Depression in Parkinson Disease

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Prevalence of depression in PD is estimated to range from 7% to 76%. The variation is largely attributed to the diversity of the populations under study, differences in the definition of depression, and the fact that some studies used point prevalence and other studies used monthly prevalence. Also, the prevalence of depression varies with fluctuations of cognitive status and other comorbidities that are an integral part of PD.

In his classic An Essay on the Shaking Palsy, published in 1817, James Parkinson recognized depression as a common feature of the disease that now bears his name: "A more melancholy object I never beheld. The patient, naturally a handsome, middle-sized, sanguine man, of a cheerful disposition, and an active mind, appeared much emaciated, stooping, and dejected." Although depression is common in Parkinson disease (PD), it is often underrecognized.

Psychiatric sequelae—including cognitive disorders, psychosis, mania, depression, anxiety, alcohol and other substance abuse, sleep disorders, sexual disorders, and paraphilias—are well known to PD. In fact, the high prevalence of psychiatric comorbidities suggests that PD is more accurately described as a neuropsychiatric disorder than a pure movement disorder. Of the psychiatric comorbidities noted, cognitive impairment and depression are the strongest determinants of quality of life. Depression increases the emotional and physical burden of PD for both patients and their caregivers.

The lack of facial expression, referred to as masked facies, may not be easily differentiated from the facial expression of depression and adds to the challenge of diagnosing depression in PD. The brief episodes of mood-incongruent lability and tearfulness associated with PD add to the diagnostic dilemma. Antidepressants are often used in the management of depression in PD; however, their effectiveness has not been well demonstrated and concerns have been raised that motor symptoms may worsen with selective serotonin reuptake inhibitors (SSRIs).

PREVALENCE

Prevalence of depression in PD is estimated to range from 7% to 76%. The variation is largely attributed to the diversity of the populations under study, differences in the definition of depression, and the fact that some studies used point prevalence and other studies used monthly prevalence. Also, the prevalence of depression varies with fluctuations of cognitive status and other comorbidities that are an integral part of PD. The majority of studies report a prevalence for depression of around 40% to 50%, with as many as 38% of the population affected at any given time. Using the stringent diagnostic criteria of the DSM-IV, 20% of patients with PD have major depression, and 20% have the milder but more chronic dysthymia.

PATHOPHYSIOLOGIC CONSIDERATIONS

It has been suggested that depression in PD has a bimodal distribution, with a reactive depression soon after the diagnosis of PD and subsequent recurrence of depression at the advanced stage of disease when medication failures arise. This idea has raised the possibility that depression in the early stages is more "psychological"—an emotional reaction to a PD diagnosis—whereas, depression occurring later in the disease process may be more "biologic"—a consequence of neurodegeneration. Adding to the complexities of depression and PD, it also has been suggested that depression may precede PD and be a risk factor for it. Multiple neuronal circuits and monoamines have been implicated in the pathophysiology of depression in PD. Positron emission tomography studies implicate dysfunction of the medial prefrontal cortex in both primary depression and depression associated with PD. Subcortical neurons, such as the basal ganglia, frontal lobes, cortico-striatal and thalamo-cortical circuits along with basotemporal-limbic circuits also have drawn attention. Likewise, derangements of dopaminergic, serotonergic, cholinergic, and noradrenergic pathways may be involved. Patients with unilateral lesions in the basal ganglia or thalamus, particularly the left-sided basal ganglia, show
Radionuclide imaging studies suggest that dysregulation of pathways between the basal ganglia and frontal lobes is responsible for depression associated with PD. Regional cerebral glucose metabolism is significantly lower in the caudate and orbital-inferior region in patients with PD and depression compared with both nondepressed patients and control subjects. In vivo radionuclide imaging studies have shown that the loss of dopamine and noradrenaline innervation in the limbic system is associated with anxiety and depression in PD. Compared with nondepressed patients, patients with PD and depression have lower levels of the serotonin metabolite cerebrospinal fluid 5-hydroxyindole acetic acid.

**DIAGNOSTIC CONSIDERATIONS**

Depression in persons with PD does not have unique features that differentiate it from depression in persons without PD. However, dysphoria, irritability, self-blame, guilt, and suicidality are less prevalent in the depression of PD. Also, depression in PD is related to the "off" periods of levodopa response and improves with control of motor symptoms.

Two key questions to ask any patient in whom depression is suspected are: (1) Has there been any change in your mood lately (feeling depressed in the past 2 weeks specifically)? (2) During the past few weeks, have you had little or no interest or pleasure in taking part in activities? If the answers to either of these questions is yes, inquire about other depressive symptoms.

**Major depression**—the sort of depression that requires clinical attention—is defined as depressed mood or diminished interest plus 4 other symptoms for 2 or more weeks. The mnemonic SIGECAPS refers to a list of the pertinent symptoms:

- Sleep increase/decrease.
- Interest in formerly pleasurable activities diminished.
- Guilt, low self-esteem.
- Energy poor.
- Concentration poor.
- Appetite increase/decrease.
- Psychomotor agitation or retardation.
- Suicidal ideation.

Note that symptoms such as anergia, apathy, insomnia, and weight loss are inherent to PD and do not in themselves indicate the presence of depression. Although depressed patients may present with and complain of somatic features, the diagnosis of depression requires the presence of one of the core psychological features: depressed mood or anhedonia.

The American Academy of Neurology (AAN) recommends 2 screening tests for patients in whom depression with PD is suspected: the Beck Depression Inventory-I and the Hamilton Depression Rating Scale.

Although suicide should always be considered when assessing depression, it is of interest that the suicide rate in patients with PD is relatively low—about one tenth that of the general US population. One could speculate that the relatively low suicide rate in these patients is a consequence of their immobility, apathy, or anergia. But in truth we do not know what accounts for this remarkably low suicide rate.

According to one study, observer-rated and patient-rated feelings of 3 specific measures alone (feeling impaired, disabled, and handicapped) contribute to about 60% of depression in PD. The strongest single predictor of depression in PD is clinician-rated disability as measured by Schwab and England scores. These scores reflect the patient's ability to perform activities of daily living in terms of speed and independence.

**TREATMENT GUIDELINES**

As with other persons with clinical depression, only about a third of affected patients with PD receive intervention for depression. For depression of moderate or greater severity, antidepressants are the mainstay of treatment both in general and in the context of depression in PD. Keep in mind that PD is a chronic progressive disorder, and just as anti-parkinsonian drugs can become less effective over time, antidepressants also may need to change, depending on the associated signs and symptoms and stage of the disease. Anxiety, anergia, anhedonia, sleep disturbances, and dementia all influence the choice of antidepressants.

The recent AAN practice parameter for the treatment of depression in PD points out that few antidepressants have been evaluated for this condition in randomized controlled trials (RCTs), and for the most part those trials yielded inconclusive results. Paradoxically, although amitriptyline is
the only antidepressant with some firm evidence of efficacy, it is not recommended as necessarily
the best treatment because of anticholinergic and other adverse effects. In the absence of RCTs,
other sources of information—uncon- trolled trials, case reports, clinical experience, pharmacology,
clinical effects and adverse effects of the available medications—must guide treatment decisions.
Depression in PD responds to tricyclic antidepressants (TCAs), SSRIs, serotonin norepinephrine
reuptake inhibitors (SNRIs), and other conventional antidepressant agents. Dopamine agonists used
for treating PD also may help with mood symptoms in early-onset depression in PD. Why some drugs
fail and some work is poorly understood. Sedating agents such as TCAs may be more useful in
patients who have sleep disturbances, whereas SSRIs, which are more stimulating, may be indicated
when anhedonia and apathy are prominent.

Consider drug interactions before embarking on treatment with an antidepressant. Amoxapine, an
antidepressant with dopamine-receptor blocking properties, should be avoided because of its
potential for dopamine blockade and the risk of producing neuroleptic malignant syndrome. Lithium also has been implicated in occasionally inducing or exacerbating parkinsonian symptoms.

SSRIs prevent serotonin reuptake, while the monoamine oxidase inhibitor selegiline prevents the
breakdown of serotonin. Thus, SSRIs in combination with selegiline increase the theoretic risk of
serotonin syndrome and should be avoided. The serotonin syndrome is characterized by increased
brain serotonin levels leading to restlessness followed by drowsiness, stupor, and coma.

Trazodone may be a better choice for elderly persons because of its lower anticholinergic potential and
decreased orthostatic adverse effects. Bupropion, mirtazapine, and selegiline should be considered as first-line choices for treating depression in PD. Bupropion has been shown to exert a beneficial effect on PD, particularly for patients suffering from parkinsonian fatigue, but induction of psychotic symptoms may be a risk associated with it. Mirtazapine has been shown to be helpful with tremors. Modafinil (Provigil) and other stimulants also may be considered for fatigue in patients with PD.

Electroconvulsive therapy should be considered for those in whom adequate medical management
has failed or in whom intolerable adverse effects from antidepressants have developed.

Psychotherapy, widely used to treat depression in general, has received scant attention as a
treatment for depression in PD. A small clinical trial and a literature review suggest that cognitive
behavioral therapy has a promising role in managing depression in PD.

SPECIAL CONSIDERATIONS

Several clinical vignettes follow the format of a recent review:

- A patient aged 55 years in whom PD and depression were recently diagnosed: consider a
dopamine agonist. The second-generation non-ergot dopamine agonists pramipexole
(Mirapex) and ropinirole (Requip) improve the motor symptoms. Pramipexole also has been
shown to be as effective as fluoxetine in the management of depression in PD. Stimulation
of D3 receptors, which are widely expressed in the mesolimbic pathways, may be responsible
for the antidepressant effects of these dopamine agonists. Of note, however, is that in
patients older than 70 years with cognitive changes, these dopamine agonists may be more
likely to induce hallucinations and delusions than levodopa.

- A patient aged 65 years with PD and depression who has excessive worries and anxiety: an
SSRI or an SNRI is a good first choice. Do not expect a significant antidepressive effect for 3
to 4 weeks, and remember that the maximum recommended dose should be tried before
switching to another antide- pressant. Adverse effects such as sedation, dry mouth, weight
gain or loss, and sexual dysfunction are not uncommon and should be discussed with the
patient in advance. An inadequate response or intolerance should not preclude the physician
from switching within the same class of drugs.

- A patient aged 65 years with PD and depression who stays in bed and has little interest in his
surroundings: A patient with apathetic affect may respond to dopamine agonists; however,
an SSRI or an SNRI should be considered if comorbid anxiety is suspected. Patients with
apathy and anhedonia in the presence of PD and depression may be on the path to
dementia. A cholinesterase inhibitor may be considered in such cases. A recent review
favors the use of cholines- terase inhibitors in the use of PD and dementia with Lewy
bodies.

- A patient aged 80 years with long-standing PD and depression who is now seeing objects that

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are not there and hearing voices: In patients with delusional, disinhibited, and psychotic features, levodopa-induced psychosis must be ruled out along with reactions to amantadine (a dopamine agonist) and selegiline. As with any other elderly patient, a urinary tract infection or upper respiratory tract infection, electrolyte imbalance, and dehydration should be considered. It can be difficult to differentiate between drug-induced psychosis and psychotic depression. Judicious use of an atypical antipsychotic agent should be considered in the case of psychotic depression.

It should be noted that these patients are prone to extrapyramidal syndromes. The only medication with a convincing beneficial effect in this context and with no worsening of PD is clozapine at a mean dosage of 25 mg/d.\textsuperscript{19,33} However, extra caution is required in prescribing clozapine and in patient selection. Use of quetiapine (Seroquel) in PD patients with psychosis is well documented and is associated with fewer complications than those seen with clozapine.\textsuperscript{34}

- **A patient aged 60 years with PD and depression who is unable to sleep:** a sedating antidepressant is an obvious choice in this case. Tricyclics and trazodone are beneficial for insomnia, but their anticholinergic adverse effects may worsen patient memory. A very common adverse effect of trazodone is sedation. This can be used to advantage. However, orthostasis and priapism occur with trazodone.

REFERENCES


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