Neuropsychiatric Aspects of Parkinson's Disease

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Parkinson's disease (PD), a disorder characterized by movement abnormalities, is frequently complicated by psychiatric syndromes. Psychiatric assessment of the PD patient requires familiarity with the motor and cognitive aspects of PD, the various effects of antiparkinsonian medications, and how these relate to mental status changes and psychiatric phenomena. This review describes the various motor and nonmotor features of PD and focuses on the differential diagnosis of affective disorders in PD and their treatment. (Psychosomatics 2000; 41:15–23)

Psychiatric syndromes as well as cognitive impairment frequently complicate Parkinson's disease (PD), a neurodegenerative disorder defined by its movement abnormalities. Development of psychopathology in PD is attributed to a number of factors, including underlying disease processes related to PD, medication effects, and psychological reactions to the illness. This review focuses on mood disturbances in PD and has two major thrusts. The first is to convey the heterogeneity of PD and how its motor and cognitive features overlap or enhance the clinical features of psychiatric illnesses. The second emphasis is on the differential diagnosis and treatment of mood disorders in PD. Although major depression is common, conditions with similar features, such as apathetic syndromes and anxiety disorders, are also encountered in PD and warrant distinct consideration and management.

CLINICAL FEATURES OF PARKINSON'S DISEASE: RELATIONSHIP TO PSYCHOPATHOLOGY

The disease is named after James Parkinson, a general practitioner in London during the 19th century, who described the features of PD in six individuals.[1] Currently, PD affects about 1% of the population over age 50 and up to 2.5% of the population over age 70. U.S. government figures from 1994 placed annual societal costs related to PD at $20 billion.[2] The clinical onset of PD is typically around age 60, although juvenile or young-adult onset of the disease has been reported. It affects all races about equally, with reported discrepancies between incidence rates among Caucasians and African Americans said to be related to population sampling.[3] Men are affected slightly more often than women.

Motor Features

The definitive diagnosis of PD is based on specific neuropathological findings: degeneration and loss of pigmented neurons of the substantia nigra (pars compacta) and intraneuronal inclusion bodies (Lewy bodies) in the substantia nigra.[4] The hallmark clinical signs of PD are its motor triad: 1) a pill-rolling rest tremor; 2) rigidity; and 3) bradykinesia/akinesia (slowness of movement and absence of movement, respectively). The clinical diagnosis of PD requires some combination of these cardinal signs, but there is a great deal of heterogeneity among patients, and none of these signs is specific to PD.[5] Furthermore, the classic motor signs may not be obvious early in the course of PD and might be mistaken for depressive phenomena.[6] For example, one clinic patient noted that others had commented for nearly 10 years before the onset of

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more obvious PD motor signs that she was not smiling in photographs. In one earlier large clinical series, only 70% of the PD patients demonstrated the classical rest tremor at the time of initial diagnosis, and about 5% presented with depression or nervousness.[7] In the same series, a subgroup complained of various somatic symptoms that, especially in the presence of facial masking or fatigue, might suggest a primary depressive illness rather than PD.

A host of symptoms are related to the PD motor triad, some of which also overlap with the core features of mood disorders. Accordingly, PD can be misdiagnosed as a primary depressive illness, and concomitant depression may go unrecognized in the PD patient. Even when both conditions (PD and depression) are diagnosed concurrently, it can be difficult to tease apart which clinical phenomena are related to primary motor vs. primary psychiatric pathology (see Table 1). For example, the slowed movements of bradykinesia are a well-recognized component of depression, usually described as psychomotor retardation. Stooped posture, reduced dexterity, decreased facial expression (hypomimia), and small handwriting (micrographia) are also related to bradykinesia.

Tremor, seen in up to 80% of PD patients,[8] can be a significant component of anxiety syndromes. Considering that postural and action tremors are also common in PD and that some patients never develop a rest tremor, tremor may go unrecognized as a feature of PD or a related neurological condition until other motor signs emerge. Some patients also report a sensation of internal tremor that is associated with anxiety.[9] Rigidity, represented by increased tone during passive motor movements, is often manifest as cramps, aches, or pains. These motor features contribute to gait and postural disturbances, with a loss of righting reflexes, unsteadiness, imbalance and falls, sometimes up to multiple times daily, as the disease progresses. Sialorrhea, dysarthria, visual and genitourinary dysfunction, sleep disturbances, sweating, seborrhea, edema, constipation, paresthesias, fatigue, and a decreased sense of smell are other common complaints throughout the course of the illness. Mood disorders and antidepressant treatments can exacerbate any of these phenomena.

TABLE 1. Symptoms common to Parkinson's disease and major depression

	Parkinson's Disease	Major Depression
Motor	Bradykinesia	Psychomotor
	Stooped posture	± Stooped posture
	Masked facies	Restricted/depressed affect
Cognitive	Impaired memory	Impaired memory
	Impaired concentration	Impaired concentration
	Indecisiveness	Indecisiveness
Vegetative	Decreased energy	Decreased energy
	Fatigue	Fatigue
	Impaired sleep	Impaired sleep
	Appetite changes	Appetite changes
Somatic	Physical complaints	Physical complaints

Cognitive Deficits

The cognitive features of PD are present to varying degrees early in the course of the disease and are multifactorial in origin, involving subcortical–frontal dopaminergic systems as well as extrastriatal systems.[10–14] The various forms of executive dysfunction, visuospatial impairment, memory impairment, and attention deficits that occur in PD can render patients less able to accomplish familiar tasks or make them feel overwhelmed in situations that were not previously challenging. The presence of a mood disorder, which can precede, accompany, or follow cognitive changes, may also confound assessment of cognitive impairment and intensify deficits.[15,16] About 25% of patients develop an Alzheimer-type dementia with cortical features of aphasia, apraxia, and memory deficits.[17,18] While depressive disorders can coexist with dementia in PD, families and clinicians may also misinterpret a tendency to reduce social interactions in early dementia as a sign of depression rather than impaired cognition only and seek antidepressant treatment. The distinction is important, since PD patients with dementia are especially vulnerable to psychoactive medication effects and the development of delirium, a leading cause of nursing home placement in PD.[19]

Treatment of Motor Features and Related Complications

Most antiparkinsonian medications reduce the primary motor symptoms through increased dopamine availability, although new therapies are emerging.[20] However, delirium, mood changes, and psychosis are common complications of therapy.[21,22] Levodopa, a dopamine precursor, is the mainstay of PD therapy and the most effective medicine for controlling PD motor symptoms. Levodopa is generally available as a combined preparation with carbidopa, an enzyme that inhibits the peripheral metabolism of dopamine. Bromocriptine, pergolide, and newer agents such as pramipexole and ropinirole are dopamine-receptor agonists that act by increasing postsynaptic dopamine activity. Deprenyl or selegiline, a monoamine oxidase-B inhibitor, and tolcapone, a catecholamine transferase inhibitor, inhibit dopamine metabolism and increase synaptic dopamine.

Amantadine and anticholinergic agents such as trihexiphenidyl and benztropine are also used to treat motor symptoms.

Over long-term treatment, the beneficial motor effects of levodopa wane, and its adverse motor side effects become seriously limiting.[23] These side effects, in combination with the disease itself, further influence mood stability.[24] The period of improved motor functioning is referred to as the "on" state and the period of reduced mobility at the end of a dosing interval is referred to as the "off" state. To relieve "on–off" motor fluctuations, higher doses of levodopa are required at more frequent intervals (e.g., every 2–3 hours), or even as a constant infusion, in rare cases, to achieve comparable efficacy. Eventually, most patients on chronic levodopa therapy also develop abnormal, involuntary hyperkinetic movements, referred to as drug-induced dyskinesias.[25] These movements are usually peak-dose choreic or dystonic motions of the extremities, trunk, or even head. The "on–off" motor fluctuations and dyskinesia can be quite dramatic, with complete immobility or "freezing" in the "off" state and extreme motor activity in the "on" state, accompanied with flailing and writhing dyskinetic movements.[26]

Motor fluctuations are a significant problem in the long-term management of the PD patient. Most remarkable, though, is how individuals vary greatly in terms of their ability to tolerate motor fluctuations. Whereas some patients find these fluctuations distressing, disabling, disfiguring, or embarrassing, other patients are indifferent. Psychiatric illness and cognitive abilities further modify how patients cope with fluctuations. Emotional triggers may provoke or intensify motor fluctuations, although sometimes there are no clear precipitants.[22] Anticipatory anxiety, for example, associated with the desire to arrive on time for an appointment, is commonly cited as a cause of motor fluctuations. Anxiety can also be a response to motor dysfunction. Sudden akinesia, or "freezing," can be disabling and even dangerous, such as when attempting to leave a public restroom, reaching for one's wallet in a checkout line, or crossing a street. In some instances, positive emotions also incite motor fluctuations. One patient, a musician, described how her passionate feelings while listening to classical music provoked extreme dyskinesias.

In addition to psychological reactions to the motor fluctuations, mood changes can be temporally related to the motor fluctuations, suggesting a primary role for dopaminergic mechanisms.[27] Typically, patients with such mood changes describe depression or anxiety in the "off" period and a neutral or elevated mood in the "on" state.[28,29] Panic states with prominent autonomic symptoms can occur as the medication wears off, but anxious states may be protracted even after there is a motor response to levodopa.[30,31] There are also descriptions of irritability, apathy, hallucinosis, psychosis, screaming, and cognitive slowing during "off" periods and hypersexuality, hypomania, withdrawal, and thought racing during "on" periods.[26] Management of mood disorders associated with motor fluctuations is complicated. Management requires primary attention to the antiparkinsonian regimen, and determination of whether treatment of a more pervasive mood disorder is also warranted.

Neurosurgical therapies for PD, started over 30 years ago, provide additional relief of symptoms and may limit complications related to medications. Pallidotomy is indicated for treatment-related dyskinesias and motor fluctuations in PD. Thalamotomy is used to treat tremor in PD and other conditions such as essential tremor or multiple sclerosis. Several analyses have shown reductions in anxiety and depression following pallidotomy that are unrelated to the improved motor function.[32–34] More recently, the availability of deep brain stimulation (DBS) offers an alternative to destructive lesions. With DBS, a patient-controlled pacemaker-like device sends electrical impulses to the thalamus or globus pallidus, as needed, to reduce tremor. Fetal brain tissue implantation remains experimental.[35]

PSYCHIATRIC COMPLICATIONS

For many years, it was thought that psychiatric phenomena in PD, particularly affective changes, were related to the lack of dopamine and the motor impairment. After availability of levodopa treatment in the 1960s, it became apparent that up to two-thirds of PD patients have persistent affective disturbances, despite antiparkinsonian treatment, and that the mood changes were amenable to antidepressant treatment.[36] In this context, it is now apparent that the underlying neurodegenerative disorder is a major cause of psychiatric disturbances in PD, although psychological reactions to the clinical illness are also important to consider. Integral to the development of PD is the loss of dopaminergic neurons in the substantia nigra and secondary effects on projection systems involving the caudate nucleus and putamen (striatum) and frontal and cingulate cortical regions. Accordingly, the diverse motor and nonmotor features of PD and their interrelationships are thought to result from dysfunction of putative cortical–basal ganglia–thalamic neural loops.[37,38]

In addition to loss of dopaminergic neurons, PD is

accompanied by degeneration of noradrenergic neurons in the locus coeruleus, serotonergic neurons in the dorsal raphe, and cholinergic neurons in the nucleus basalis and their attendant projections systems. Differential degrees of pathology among these neuronal systems are thought to underlie the heterogeneous motor, cognitive, and psychiatric features of PD. For example, Paulus and Jellinger[39] showed different neuropathological patterns in akinetic-rigid PD, compared with tremor-dominant PD. Also, the series by Paulus and Jellinger showed more cortical Alzheimer-type lesions and greater neuronal loss in the medial substantia nigra in the dementia subjects they studied, whereas the depressed patients had increased neuronal loss in the dorsal raphe. However, the patients with psychosis had no specific neuropathologic features.

The interrelations of motor, cognitive, and psychiatric phenomena in PD create unique challenges for assessment of psychopathology in a given patient. Clearly, the mere experience of motor disability influences mental state. However, some patients with very mild motor impairment are greatly incapacitated by psychiatric disturbances, whereas others with severe motor symptoms maintain their mental health. Cognitive deficits exert additional independent effects on mental state but further influence how one copes with the motor disability. In turn, psychiatric phenomena can exacerbate cognitive and motor dysfunction and influence mental status in their own right. Further complicating assessment is the dynamic nature of psychopathology in PD due to fluctuating psychoactive medication effects, plus the progressive nature of the disease. In addition to PD-specific factors, equally important are the usual factors relevant to any psychiatric evaluation (e.g., prior psychiatric conditions, family history, temperament, coping styles, social resources, and life events). The clinician's challenge is to integrate and understand the role of various PD-related and non–PD-related factors on psychopathology and determine the salient influences, which are then targets of psychiatric treatment.

MOOD DISTURBANCES

Up to 90% of PD patients with idiopathic PD experience psychiatric complications, including major mood disorders (major depression, dysthymia, or bipolar disorder); adjustment disorders; disabling anxiety syndromes; drug-induced mood changes; pathological tearfulness; dementia; apathetic states; psychosis; or delirium.[40] Mood disturbances, the emphasis in this review, are especially common and present diagnostic and management challenges to clinicians. Since most studies of affective disturbances in PD have focused on depression, clinical practice has followed accordingly. Less attention has been paid to the differential diagnosis of depressive phenomena and the characterization and management of related affective syndromes. Discernment of these syndromes requires insight into the various motor and cognitive features of PD, as described earlier, as well as the phenomenology of each discrete condition.

Depression

The prevalence of major depression in PD is estimated to be 40%,[41] with reported prevalence rates ranging from 4% to 70%.[42] Major depression accounts for about half of the cases with significant depression, whereas others experience adjustment disorders, dysthymia, or bipolar disorder. The major depressive syndrome is generally of moderate-to-severe intensity and is frequently accompanied by anxiety symptoms.[43] In general, studies have shown that there is no clear relationship to age at onset or duration of PD, family history of mood disorders, or a personal history of previous depressive episodes.[42]

A central issue is whether the major depressive syndrome in PD is a reaction to the motor disability or whether the syndrome is intrinsic to the disease processes of PD. In support of the latter idea is considerable evidence that depression can precede development of motor symptoms, suggesting that the depression is in itself a neurological sign.[15,16,44,45] Other studies suggest that depression is a reaction to the disability, on the basis of correlations between depression severity and motor impairment.[46,47] Although these relationships are not always detected,[15,44,48] correlations between depression severity and motor impairment in late-stage PD suggest a differential basis for depressive syndromes as the disease progresses.[48]

Clearly, the relationship between mood and motor phenomena in PD is complex. Interestingly, motor improvement with medications is not associated with improved mood,[49–51] but successful treatment of depression is associated with better motor function.[48] A few studies also demonstrate close relationships between depression and impaired cognition during depressive episodes that reverse after treatment of the mood syndrome.[15,48,52,53]

A number of studies implicate serotonin in the pathogenesis of depression in PD. Neurochemical studies show reduced peripheral and central serotonin metabolites (5-HIAA),[16,54] improved depressive symptoms with serotonergic therapies,[55] and decreased platelet-imipramine binding in depressed PD patients.[56,57] A neuroanatomical

basis for depression in PD is suggested by neuroimaging studies. These show relative hypometabolism in the caudate and inferior orbital-frontal regions[58] and in the medial-frontal lobes[59] in depressed PD patients relative to non-depressed PD patients and control subjects.

Apathy

Apathy, defined as a state of diminished motivation, can present in PD as a symptom of major depression, delirium, dementia, or demoralization or as an independent syndrome.[60] With the latter, the patient's inactivity and indifference are particularly frustrating for families and caregivers who frequently perceive the patient as depressed. Two studies have examined apathy in PD in detail.[61,62] In the earlier study,[61] depression and apathy coexisted in 30% of the sample, and 12% of subjects had apathy alone. Compared with the euthymic PD patients, there were no differences in age, gender, duration of PD, or motor impairment, but the patients with apathetic syndromes tended to have a later age-at-onset relative to those with PD plus depression. Also, the patients with apathy had specific deficits on neuropsychological tests, although this finding was not confirmed in the later report.[62]

The features of apathy are analogous to other aspects of PD, in particular bradyphrenia and bradykinesia,[63] suggesting that some cognitive, behavioral, and motor features in PD are related to shared pathophysiology. Evidence that bradyphrenia is related to neuronal loss in the locus coeruleus implicates a role for noradrenergic dysfunction.[64,65]

Emotionalism

Several studies have recognized an increased frequency of crying or emotional lability in PD patients relative to control subjects.[36,65–67] Emotionalism in PD refers to heightened and excessive sentimentality that is inappropriate, unmotivated, and involuntary. It is usually fleeting, but there are often visible tears or weeping. Excessive tearfulness in PD can occur as a feature of major depression, emotional incontinence (also referred to as pathological laughter or crying), delirium, or with benzodiazapine use. Pathological laughter can also occur but is less common.[68] Patients describe how uncontrollable and excessive emotionality is triggered by a variety of positive and negative stimuli, such as poignant scenes on television, concerns about the future, or watching someone do a kind deed. For some patients, emotionalism leads to severe social embarrassment, along with phobic avoidance. Patients and/or their families will often conclude that the crying means they "must be depressed," and are relieved to learn that this phenomenon occurs frequently in PD, often in the absence of a more pervasive depressive syndrome. Closer examination of emotionalism in PD showed that nearly 40% of patients reported increased tearfulness since the onset of PD, and 11% had more pervasive emotionalism.[65] There were no consistent associations between emotionalism and cognitive impairment or major depressive syndromes.

Anxiety

Anxiety is a common problem in PD, but relatively little attention has been paid to this phenomenon.[42] While anxiety can present as an isolated symptom or as a feature of depression,[69] clinically significant anxiety syndromes occur in up to 40% of PD patients.[70] Particularly common are generalized anxiety disorder, social phobia, and panic disorder, which has a prevalence rate of 25% in some series.[30,71,72] These syndromes may also precede or accompany a major depressive syndrome, and can persist after the depressive illness is treated. Above all, they should be regarded as distinct from anxiety, which is an understandable psychological response to motor impairment or other personal concerns. These syndromes are also independent of anxiety that occurs with fluctuations in levodopa levels.[29] Autonomic dysfunction, a common complication of PD regardless of psychiatric status, can also be associated with anxiety or depression. Accordingly, somatic complaints related to autonomic symptoms (e.g., flushing, dizziness, urinary frequency, or changes in heart rate) must be evaluated carefully because they can be misdiagnosed (and mistreated), as if they represented affective syndromes.[73]

The anxiety syndromes in PD appear related to underlying brain disease, with evidence implicating noradrenergic dysfunction.[74–76] In several studies, anxiety syndromes preceded the onset of motor symptoms,[33,72,77] but anxiety disorders can also develop later.[30,78] Some studies show relationships between panic symptoms and fluctuations in antiparkinsonian medications and motor symptoms,[30,43] but clear relationships among anxiety and disability ratings, motor symptoms, and dopaminergic medications have not been established.[69,72,78,79] However, discrete anxiety syndromes in PD may represent regional differences in PD-related pathology. In a recent analysis, cognitive performance in PD patients with and without anxiety disorders was relatively better in the anxious group, especially on tasks involving frontal lobe cognitive processes.[31]

Psychosis

Hallucinations and delusions occur in up to 40% of PD patients and are a major precipitant of nursing home placement.[19] Psychosis is related to dopaminergic medications in about 20% of PD patients,[80] a relationship that tends to overshadow other important causes of psychosis in PD. Psychosis can also develop spontaneously or in association with cognitive impairment, on–off fluctuations, mood disturbance, other psychoactive medications, and/or delirium.[22] The psychotic syndromes are frequently categorized into three general groups:[81] The first group consists of visual hallucinations that tend to be vivid depictions of animals or people that occur in a clear sensorium and are accompanied by insight. The second type generally involves more persistent hallucinations or delusions in a clear sensorium but with diminished insight. This second state often requires definitive antipsychotic treatment. In the third group, hallucinations or delusions occur in the context of a delirium.

Hallucinations and delusions also occur as features of major depressive or manic syndromes, diagnoses that can be overlooked when patients are especially agitated. A population-based study of psychosis showed associations among psychotic symptoms and age, stage, and diagnostic subgroup of PD, severity of depression, and cognitive impairment, whereas antiparkinsonian medications did not discriminate between the PD patients with and without psychosis.[82] This finding suggests more widespread pathologic brain involvement in the setting of psychosis and argues against a prominent role for antiparkinsonian medicines in the development of psychosis. A role for cholinergic deficits in the psychosis of PD has also been suggested.[83]

TREATMENT

Several reviews describe the treatment of psychiatric conditions in PD, including strategies for prescribing medications and nonpharmacological approaches.[22,80,84–87] However, there are few empirical data to guide treatment; the majority of the reports involve open-label trials or descriptive case studies. A recent meta-analysis noted only 12 controlled trials in the literature on treatment of depression in PD and noted that the quality of most studies was poor.[88] Further, none involved newer antidepressants available over the last decade. The situation is similar for treatment of psychosis in PD, except for one recent, large, multicenter, double-blind, placebo-controlled trial that demonstrated efficacy of low-dose clozapine (6.25 mg–50 mg/day).[89] Behavioral or medical treatments of anxiety, emotionalism, or apathy in PD have not been studied.

Most treatments are aimed at the specific syndromes just described. When psychotropic medications are indicated, the most important point to remember is that the underlying brain disease and older age of most PD patients renders them especially vulnerable to adverse effects. Also, psychiatric medications run the risk of aggravating motor and cognitive symptoms. For every patient, the first step should include careful review of antiparkinsonian and other medical treatments, elimination of unwarranted polypharmacy, and minimization of medication fluctuations and adverse drug–drug interactions. Many patients use nonprescription and herbal treatments, and these should be considered in the overall treatment plan. As treatment proceeds, motor, cognitive, and psychiatric functioning, including the risks of falls, confusion, oversedation, and enhanced parkinsonism, should be monitored carefully, with adjustments made to balance treatment effects.

Dosing and treatment duration play a role in nonresponse or side effects. Often, patients respond to small amounts of medicine (e.g., nortriptyline elixir, 5 mg qhs or clozapine, 6.25 mg qod), but other patients require and tolerate standard or higher doses. The risk of developing serotonin syndrome or hypertensive reactions when combining selegiline with antidepressant medications is often discussed;[90] however, most patients tolerate this combination.[22]

Given limited data on the use of antidepressant agents in PD, medication choices are usually based on consideration of side-effect profiles. Controlled antidepressant trials, conducted most recently in the 1980s, show particular efficacy for tricyclic antidepressants such as nortriptyline, which inhibits serotonin–norepinephrine reuptake, and bupropion, which inhibits norepinephrine and dopamine reuptake.[88,91–93] A few studies describe effects of more recently developed antidepressants.[86] The putative role of serotonin in PD-related depression suggests a role for serotonin reuptake inhibitors. Response to these varies,[50,94,95] and motor symptoms can worsen.[96,97] Electroconvulsive therapy (ECT) is another safe and effective treatment for depression in PD.[98] Studies of the use of ECT for PD patients without depression show sustained motor improvement up to 1 year in some individuals.[99] In general, benzodiazapines are poorly tolerated for treatment of anxiety, agitation, or sleep disturbances associated with depression because of adverse cognitive effects, although there are exceptions. Low-dose trazodone (e.g., 25 mg–100 mg) can help with insomnia.

Treatment of psychosis generally involves adjusting

antiparkinsonian medications, addressing problems with sleep and anxiety, patient and caregiver education, and, ultimately, if necessary, antipsychotics. ECT is used to treat psychotic depression as well as dopamine-induced psychosis.[100] Since most antipsychotic medications block dopamine type II receptors, there is the risk of increased and markedly disabling parkinsonism. However, atypical agents (e.g., clozapine, olanzapine, quetiapine, and risperidone) have been shown to be effective at low doses for the treatment of psychosis.[80,87,89] Unfortunately, many patients still do not tolerate these agents, either developing confusion/delirium, intolerable sedation, or increased parkinsonism. Odansetron, a pure 5-HT3 inhibitor is also an effective antipsychotic,[101] but its expense often precludes continuing treatment. I have found odansetron useful for postoperative agitation. Cholinergic agents (e.g., donepezil) may also reduce psychosis in PD, implicating nondopaminergic mechanisms.[83]

Given the complexity and risks of medications for treatment of psychiatric problems in PD, nonpharmacologic treatments are a significant cornerstone of treatment.[84] Many patients have never been evaluated psychiatrically, so the initial consultation can prove beneficial to patients and family members. Education on the signs and symptoms of psychiatric conditions, their potential relationship to the underlying neurodegenerative disease, and the relative contributions of the motor features of PD helps patients and their families cope better with the presenting problems. Psychotherapy ranges from supportive to insight-oriented therapy, including grief counseling.[102] Coping styles and strategies as well as caretaker status also need to be addressed. Homecare programs can assist in patient management and enhance function through services such as occupational, physical, and speech therapy. Visiting nurses, including those with psychiatric training, and social workers allow more frequent observation of the patient than is possible with an office-based practice and provide additional caretaker support.[103] Patients are also encouraged to take part in relaxation training, physical exercise, and support groups to promote overall well-being and functioning.

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References

1. Parkinson J: An Essay on the Shaking Palsy. London, UK, Sherwood, Neely, and Jones, 1817
2. Cummings JL: Understanding Parkinson disease. JAMA 1999; 281:376–378
3. Tanner CM, Hubble JP, Chan P: Epidemiology and genetics of Parkinson's disease, in Movement Disorders: Neurologic Principles and Practice. Edited by Watts RK, Koller WC. New York, McGraw-Hill, 1997, pp 137–152
4. Hughes AJ, Daniel SE, Kilford L, et al: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55:181–184
5. Gelb DJ, Oliver E, Gilman S: Diagnostic criteria for Parkinson disease. Arch Neurol 1999; 56:33–39
6. Gonera EG, van't Hof M, Berger JC, et al: Symptoms and duration of the prodromal phase in Parkinson's disease. Mov Disord 1997; 12:871–876
7. Hoehn MM, Yahr MD: Parkinsonism: onset, progression, and mortality. Neurology 1967; 17:427–442
8. Martin WE, Loewenson RB, Resch JA, et al: Parkinson's disease: clinical analysis of 100 patients. Neurology 1973; 23:783–790
9. Shulman LM, Singer C, Bean JA, et al: Internal tremor in patients with Parkinson's disease. Mov Disord 1996; 11:3–7
10. Cooper JA, Sagar HJ, Jordan N, et al: Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. Brain 1991; 114:2095–2122
11. Cooper JA, Sagar HJ, Doherty SM, et al: Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease: a follow-up study of untreated patients. Brain 1992; 115:1701–1725
12. Levin BE, Katzen HL: Early cognitive changes and nondementing behavioral abnormalities in Parkinson's disease. Adv Neurol 1995; 65:85–95
13. Dubois B, Pillon B: Cognitive deficits in Parkinson's disease. J Neurol 1997; 244:2–8
14. Gotham AM, Brown RG, Marsden CD: "Frontal" cognitive function in patients with Parkinson's disease "on" and "off" levodopa. Brain 1988; 111:299–321
15. Mayeux R, Stern Y, Rosen J, et al: Depression, intellectual impairment, and Parkinson disease. Neurology 1981; 31:645–650
16. Sano M, Stern Y, Williams J, et al: Coexisting dementia and depression in Parkinson's disease. Arch Neurol 1989; 46:1284–1286
17. Mohr E, Litvan I, Williams J, et al: Selective deficits in Alzheimer and parkinsonian dementia: visuospatial function. Can J Neurol Sci 1990; 17:292–297
18. Mohr E, Mendis T, Grimes JD: Late cognitive changes in Parkinson's disease with an emphasis on dementia. Adv Neurol 1995; 65:97–113
19. Goetz CG, Stebbins GT: Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993; 43:2227–2229
20. Jankovic J: New and emerging therapies for Parkinson's disease. Arch Neurol 1999; 56:785–790
21. Young BK, Camicioli R, Ganzini L: Neuropsychiatric adverse effects of antiparkinsonian drugs: characteristics, evaluation and treatment. Drugs Aging 1997; 10:367–383
22. Olanow CW, Koller WC: An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. American Academy of Neurology. Neurology 1998; 50(suppl 3):S1–S57
23. Koller WC, Rueda MG: Mechanism of action of dopaminergic

agents in Parkinson's disease. Neurology 1998; 50(suppl 6):S11–S14
24. Cantello R, Gilli M, Riccio A, et al: Mood changes associated with "end-of-dose deterioration" in Parkinson's disease: a controlled study. J Neurol Neurosurg Psychiatry 1986; 49:1182–1190
25. Marsden CD, Parkes JD: Success and problems of long-term levodopa therapy in Parkinson's disease. Lancet 1977; 1:345–349
26. Quinn NP: Classification of fluctuations in patients with Parkinson's disease. Neurology 1998; 51 (suppl 2):S25–S29
27. Brown RG, Marsden CD, Quinn N, et al: Alterations in cognitive performance and affect-arousal state during fluctuations in motor function in Parkinson's disease. J Neurol Neurosurg Psychiatry 1984; 47:454–465
28. Nissenbaum H, Quinn NP, Brown RG, et al: Mood swings associated with the "on-off" phenomenon in Parkinson's disease. Psychol Med 1987; 17:899–904
29. Maricle RA, Nutt JG, Carter JH: Mood and anxiety fluctuation in Parkinson's disease associated with levodopa infusion: preliminary findings. Mov Disord 1995; 10:329–332
30. Vazquez A, Jimenez-Jimenez FJ, Garcia-Ruiz P, et al: "Panic attacks" in Parkinson's disease: a long-term complication of levodopa therapy. Acta Neurol Scand 1993; 87:14–18
31. Marsh L, Cahn DA, Spears S, et al. Anxiety in Parkinson's disease: relationship to cognitive function (abstract). J Neuropsychiatry Clin Neurosci 1998; 9:653
32. Riordan HJ, Flashman LA, Roberts DW: Neurocognitive and psychosocial correlates of ventroposterolateral pallidotomy surgery in Parkinson's disease. Neurosurg Focus 1997; 2:1–9
33. Marsh L, Solvasson B, Cahn DA, et al: Psychiatric outcome after pallidotomy for Parkinson's disease (abstract). Biol Psychiatry 1997; 41(suppl):107S
34. Masterman D, DeSalles A, Baloh RW, et al: Motor, cognitive, and behavioral performance following unilateral ventroposterior pallidotomy for Parkinson disease. Arch Neurol 1998; 55:1201–1208
35. Olanow CW, Kordower JH, Freeman TB: Fetal nigral transplantation as a therapy for Parkinson's disease. Trends Neurosci 1996; 19:102–109
36. Mindham RH: Psychiatric symptoms in Parkinsonism. J Neurol Neurosurg Psychiatry 1970; 33:188–191
37. Alexander GE, DeLong MR, Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986; 9:357–381
38. Wichmann T, DeLong MR: Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996; 6:751–758
39. Paulus W, Jellinger K: The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 1991; 50:743–755
40. Starkstein SE, Mayberg HS: Depression in Parkinson's disease, in Depression in Neurologic Disease, edited by Starkstein SE, Robinson RG. Baltimore, MD, Johns Hopkins University Press, 1993, pp 97–116
41. Mayeux R: The mental state in Parkinson's disease, in Handbook of Parkinson's Disease, 2nd Edition. Edited by Koller WC. New York, Marcel Dekker, 1992, pp 159–184
42. Cummings JL: Depression and Parkinson's disease: a review. Am J Psychiatry 1992; 149:443–454
43. Schiffer RB, Kurlan R, Rubin A, et al: Evidence for atypical depression in Parkinson's disease. Am J Psychiatry 1988; 145:1020–1022
44. Santamaria J, Tolosa E, Valles A: Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism. Neurology 1986; 36:1130–1133
45. Fukunishi I, Hosokawa K, Ozaki S: Depression antedating the onset of Parkinson's disease. Jpn J Psychiatry Neurol 1991; 45:7–11
46. Gotham AM, Brown RG, Marsden CD: Depression in Parkinson's disease: a quantitative and qualitative analysis. J Neurol Neurosurg Psychiatry 1986; 49:381–389
47. Huber S, Paulson GW, Shuttleworth EC: Depression in Parkinson's disease. Neuropsychiatry Neuropsychol Behav Neurol 1988; 1:47–51
48. Starkstein SE, Preziosi TJ, Bolduc PL, et al: Depression in Parkinson's disease. J Nerv Ment Dis 1990; 178:27–31
49. Horn S: Some psychological factors in Parkinsonism. J Neurol Neurosurg Psychiatry 1974; 37:27–31
50. Marsh GG, Markham CH: Does levodopa alter depression and psychopathology in Parkinsonism patients? J Neurol Neurosurg Psychiatry 1973; 36:925–935
51. Robins AH: Depression in patients with Parkinsonism. Br J Psychiatry 1976; 128:141–145
52. Brown GL, Wilson WP: Parkinsonism and depression. South Med J 1972; 65:540–545
53. Starkstein SE, Robinson RG: Dementia of depression in Parkinson's disease and stroke. J Nerv Ment Dis 1991; 179:593–601
54. Mayeux R, Stern Y, Cote L, et al: Altered serotonin metabolism in depressed patients with Parkinson's disease. Neurology 1984; 34:642–646
55. Mayeux R, Stern Y, Sano M, et al: The relationship of serotonin to depression in Parkinson's disease. Mov Disord 1988; 3:237–244
56. Langer SZ, Galzin AM, Poirier MF, et al: Association of the (^{3}H)-imipramine and (^{3}H)-paroxetine binding with the 5HT transporter in brain and platelets: relevance to studies in depression. J Receptor Res 1987; 7:499–521
57. Raisman R, Cash R, Agid Y: Parkinson's disease: decreased density of (^{3}H)-imipramine and (^{3}H)-paroxetine binding sites in putamen. Neurology 1986; 36:556–560
58. Mayberg HS, Starkstein SE, Sadzot B, et al: Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. Ann Neurol 1990; 28:57–64
59. Ring HA, Bench CJ, Trimble MR, et al: Depression in Parkinson's disease: a positron emission study. Br J Psychiatry 1994; 165:333–339
60. Marin RS: Differential diagnosis of apathy and related disorders of diminished motivation. Psychiatric Annals 1997; 27:30–33
61. Starkstein SE, Mayberg HS, Preziosi TJ, et al: Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992; 4:134–139
62. Levy ML, Cummings JL, Fairbanks LA, et al: Apathy is not depression. J Neuropsychiatry Clin Neurosci 1998; 10:314–319
63. Rogers D, Lees AJ, Smith E, et al: Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. Brain 1987; 1987:761–776
64. Mayeux R, Stern Y, Sano M, et al: Clinical and biochemical correlates of bradyphrenia in Parkinson's disease. Neurology 1987; 37:1130–1134
65. Madeley P, Biggins CA, Boyd JL, et al: Emotionalism in Parkinson's disease. Ir J Pychol Med 1992; 9:24–25
66. Levin BE, Llabre MM, Weiner WJ: Parkinson's disease and depression: psychometric properties of the Beck Depression Inventory. J Neurol Neurosurg Psychiatry 1988; 51:1401–1404
67. Diller L, Ricklan M: Psychosocial factors in Parkinson's disease. J Am Geriatr Soc 1956; 4:1291–1300
68. Mendez MF, Nakawatase TV, Brown CV: Involuntary laughter and inappropriate hilarity. J Neuropsychiatry Clin Neurosci 1999; 11:253–258
69. Menza MA, Robertson-Hoffman DE, Bonapace AS: Parkinson's

disease and anxiety: comorbidity with depression. Biol Psychiatry 1993; 34:465–470
70. Richard IH, Schiffer RB, Kurlan R: Anxiety and Parkinson's disease. J Neuropsychiatry Clin Neurosci 1996; 8:383–392
71. Rubin AJ, Kurlan R, Miller C, et al: Atypical depression and Parkinson's disease (abstract). Ann Neurol 1986; 20:150
72. Stein MB, Heuser IJ, Juncos JL, et al: Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry 1990; 147:217–220
73. Berrios GE, Campbell C, Politynska BE: Autonomic failure, depression and anxiety in Parkinson's disease. Br J Psychiatry 1995; 166:789–792
74. Iruela LM, Ibanez-Rojo V, Palanca I, et al: Anxiety disorders and Parkinson's disease. Am J Psychiatry 1992; 149:719–720
75. Cash R, Dennis T, L'Heureux R, et al: Parkinson's disease and dementia: norepinephrine and dopamine in locus ceruleus. Neurology 1987; 37:42–46
76. Lauterbach EC: The locus ceruleus and anxiety disorders in demented and nondemented familial parkinsonism (letter). Am J Psychiatry 1993; 150:994
77. Lauterbach EC, Duvoisin RC: Anxiety disorders in familial parkinsonism (letter). Am J Psychiatry 1992; 148:274
78. Henderson R, Kurlan R, Kersun JM, et al: Preliminary examination of the comorbidity of anxiety and depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992; 4:257–264
79. Seimers ER, Shekhar A, Quaid K, et al: Anxiety and motor performance in Parkinson's disease. Mov Disord 1993; 8:501–506
80. Wolters EC: Dopaminomimetic psychosis in Parkinson's disease patients. Neurology 1999; 52(suppl 3):S10–S13
81. Peyser CE, Naimark D, Zuniga R, et al: Psychoses in Parkinson's Disease. Semin Clin Neuropsychiatry 1998; 3:41–50
82. Aarsland D, Larsen JP, Cummings JL, et al: Prevalence and clinical correlates of psychotic symptoms in Parkinson's disease: a community-based study. Arch Neurol 1999; 56:595–601
83. Hutchinson M, Fazzini E: Cholinesterase inhibition in Parkinson's disease (letter). J Neurol Neurosurg Psychiatry 1996; 61:324–325
84. Lieberman A: Managing the neuropsychiatric symptoms of Parkinson's disease. Neurology 1998; 50(suppl 6):S33–S38
85. Starkstein SE, Petracca G: Parkinson's disease, in Psychiatric Treatment of the Medically Ill. Edited by Robinson RG, Yates WR. New York, Marcel Dekker, 1999, pp 443–457
86. Poewe W, Luginger E: Depression in Parkinson's disease: impediments to recognition and treatment options. Neurology 1999; 52(suppl 3):S2–S6
87. Juncos JL: Management of psychotic aspects of Parkinson's Disease. J Clin Psychiatry 1999; 60:42–53
88. Klaassen T, Verhey FR, Sneijders GH, et al: Treatment of depression in Parkinson's disease: a meta-analysis. J Neuropsychiatry Clin Neurosci 1995; 7:281–286
89. Parkinson Study Group: Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med 1999; 340:757–763
90. Suchowersky O, de Vries JD: Interaction of fluoxetine and selegeline. Can J Psychiatry 1990; 35:571–572
91. Andersen J, Aabro E, Gulmann N, et al: Antidepressant treatment in Parkinson's disease: a controlled trial of the effect of nortriptyline in patients with Parkinson's disease treated with L-dopa. Acta Neurol Scand 1980; 62:210–219
92. Laitinen L: Desipramine in treatment of Parkinson's disease: a placebo-controlled study. Acta Neurol Scand 1969; 45:109–113
93. Goetz CG, Tanner CM, Klawans HL: Bupropion in Parkinson's disease. Neurology 1984; 34:1092–1094
94. McCance-Katz EF, Marek KL, Price LH: Serotonergic dysfunction in depression associated with Parkinson's disease. Neurology 1992; 42:1813–1814
95. Hauser RA, Zesiewicz TA: Sertraline for the treatment of depression in Parkinson's disease. Mov Disord 1997; 12:756–759
96. Jansen Steur E: Increase of Parkinson disability after fluoxetine medication. Neurology 1993; 43:211–213
97. Chouinard G, Sultan S: A case of Parkinson's disease exacerbated by fluoxetine. Human Psychopharmacology 1992; 7:63–66
98. Faber R, Trimble MR: Electroconvulsive therapy in Parkinson's disease and other movement disorders. Mov Disord 1991; 6:293–303
99. Fall PA, Ekman R, Granerus AK, et al: ECT in Parkinson's disease: changes in motor symptoms, monoamine metabolites, and neuropeptides. J Neural Transm Park Dis Dement Sect 1995; 10:129–140
100. Factor SA, Molho ES, Podskalny GD, et al: Parkinson's disease: drug-induced psychiatric states. Adv Neurol 1995; 65:115–138
101. Zoldan J, Friedberg G, Weizman A, et al: Ondansetron, a 5-HT3 antagonist for visual hallucinations and paranoid delusional disorder associated with chronic L-DOPA therapy in advanced Parkinson's disease. Adv Neurol 1996; 69:541–544
102. Ellring H, Seiler S, Perleth B, et al: Psychosocial aspects of Parkinson's disease. Neurology 1993; 43(suppl 6):S41–S44
103. MacMahon DG: Parkinson's disease nurse-specialists: an important role in disease management. Neurology 1999; 52(suppl 3):S21–S25