereafter. For the general population, clozapine can only be initiated if the ANC is 1500/µg or greater. If the ANC drops to between 500/µg and 999/µg, treatment must be interrupted for suspected clozapine-induced neutropenia and can be resumed when ANC is 1000/µg or greater. If patients develop severe neutropenia (ANC < 500/µg), clozapine must be discontinued, and drug rechallenge is not recommended unless the benefits outweigh the risks. Despite the demonstration of efficacy for the management of PDP, the safety concerns associated with clozapine and the requirement for indefinite ANC monitoring are barriers to use by some clinicians and facilities.[42]

Olanzapine

The AAN evidence-based practice parameter on the treatment of psychosis in PD concludes that olanzapine not be routinely considered for the management of PDP.[35] The MDS concluded in an evidence-based report[36] that olanzapine can be rated as unlikely efficacious for the treatment of psychosis in PD, and use of olanzapine has an unacceptable risk of motor deterioration. Additionally, the EFNS/MDS-ES identified high-quality studies demonstrating that olanzapine was ineffective and associated with a substantive risk of worsening parkinsonism.[23]

Quetiapine

Quetiapine is indicated for the treatment of schizophrenia and bipolar disorder. However, quetiapine is used off-label for the management of PDP symptoms. In practice, quetiapine dosing for patients with PDP is titrated from 12.5 mg nightly up to a range of 50 to 150 mg/d. In clinical

practice, the onset of benefit is generally observed within days. Administration in the evening is preferred because of a potential adverse effect of drowsiness. Quetiapine is similar in structure to clozapine and has antagonist activity at dopaminergic D_2, histamine, muscarinic, and serotonin 5-HT$_{2A}$ receptors.[26] In the AAN evidence-based practice parameter on the treatment of psychosis in PD, quetiapine was classified as level C (ie, possibly effective) for the management of PDP.[35] The MDS concluded in an evidence-based report that because of conflicting data on the efficacy of quetiapine and study methodology concerns (eg, small sample size, low-quality rating), there is insufficient evidence for quetiapine for the treatment of PDP.[36] The EFNS/MDS-ES recommends quetiapine as possibly useful.[23]

In a recent systematic review of 7 studies (2 active comparator controlled and 5 placebo controlled) of quetiapine for PDP, analysis of the comparator studies found no difference in efficacy between quetiapine and clozapine.[43] Of the placebo-controlled studies, 4 found no statistically significant difference between quetiapine and placebo in reducing psychotic symptoms when assessed on the Brief Psychiatric Rating Scale.[43] Among the 7 studies, the mean duration was 12 weeks and mean daily quetiapine dosage was 103 mg. It should be noted that high dropout rates (due to loss of follow-ups and adverse effects) were observed and may have reduced the power of the studies to detect a significant difference.[43] Additionally, a high placebo response rate may have diminished the ability to detect a statistically significant difference. Reported adverse events for quetiapine included dizziness, somnolence, orthostatic hypotension, sedation, and worsening parkinsonism.

In a meta-analysis[39] of 3 randomized, controlled trials, quetiapine did not appear to significantly improve psychotic symptoms in PDP when compared to placebo. The authors also noted the quetiapine studies were characterized by small sample sizes and high dropout rates in the quetiapine groups, ranging between 19% and 64%. Therefore, the studies appeared to be underpowered. In terms of adverse events, sedation was a common cause for study dropout in the quetiapine groups. This is particularly important because excessive daytime sleepiness is common in PD. Additionally, quetiapine is associated with increased all-cause mortality in patients with PD (hazard ratio, 2.16; 95% CI, 1.88 to 2.48, over nonuse).[24]

Risperidone

The EFNS/MDS-ES guidelines state that risperidone improves psychosis but is not recommended because of frequent motor worsening.[23]

Cholinesterase Inhibitors

For patients unresponsive to or intolerant of atypical antipsychotics, a trial of cholinesterase inhibitors (eg, donepezil, rivastigmine) is warranted, regardless of whether the patient has comorbid dementia.[44-46] Open-label and controlled studies indicate that cholinesterase inhibitors can improve symptoms of PDP and are generally well tolerated.[44-46] In the PD population, the most common side effects of cholinesterase inhibitors are gastrointestinal disturbances. Although not common, worsening of motor symptoms (eg, tremor) may occur.[44-46]

Summary and Conclusion

Parkinson disease psychosis is common in PD. The initial approach to the management of PDP begins with addressing concurrent systemic conditions associated with psychotic behavior, such as delirium, medical conditions (eg, infections), and psychiatric disorders. A review of current medications is recommended, and medications that may trigger psychotic symptoms should be eliminated. If possible, antiparkinson medications should be reduced to the minimum therapeutic dose or discontinued in a sequential manner. The aim of antiparkinson medication dose reduction is to achieve a balance between improving drug-related psychotic symptoms and not significantly worsening the motor symptoms of PD. If additional measures are needed for chronic PDP treatment, the use of atypical antipsychotics, such as clozapine, pimavanserin, or quetiapine, must be considered. The choice of atypical antipsychotic is based on patient-specific parameters, potential benefit, and side effects. In patients unresponsive to or intolerant of atypical antipsychotics, a trial of a cholinesterase inhibitor is warranted.

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