Managing the Psychiatric Manifestations of Parkinson Disease: An Update

November 01, 2007 | Bipolar Disorder [1], Geriatric Psychiatry [2], Mood Disorders [3], Nocturnal Paroxysmal Dystonia [4], Gambling [5], Lewy Body [6], Major Depressive Disorder [7], Addiction [8], Akinetic Mutism [9], Alcohol Abuse [10] By Tiffini Voss, MD [11] and Bernard Ravina, MD, MSCE [12]

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Parkinson disease (PD) is a progressive neurodegenerative disorder affecting 1% of people 65 years and older. The core symptoms include the motor manifestations of tremor, bradykinesia, and rigidity. Asymmetric onset and response to dopaminergic therapy are typical of idiopathic PD compared with other causes of parkinsonism. As the disease progresses, postural instability, motor fluctuations, and dyskinesias develop, and treatments become less effective.

Dementia and psychosis occur frequently in advanced PD. Not only does psychosis severely limit therapeutic options for motor symptoms but it also becomes a highly disabling symptom. Increasingly, nonmotor aspects of PD are recognized as important causes of morbidity and mortality, which is consistent with evidence of disease pathology beyond the dopaminergic neurons of the substantia nigra. In this article, we review the overall clinical course of PD and the major psychiatric manifestations associated with the illness. Clinical Course and Treatment Options

There are several choices for the initial treatment of early PD. Dopamine agonists delay the onset of motor fluctuations and dyskinesia; compared with levodopa, however, they are less effective for reducing motor signs; they are more expensive; and they cause more severe and more frequent adverse effects, including nausea, vomiting, somnolence, confusion, peripheral edema, orthostatic hypotension, and hallucinations. As a result, levodopa is preferred in older patients and in those with comorbidities. Compared with immediate-release preparations, controlled-release forms of carbidopa/levodopa may be inconsistently absorbed, which may lead to dose failures and evening dyskinesias.

The non-ergot-derived agonists ropinirole and pramipexole are preferred, because ergot-derived agonists are associated with an increased risk of cardiac valve damage and retroperitoneal fibrosis. Recently, rotigotine has been approved as a 24-hour patch for use in early PD. Table 1 summarizes available pharmacotherapy for PD.

Patients with more advanced PD develop several motor complications. Loss of response to levodopa leads to wearing-off between doses, motor fluctuations (ie, on-off phenomena), and dyskinesias. Reducing off time is achieved by more frequent dosing of levodopa formulations and adding supportive medications such as dopamine agonists, monoamine oxidase type B inhibitors, and catechol-O-methyltransferase (COMT) inhibitors. (COMT inhibitors are only effective in combination with levodopa and should not be used as monotherapy.) Usually, dyskinesias are directly related to peak-dose dopamine therapy and may be difficult to treat without exacerbating rigidity and bradykinesia. Management of troublesome dyskinesias involves decreasing the levodopa dose and/or adding longer-acting dopamine agonists and COMT inhibitors. Amantadine may also be effective in reducing dyskinesias.

Cognitively intact patients who become medically refractory after a good initial response to levodopa may be candidates for bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus interna. Deep brain stimulation reduces motor signs, motor fluctuations, off time, and dyskinesias, but is not as effective at treating postural instability, freezing, and falls. Some studies suggest that deep brain stimulation of the pedunculopontine nucleus may be effective in treating these symptoms, but those results require replication. Deep brain stimulation is generally well tolerated in properly selected patients. Most studies report no changes in mood or cognition, or only transient perioperative effects. Other studies have documented persistent decreased verbal fluency and positive affect as well as increased irritability.
although there was no effect on overall quality of life.\textsuperscript{15,16} Subthallamic nucleus stimulation may be more effective for reducing motor symptoms and lowering levodopa dosing but possibly at the expense of adverse effects on mood and cognition. Stimulation of globus pallidus interna may be more effective for treating dyskinesias and may not be associated with neuropsychiatric adverse effects.\textsuperscript{16} Further research is under way to better define the risks and benefits of each treatment.

**Medical Management of PD Depression**

Clinically significant depressive symptoms affect an estimated 40% to 50% of patients with PD during the course of their illness; such symptoms are associated with increased disability\textsuperscript{17} as well as impaired quality of life.\textsuperscript{18} The cause of depression in PD remains uncertain, but it appears to be related to the underlying neurodegenerative process. Imaging and autopsy data suggest that structural and neurochemical changes are similar to those seen in non-PD depression.\textsuperscript{19,20} Multiple nuclei that degenerate in PD, such as the substantia nigra, ventral tegmental area, and locus ceruleus, are implicated in depression. Finally, certain clinical PD phenotypes appear to correlate with depression; for example, depression is more common in the akinetic-rigid form of PD than in the tremor-predominant phenotype.\textsuperscript{20}

Diagnosing depression in a patient with PD can be complex, particularly because it is unclear whether the available diagnostic categories for unipolar depression are appropriate for PD. Depression may be underdiagnosed when symptoms are attributed to somatic symptoms of PD, and patients with PD may be apathetic and socially withdrawn without being depressed. Minor depression is more common in patients with PD than in those with major depression.\textsuperscript{18} Also, the symptom palette may be different from that of major depression, including more anxiety and pessimism with less guilt and self-reproach.\textsuperscript{20} Evaluation for depression should ideally occur when the patient is "on," because patients with PD can experience dysphoria, anxiety, or frank panic attacks during "off" periods of motor fluctuations.

Evidence is limited regarding pharmacotherapy for depression in patients with PD, and most available data are from small trials of varying quality. Consequently, in a 2006 practice parameter, the American Academy of Neurology chose to recommend only amitriptyline. However, given their anticholinergic adverse effects, tricyclics can be problematic in the elderly. This problem is magnified in patients with PD, because orthostasis and cognitive impairment are often present. As a result, an SSRI is prescribed for most patients with depression. The data on SSRIs and heterocyclics for depression in patients with PD are summarized in Table 2.

Emerging evidence suggests that pramipexole may have potential antidepressant effects, presumably because of its effect on D\textsubscript{3} receptors. In an observational cohort of 657 patients with PD, Lemke and colleagues\textsuperscript{21} noted a significant reduction in depression and anhedonia during treatment with pramipexole. In a prospective, randomized, single-blind study of pramipexole and pergolide, Rektorová and colleagues\textsuperscript{22} discovered an antidepressant effect for pramipexole but not for pergolide. Pramipexole has also been shown to be effective in bipolar depression in preliminary controlled trials.\textsuperscript{23} This evidence suggests that the antidepressant response in patients with PD is not simply due to improvement in motor functioning.

No controlled trials are available regarding other therapies, such as psychotherapy, electroconvulsive therapy, or transcranial magnetic stimulation.\textbf{Psychosis}

The onset of psychosis in patients with PD is a serious complication associated with increased risk of nursing home placement, dementia, and death.\textsuperscript{24} Patients with advanced PD and disease duration of more than 10 years are at highest risk for psychosis; prevalence ranges from 25% to 30% in referral clinics.\textsuperscript{25} As compared with other psychotic conditions, PD psychosis generally involves well-formed visual hallucinations, presence hallucinations, and paranoid delusions, often about spousal infidelity or abandonment. Hallucinations involving other sensory modalities are much less common and usually occur along with visual hallucinations.\textsuperscript{26}

Psychotic symptoms are intermittent but recurrent and are usually worse at night. Many patients with PD initially report retained insight, and therefore benign hallucinations are diagnosed. However, in most patients, insight is gradually lost and the hallucinations become more threatening.\textsuperscript{27} Therefore, the term "benign hallucinations" is discouraged because it merely represents the early stages of a progressively disabling course.

The pathophysiology of PD psychosis is not fully understood. Although dopaminergic drugs have long been associated with the development of psychosis, it is hard to assess true causality because psychosis occurs late in the disease when nearly all patients require dopaminergic therapy for motor symptoms. Moreover, an increase in dopaminergic therapy does not always worsen psychosis, and the removal of dopaminergic therapy does not always resolve psychosis. Similarly, other clinical features, such as dementia, are associated with psychosis. These suggest that PD psychosis results
from the interaction of PD pathology and medications and is not purely drug-induced.\textsuperscript{24} Treatment options for PD psychosis are limited. Typical antipsychotics are not recommended in PD because they worsen parkinsonism and may cause acute severe akinesia and rigidity. Clozapine is the only antipsychotic shown to be effective in the treatment of PD psychosis in a randomized, double-blind, placebo-controlled trial.\textsuperscript{28} Unfortunately, the risk of agranulocytosis requires frequent blood monitoring, which limits the use of clozapine. Despite the lack of definitive evidence of efficacy, quetiapine is often used first because of its favorable safety profile and apparent lack of adverse effects on motor symptoms in PD.\textsuperscript{29,30} Olanzapine worsens parkinsonism and is not recommended.\textsuperscript{31,32} Aripiprazole is a partial D\textsubscript{2} agonist, with a potentially appealing profile in PD. Despite this, results of studies of aripiprazole in PD have been mixed.\textsuperscript{33,35} Risperidone is a potent dopamine blocker more similar to the typical antipsychotics in action, but it is generally not recommended despite an open-label study supporting its use.\textsuperscript{36,37} Because treatment options are limited, management generally begins with the removal of potentially exacerbating medications, such as anticholinergics, monoamine oxidase inhibitors, and dopamine agonists. Levodopa dosing is reduced as much as is tolerated. Subsequently, quetiapine or clozapine is started. Although evidence now links atypical antipsychotics to increased risk of cardiovascular death, this potential risk must be weighed against the poor prognosis associated with psychosis in PD.\textsuperscript{24} 

\section*{Dementia}
In a meta-analysis of prevalence studies, dementia occurred in 30\% of patients with PD, and PD dementia accounted for 3\% to 4\% of all dementia in the general population.\textsuperscript{38} There is clinical overlap of dementia with Lewy bodies; currently, patients showing dementia before or within 1 year of onset of motor symptoms are considered to have dementia with Lewy bodies.\textsuperscript{39} Researchers continue to debate whether dementia with Lewy bodies and PD are separate pathological entities or if they represent a continuum of Lewy body disease. Nonetheless, the clinical separation appears helpful from a management and prognostic perspective. Pathologically, converging evidence suggests that Lewy body pathology, not amyloid pathology, underlies PD dementia.\textsuperscript{40} Currently, donepezil and rivastigmine appear to be modestly effective in delaying time to nursing home placement as well as preserving cognition, with an effect size similar to that seen in Alzheimer disease. In one study of piracetam, researchers found no effect on dementia.\textsuperscript{29} 

\section*{Sleep disorders}
Sleep is disrupted in up to 65\% of patients with PD, and sleep disruption is more common in those with PD than in age-matched healthy controls and controls with diabetes mellitus.\textsuperscript{41} Sleep disturbance is multifactorial, and many patients have multiple sleep problems. As a result, excessive daytime somnolence is one of the most common sleep issues in PD. Autonomic involvement may lead to urinary urgency and frequency with subsequent nocturia. Nocturnal pain can develop from rigidity, akinesia, or dystonia. Comorbid conditions such as restless legs syndrome and rapid eye movement sleep behavior disorder also impair sleep quality. Management generally involves sleep hygiene, maximal treatment of sleep disruptors, and in some cases, modafanil or other stimulants, although these have not been well studied in the PD population. 

\section*{Impulse control disorders}
In the past few years, repetitive, reward-based behaviors have been reported in PD, including pathological gambling, compulsive eating, hypersexuality, punding, and dopamine dysregulation syndrome.\textsuperscript{42} The causes of these behavioral patterns are not known for certain, but it is thought that they may be related to nonphysiological dopaminergic stimulation altering the frontal-limbic-striatal circuitry. As a group, these conditions are not consistently related to medication doses, disease severity, or disease duration and are only present in a subset of patients; this suggests an idiosyncratic susceptibility modified by PD-specific pathophysiology. Because patients frequently hide or are not distressed by these behaviors, diagnoses may be rare despite a prevalence of 6.1\% for all disorders.\textsuperscript{43} The relationship between impulse control disorders and dopaminergic medications is not clear, but one study noted a prevalence of 0.7\% with levodopa versus 13.7\% with dopamine agonists as a class.\textsuperscript{43} No one specific agonist appears to be more closely linked to impulse control disorders. Management of these disorders is not well studied in PD and generally involves removing the suspected offending agent, if possible, and treating any underlying mood disorder.

\section*{Summary}
PD is a progressive neurodegenerative disorder with symptoms affecting multiple brain areas. The cognitive and behavioral aspects of PD are important because of their impact on the patient and because of their importance to understanding the pathophysiology of this complex disease. Further research is needed to more precisely define and measure nonmotor symptoms, to provide better symptomatic therapies, and to pursue the ultimate goal of protecting or restoring neuronal function.

\section*{References}


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