Current PSYCHIATRY

Psychiatric symptoms in Parkinson's disease

A team approach to successful management

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How can you make sound treatment decisions when almost no evidence exists on the use of psychotropics in patients with Parkinson's disease? A psychiatrist and a neurologist argue that collaboration is key to treating PD patients' psychiatric symptoms.

Depression, anxiety, and psychosis are common complications of Parkinson's disease (PD) and of the medications used in antiparkinsonian treatment. These psychiatric problems impair patients' functioning throughout the course of the chronic degenerative disease.

Because medication side effects often call for adjustments and trade-offs in PD treatment, a team effort by the psychiatrist, neurologist, patient, and caregiver is the most effective approach to decision-making. From our experience in such collaborations, here's what you need to know about PD to be a most-valuable player on that treatment team.

Presentation of PD

The classic triad of PD features consists of a pill-rolling tremor, rigidity, and bradykinesia or slowness of movement. Other common features include postural instability, flexed posture, and other motor-freezing phenomena.

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Freezing phenomena occur in the later stages of PD, as the response to dopaminergic therapy becomes erratic and unpredictable. Freezing can range from hesitation—such as when the patient tries to turn or is in a doorway—to transient episodes of total inability to move. These episodes are extremely distressing for both patients and caregivers.

Patients rarely present with the full complement of symptoms, but the presence of tremor at rest and/or bradykinesia is essential for the diagnosis. While motor signs dominate the presentation, cognitive symptoms such as shortened attention span, visuospatial impairment, personality changes, and dementia are also frequently present.

Average age of diagnosis is 60, and more men are affected than women (male-to-female ratio is 3:2). Many causative factors—including genetics and environmental toxins—have been implicated, but the disorder's etiology remains unknown.

Drug treatment side effects

PD results from the loss of neurons in the substantia nigra that produce the neurotransmitter dopamine. Pharmacologic treatment emphasizes dopamine replacement, dopamine receptor stimulation, or prevention of enzymatic breakdown of dopamine in the synaptic cleft. As treatment of PD is symptomatic and not curative, medications are instituted only when the disease begins to cause functional impairment.

Treatment begins with dopamine agonists (*Table*). As dopamine agonist monotherapy becomes less effective, levodopa therapy is initiated. Blocking the enzymatic breakdown of dopamine with catechol-O-methyltransferase inhibitors is the next therapeutic strategy.

Within 5 years of starting levodopa therapy 75% of patients experience unsatisfactory motor response, from unpredictable fluctuations to wearing-off phenomena (in which a dose of levodopa does not last as long as it once did). Treatment of advanced PD is complicated by the emergence of psychiatric symptoms, such as hallucinations and psychosis, as dopamine levels are increased in an attempt to smooth the motor response.

The significantly distressing level of disability associated with the prominent side effects of pharmacologic treatment has led to interest in surgical interventions. These range from pallidotomy to implantation of basal ganglia stimulators to transplantation of fetal striatal neurons. The possibility of neuroprotection has also been extensively investigated, with mixed results.

Psychiatric complications of PD

Depression. Clearly, the stress of anticipating and coping with a relentless degenerative disease helps to trigger depression and anxiety in patients with PD. Depression is the most common psychiatric syndrome, with prevalence in PD as high as 42%.[1] Patients with a history of depression are at particular risk.[2] Those with recent deterioration or advancing severity of PD, akinesia, history of falls, or cognitive impairment are also at increased risk for depression.

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Table

MEDICATIONS COMMONLY USED IN MANAGING PARKINSON'S DISEASE

Medication class	Example	Indication for use
MAO-B inhibitor	Selegiline	? Neuroprotection
Anticholinergic agents	Trihexyphenidyl, benztropine, biperiden, hyoscyamine, diphenhydramine	Tremor
Dopamine agonist	Pramipexole, pergolide, ropinirole	? Neuroprotection Treatment of movement disorder
Dopamine replacement	Carbidopa-levodopa	Treatment of movement disorder
Catechol-O-methyltransferase inhibitor	Entacapone, tolcapone	Smooth motor fluctuations

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Depression correlates well with the patient's perception of his or her degree of PD-related disability. Depression symptoms seem to peak early in the illness following diagnosis and in advanced disease.[3]

Patients may present with symptoms meeting diagnostic criteria ranging from dysthymic disorder to minor depression to major depressive disorder.[1,4] Although they will frequently endorse suicidal ideation, patients with PD have a low rate of suicide. Diagnosing depression, however, may be difficult because its symptoms overlap with those of the underlying neurologic disease:

- Diminished affect and psychomotor slowing may be secondary to the motor features of parkinsonism.
- Diminished concentration may be secondary to cognitive decline rather than depression.

Patients also frequently have a chief complaint of diminished energy or fatigue that should trigger further investigation into other depressive symptoms.[4,5]

In addition to the obvious additional suffering it causes, depression in PD predicts impaired social, physical, and role functioning.[6] Depression in the PD patient also results in higher distress for caregivers.[7] In one study, depression was identified as a risk factor for development of psychosis in PD patients.[8]

Anxiety is a frequent problem for PD patients, with a prevalence of 33 to 40%.[9,10] Anxiety in PD typically presents with symptoms of panic disorder, generalized anxiety disorder, or social phobia.[11] It is comorbid with depression in up to 92% of cases and— like depression—frequently predates the onset of motor symptoms.[12]

Anxiety symptoms have been correlated, although not consistently, with the on-off motor phenomenon often found in advanced PD.[13] They can also be an adverse effect of many of the antiparkinsonian medications, including anticholinergics, dopamine agonists, catechol-O-methyltransferase inhibitors, and selegiline. Both anxiety and depression have been associated with an increased risk for falls.[14]

Psychotic symptoms. Up to 25% of PD patients experience delusions or hallucinations.[15] Risk factors include dementia, sleep disturbance, and—most commonly—the use of dopaminergic agents. Up to one-fifth of patients using dopaminergic drugs experience psychotic symptoms.[16]

Psychotic symptoms can occur with or without the clouded sensorium characteristic of delirium. Psychotic symptoms with an associated confusional state can be associated with use of anticholinergic agents and drugs such as selegiline and amantadine.[17] Catechol-O-methyltransferase inhibitors cause more sustained dopaminergic activity of levodopa, which can result in psychotic symptoms. Therefore, the use of all known classes of antiparkinsonian medications has been associated with drug-induced psychosis.

In advanced PD, paranoid delusions, delusions of spousal infidelity, and visual hallucinations are common, whereas negative symptoms and thought disturbances are not.[18] Psychosis may be a more important contributor to caregiver distress than the motor symptoms of PD and may be more likely than any other factor to lead to nursing home placement of the PD patient (*Box 1*).[15]

All known classes of antiparkinson's medications can cause drug-induced psychosis

Psychiatric interventions

Goals for psychiatric treatment of depression, anxiety, and psychosis associated with PD seem relatively straightforward:

- improvement or remission of psychiatric symptoms
- restoration of optimal patient functioning.

Ideally, these goals would be achieved without causing sedation, orthostatic hypotension, or exacerbating motor symptoms. The older age of patients and the progressive nature of this neurodegenerative disorder predispose patients to cognitive side effects. Unfortunately, despite the high prevalence of psychiatric disturbances in PD, evidence with which to evaluate treatment efficacy and safety and to guide treatment selection is extremely limited.

For depression associated with PD, extensive clinical experience supports the efficacy of tricyclic antidepressants. Even so, selective serotonin reuptake inhibitors (SSRIs) are the preferred treatment, although only open-label trials and case reports support their efficacy.[5,12] Compared with tricyclics, SSRIs exhibit a relative lack of problems with sedation, orthostatic hypotension, and memory-impairing anticholinergic side effects. While case reports have cited worsening of motor symptoms with SSRIs, a recent prospective study found no significant worsening of PD symptoms during treatment with citalopram, fluoxetine, fluvoxamine, or sertraline.[19] Coadministration of an SSRI with selegiline is not absolutely

Box 1

CASE REPORT: A downward spiral

Mr. J had a 6-year history of PD with pronounced bradykinesia and gait disturbance treated with amantadine and carbidopa-levodopa. His rigidity began to worsen, so the dosage of carbidopa-levodopa was increased. His wife then reported that he had increased confusion and balance problems. On evaluation, he was found to have a urinary tract infection. Following antibiotic treatment, mental status and gait returned to usual baseline.

One year later, Mr. J began having trouble getting out of bed, with unpredictable motor freezing episodes. Pramipexole was added to his regimen, and he began having prominent visual hallucinations. Low-dose trifluoperazine was added, and hallucinations improved. The patient became increasingly depressed, and sertraline was started.

Over the next year, his function progressively worsened, with increased motor freezing and unpredictable dyskinesias. Hallucinations complicated attempts to change his medications. Amantadine was stopped without improvement. He was referred for surgical evaluation, but because of his cognitive status and depression was deemed not to be a candidate.

He began to fall repeatedly and developed orthostatic hypotension. His clinical course continued to be complicated by hallucinations and delusions that his wife was being unfaithful. Ongoing psychosis and severe gait instability led to his admission to a nursing home.

contraindicated, but the combination does carry a very small risk of development of serotonin syndrome.[1,5]

Data are even more scant on the safe use of other antidepressants in PD. Electroconvulsive therapy has been proven helpful in refractory cases and sometimes results in transient motor symptom improvement.[1,5,12] While clinical experience suggests that psychotherapy frequently helps, no extensive controlled studies exist. One small study suggests the efficacy of structured cognitive psychotherapy.[20]

ECT can be helpful in refractory depression and sometimes improves motor symptoms transiently

Anxiety. No studies have examined the treatment of anxiety in PD patients. Given the extremely high comorbidity of anxiety with depression, antidepressants should probably be considered as a first-line pharmacotherapy. Benzodiazepines should be used cautiously, as they increase the risk of falls, sedation, and confusion in older patients. One small controlled study found that buspirone was well tolerated in PD patients at low dosages (10 to 40 mg/d), but anxiety did not improve. At high dosages (100 mg/d), anxiety worsened.[21]

Psychosis. Data on use of antipsychotic agents in PD are also limited, but some evidence supports their use in treating PD-related psychotic symptoms. While conventional antipsychotics can help control psychosis, the potential is high for worsening of parkinsonian symptoms due to D2 receptor blockade.

Among the atypical antipsychotics, clozapine has been most extensively studied in PD and has been shown in open and double-blind trials to be effective and well tolerated at low dosages (6.25 to 50 mg/d). A limited number of open studies of some of the newer atypicals have been performed. While extreme caution must be used in comparing data from these studies due to highly variable dosing and other study design issues, clozapine and quetiapine appear to be the agents best tolerated by PD patients.[12,18,22] Initial antipsychotic dosing should be low and escalation cautious—regardless of the agent chosen—because of the dose-related potential for worsening of parkinsonian symptoms, sedation, and orthostatic hypotension.

A team approach to treatment

Because psychiatric and PD symptoms and treatments are closely interrelated, the psychiatrist, neurologist, patient, and caregiver must collaborate for the best therapeutic result. A simplistic approach to treatment can result in a catastrophic downward spiral in patient functioning.

Often, compromises must be made between optimal control of parkinsonian and psychiatric symptoms to achieve the best overall patient function. Patients and caregivers must be counseled about possible psychiatric symptoms associated with PD and antiparkinsonian therapy, as well as the potential for adverse effects from psychiatric medications. With this knowledge, patients and caregivers can

help assess the severity of symptoms and set treatment priorities, depending on how symptoms may be affecting the patient's level of functioning. For example, if an effective antiparkinsonian regimen has triggered infrequent, nondistressing hallucinations with preserved insight, intervention may not be required beyond patient and caregiver education (*Box 2*).

Patient workup. When intervention is required for psychiatric symptoms, it should begin with careful neurologic evaluation. Triggering factors such as infections (commonly urinary tract infections and pneumonia), metabolic disorders (hyperglycemia, hypothyroidism), subdural hematomas (if the patient is falling), and drug interactions should be ruled out or appropriately addressed.

Next, try to sequentially eliminate antiparkinsonian medications until the psychosis resolves or motor function worsens.[23] Because of considerable overlap between PD symptoms and depression (psychomotor retardation, fatigue, and anergia), optimizing PD therapy sometimes can result in substantial psychiatric improvement. Some evidence also suggests that the dopamine agonist pramipexole may be effective in treating both PD and depression.[5]

When psychiatric medications are necessary for depression, anxiety, or psychosis, carefully review target symptoms, treatment expectations, and possible adverse effects with the patient and caregiver. Keep in mind the progressive nature of PD and, in addition to frequent monitoring, educate and encourage caregivers to immediately report any suspected adverse effects.

Any motor function deterioration should trigger a re-evaluation of psychotropic medications before you presume that the patient's PD is progressing. Because antiparkinsonian drug regimens change over time, review the patient's medications at each appointment, and alert patients and caregivers to potential psychiatric complications of any new medication.

Caregiver treatment In addition to treating the patient, it is important to monitor the impact of psychiatric symptoms and PD on the patient's caregiver. Frequently assess whether the caregiver and patient have adequate social supports, and address any emerging needs. Useful interventions include caregiver counseling, referrals to support groups, and respite care.[24]

Box 2

CASE REPORT: Panic attacks or hallucinations?

Mrs. K had a 4-year history of rapidly progressing PD treated with entacapone, carbidopa-levodopa, and a deep brain stimulator. Increasing periods of motor freezing, which were often accompanied by panic attacks, led her to become increasingly depressed and demanding of her caregiver husband. Eventually, she was admitted to an inpatient psychiatry unit because of suicidal ideation.

After a neurologic evaluation, the dosing times of her carbidopa-levodopa and entacapone were changed, but she continued to have panic attacks and remained depressed. Alprazolam promptly reduced her panic symptoms, and paroxetine was initiated for depression. A discussion with the patient and her husband revealed that they had some longstanding issues in their marriage that were exacerbated by Mrs K's increasing dependency. The couple was referred for marital therapy, and Mrs. K agreed to begin attending a senior center.

Following discharge, the panic remained controlled and depression improved. Entacapone was replaced with tolcapone to see if motor freezing would decrease. Mrs. K's movements improved, but her husband reported she had awakened on several nights with visual hallucinations. The hallucinations were infrequent, unaccompanied by agitation, and not distressing to the patient. Following a discussion of therapeutic options with Mrs. K and her husband, antipsychotic therapy was not instituted. The patient continues to live at home and attends the senior center regularly.

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Related resources

- Parkinson's Disease Foundation: http://www.pdf.org
- American Parkinson Disease Association: http://apdaparkinson.com
- National Parkinson Foundation: http://www.parkinson.org
- Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease 2001: treatment guidelines. *Neurology* 2001;56:5(suppl):S1-S88.

DRUG BRAND NAMES

Alprazolam • Xanax
Amantadine • Symmetrel
Benztropine • Cogentin
Biperiden • Akineton
Buspirone • Buspar
Carbidopa-levodopa • Sinemet
Citalopram • Celexa
Clozapine • Clozaril
Entacapone • Comtan
Fluvoxamine • Luvox
Hyoscyamine • Levsin
Paroxetine • Paxil
Pergolide • Permax
Pramipexole • Mirapex
Ropinirole • Requip
Selegeline • Eldepryl
Sertraline • Zoloft
Tolcapone • Tasmar
Trihexyphenidyl • Artane
Trifluoperazine • Stelazine

DISCLOSURE
The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Bottom Line

Depression, anxiety, and psychosis are common complications of Parkinson's disease and its treatment. Because of the interrelationship between PD's neurologic and psychiatric symptoms, treatment adjustments are often required. Working together, the psychiatrist, neurologist, patient, and caregiver can achieve the optimum therapeutic result.

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