

Parkinson's Disease— Part 3: Neuropsychiatric Symptoms

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Parkinson's disease (PD) is the second most common degenerative neurologic disease. Patients with PD live with significant disability, a poor health-related quality of life (HRQOL), and a higher risk for early death compared with the general population.¹⁻⁵ Healthcare costs for the management of PD are substantial and expected to rise in the future.⁶

With the improvements in the treatment of motor symptoms, nonmotor symptoms of PD have been increasingly recognized as a major cause of disability, particularly neuropsychiatric disorders and cognitive impairment.^{7,8} A recent large patient survey found a greater impact of psychiatric-related symptoms on HRQOL in earlier phases of the disease compared with later stages.⁹ In studies, nonmotor symptoms, particularly depression and cognitive dysfunction, have been shown to contribute equally or more so to impairment in activities of daily living than limitations imposed by motor impairment.^{8,10} Collectively, these data suggest the need for earlier evaluation and treatment of nonmotor symptoms in PD, which potentially could improve HRQOL and patient productivity, reduce morbidity, and minimize direct and indirect healthcare costs.

However, most PD-related neuropsychiatric symptoms remain underrecognized and undertreated in clinical practice.¹¹⁻¹³ Given the increasing number of PD cases, there is a need to more adequately recognize, diagnose, and treat comorbid psychiatric and cognitive disorders. This article focuses on neuropsychiatric manifestations, which, for the purposes of this article, will include depression, anxiety, sleep disorders, psychosis, cognitive impairment/dementia, and impulse control disorders.

Depression

Depression is a common neuropsychiatric feature of PD, and may be more common in PD than in other conditions with similar levels of disability.^{3,14,15} This depression is often associated with increased disability, a worse HRQOL, more rapid progression of motor impairment/disability, and an increased mortality hazard ratio (2.66).^{8,10,16} The prevalence of depression in PD ranges from 20% to 50%.^{10,11,16} Between 5% and 20% of these patients are diagnosed with major depression, with the remainder classified as nonmajor depression, including minor depression, subsyndromal depression, and dys-

Abstract

The nonmotor neuropsychiatric symptoms of Parkinson's disease, particularly depression, psychosis, and cognitive impairment/dementia, are major contributors to disability and a decline in quality of life. Their effect on patients may be more disabling than motor symptoms. Increasing awareness of the importance of recognizing and treating neuropsychiatric symptoms of this disease in the medical community is a focus of specialists and organizations. This article looks at useful screening measures to help clinicians recognize neuropsychiatric symptoms and offers suggestions for their effective treatment.

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thymia.¹⁰ Patients with nonmajor depression present a dilemma with respect to clinical management, as nonmajor depression is associated with functional impairment, yet it is unclear to what extent it responds to treatment.

Risk factors for depression in PD include increasing severity of cognitive impairment, female sex, possibly early-onset PD, and personal history of depression before diagnosis of PD.^{10,16} Anxiety symptoms or disorders are highly comorbid with depression.^{3,13,16} Although depression is associated with psychosis in PD, a recent study has shown that each is a distinct neurobehavioral disorder in the disease.¹⁷

Depression is seen in all stages of PD and may present prior to the onset of motor symptoms.^{3,11,14} Whether depression in PD is “reactive” or related solely to neuropathology is somewhat controversial. Most lines of evidence suggest a biological basis, stemming partly from studies that show a relationship between a history of depression and subsequent development of PD.^{2,14} Depression in PD is most likely related to a combination of neurobiologic and psychologic factors.¹⁰

Of importance to managed care are recent studies that have underscored the lack of recognition and appropriate treatment of depression in PD.^{12,13} Most patients meeting criteria for depression are not being treated or may be receiving suboptimal or ineffective treatment.¹³ Underrecognition and undertreatment can lead to a rise in healthcare costs related to ongoing disability. Office time constraints and focus on motor symptoms are thought to increase underdiagnosis of depression. A simple, reliable, routine screening method for depression in PD is needed, as well as heightened clinician awareness of the best treatment strategies.

The Geriatric Depression Scale-Short Form has been suggested by specialists as a simple tool for use in routine practice. This form can be self-reported or clinician-administered, takes only 5 minutes to complete, and lacks confounding items for motor symptoms. As mentioned in Part 1,¹⁸ the Beck Depression Inventory, Hamilton Depression Rating Scale, and Montgomery-Asberg Depression Rating Scale are also useful for office screening, and have been recommended by the American Academy of Neurology (AAN) for this purpose.⁷ Even more simplistically, asking the

patient 2 questions may bring to light an underlying depression:

1. Do you often have a sad mood, which has continued for some time?
2. Have you lost interest or pleasure in day-to-day activities?

Treatment. Despite the high prevalence of depression in PD, there are relatively few clinical studies that have evaluated the efficacy of antidepressants in this population. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been studied most frequently, and in small or open-label studies these agents have shown positive effects, although often modest.^{10,16,19,20} The paucity of well-controlled studies and/or inadequate trial design appear responsible for the disappointing efficacy experienced in clinical practice, due to the lack of clear guidelines. In a recent literature review and meta-analysis,²¹ fewer than 30 studies evaluating the effectiveness of antidepressants in PD were identified. Of these studies, 11 were found to be suitable for inclusion in the meta-analysis and only 2 were placebo controlled. All studies involved small populations (N = 8-93), and diagnostic criteria for depression were used in fewer than half. Almost all studies failed to define what constituted a response to treatment. The meta-analysis revealed large effect sizes, reflecting benefit, for both placebo and antidepressant treatment, but these were not significantly different.

The main conclusion of this meta-analysis was that antidepressants have not been adequately evaluated for depression in PD. The large effect size for active treatment suggests that antidepressants have a beneficial effect, but those effects may be nonspecific. Well-conducted, controlled studies with a sufficient number of patients to detect clinically and statistically significant treatment effects are lacking. Similar conclusions were drawn by the AAN in their evidence-based review, citing similar deficiencies in available studies.⁷ Based on their review of the literature, the AAN did recommend amitriptyline, a TCA, for depression in PD, although TCAs may not be well tolerated by some patients with PD.

It does appear that the most frequently used antidepressants, the SSRIs, are generally well tolerated in patients with PD.^{20,21} Contrary to prior

belief, SSRIs do not appear on average to worsen motor symptoms of PD; in fact, motor symptoms may improve in some patients.^{10,20,21} In open trials, most PD patients (>85%) were able to complete antidepressant treatment without significant adverse effects.

Antidepressants should continue to be prescribed for depression associated with PD, since they can be effective and may help comorbid psychiatric symptoms, including anxiety and sleep disorder symptoms.¹⁹ **Table 1**^{10,16,20,22,23} lists some commonly prescribed antidepressants that have been used specifically in patients with PD and their cost. SSRIs are preferred for initial therapy, because of their good tolerability, and maximal doses should be given, if needed and tolerated, to optimize benefit. There is no good evidence that one SSRI is more effective or causes fewer adverse effects than another.²² However, citalopram, escitalopram, and sertraline are less prone to drug–drug interactions than paroxetine (or fluoxetine, not shown)²² and may be better suited for the patient with PD. Formal cost-effectiveness analyses for PD depression are unavailable, although effective management of depression is a clear priority that will likely lead to long-term cost savings.

TCA's might be considered in patients unresponsive to an SSRI, although their anticholinergic effects are especially problematic in patients with PD since they may also worsen cognition or aggravate orthostatic hypotension.^{7,10} Other non-SSRI antidepressants, including venlafaxine, duloxetine, mirtazapine, and bupropion, may also be useful to augment or replace therapy in SSRI partial or nonresponders.

In those patients failing to respond adequately, or if depression is severe or complicated by suicidal ideation, referral to a psychiatrist is advised.

Anxiety

Anxiety in PD has not been as well studied as depression. However, the majority of patients with depression will also meet criteria for an anxiety disorder and vice versa.^{3,10} Anxiety can be associated with greater physical and psychological distress than depression in PD.

Anxiety disorders in PD can be categorized as generalized anxiety disorder, panic disorder, social phobia, and obsessive-compulsive disorder (OCD).

Table 1. Some Antidepressants Used in Parkinson's Disease

Drug	Usual Initial Dose (mg/day)	Usual Maintenance Dose (mg/day)	Cost of Therapy (\$)*	Primary Adverse Effects
SSRIs				
Citalopram				
Celexa®	20	20-40	98.00	SSRIs (class)
Generic	20	20-40	72.00	Insomnia
Paroxetine				
Paxil®	10-20	10-40	97.00	Jitteriness
Generic	10-20	10-40	50.00	Dizziness
Sertraline				
Zoloft®	25-50	25-200	91.00	Nausea
Generic	25-50	25-200	80.00	Diarrhea
Escitalopram				
Lexapro®	10	10-20	83.00	Headache
Tricyclic				
Nortriptyline				
Pamelor®	10-25	10-75	110.00	Sexual dysfunction
Generic	10-25	10-75 (target nortriptyline level of 80-120 ng/mL)	12.00	Orthostatic hypotension
				Worsening cognition in PD
*Approximate cost of treatment for 30 days with the lowest usual maintenance dose. SSRIs indicates selective serotonin reuptake inhibitors; PD, Parkinson's disease. Adapted from manufacturer product information and references 10, 16, 20, 22, 23.				

Generalized anxiety disorder and panic attacks are the most common manifestations. While patients often suffer from avoidance of being seen in a public place due to fear of embarrassment, this does not qualify for the diagnosis of social phobia. True OCD is uncommon. OCD and related symptoms may actually be no more prevalent in PD than in subjects without PD.²⁴

There is some evidence that generalized anxiety or panic attacks in PD are a reaction to the distressing components of the disease (eg, to the discomfort and fear of loss of motor control).¹⁶ However, many specialists feel that both psychosocial and neuropathologic factors are contributory.

Patients with PD should be screened for anxiety disorders. Although no well-established instrument is available, the self-administered Beck Anxiety Inventory (BAI) has shown usefulness for distinguishing anxiety from depression. This scale is com-

prised of 21 items and takes 5 to 10 minutes to administer. The Spielberger State-Trait Anxiety Inventory is also useful to distinguish anxiety, but consists of more questions than the BAI and takes about 10 minutes to complete. Similar to depression, simply asking the patient a few questions about generalized anxiety symptoms, or if they have experienced anxiety attacks, may be equally as useful and informative as the use of rating scales.

Treatment. Behavior modification techniques may benefit some patients with anxiety disorders related to PD. However, pharmacologic therapy is often needed. Certain antidepressants are approved for the treatment of a range of anxiety disorders; these agents include paroxetine, escitalopram, and venlafaxine.²² Benzodiazepines should be considered for more severe anxiety, although patients should be counseled in regard to potential adverse effects, such as sedation, further cognitive impairment, and balance problems, which may increase the risk of falls. Buspirone is well tolerated, but it has not been formally tested for anxiety in PD. Similar to the general population, SSRIs may be helpful in the treatment of panic disorder, social phobia, and OCD in PD.

Disorders of Sleep and Wakefulness

Symptoms of sleep disturbance and wakefulness are seen in nearly all PD patients, manifesting either as parasomnias, nocturnal insomnia, with difficulty initiating or maintaining sleep, or daytime hypersomnolence. Both insomnia and hypersomnia can occur in the same patient, and both can negatively affect HRQOL.^{3,25,26}

Nocturnal Insomnia and Parasomnias. Patients with nocturnal insomnia may fall asleep, but soon awaken, sometimes for prolonged periods. Studies show that some patients remain awake for 30% to 40% of the night.²⁵ Nocturnal sleep problems may result from “wearing-off” motor disability, nocturia, neuropathologic changes (eg, lesions in sleep-regulating systems), and effects of some drugs given for PD, such as selegiline, related to its amphetamine-derivative metabolites.^{3,25,26} The depression and anxiety of PD are also major causes of early awakenings.^{25,26} Other contributing factors are sleep apnea, periodic leg movements, and restless legs syndrome (RLS).

Rapid-eye movement (REM) sleep behavior disorder (RBD) is another nighttime sleep disturbance, characterized by loss of normal muscle atonia during REM sleep.²⁵ Patients with RBD enact their dreams and nightmares, which can result in verbalizations and purposeful hand and arm movements, at times violent.^{25,26} Clinically important RBD is seen in about 25% of patients with PD, and some form of RBD will manifest in up to half of patients. Sleep disturbances in PD, and RBD in particular, are considered risk factors for psychosis.^{16,25}

Disordered breathing during sleep related to obstructive sleep apnea occurs in many patients with PD,^{2,25} and is not necessarily associated with obesity.² This results in repeat awakenings and contributes to daytime somnolence.²⁵ Sleep apnea is likely related to underlying PD neuropathology, such as degeneration of brainstem nuclei involved in respiration. Rigidity in pharyngeal and/or respiratory muscles may be another factor.

RLS can severely interrupt sleep and occurs in at least 20% of patients with PD.^{25,27,28} Although both PD and RLS are characterized by underpinning dopaminergic abnormalities and a clinical response to dopaminergic therapy, it remains unclear if the 2 conditions share common pathophysiologic mechanisms.^{27,28}

Treatment. Physical activity and exercise may improve sleep quality in those patients who are not limited by their motor impairment. Treating depression will also likely improve sleep dysfunction. Medications taken by the patient should be reviewed with appropriate adjustments, such as avoidance of a nighttime dose of selegiline. The other available monoamine oxidase type B inhibitor, rasagiline, may be less likely to affect sleep.

Pharmacologic treatment depends on the cause of the sleep disorder. Judicious use of additional small doses of immediate-release levodopa/carbidopa may alleviate insomnia caused by motor symptoms.^{25,26} Alternatively, a controlled-release formulation of levodopa/carbidopa or a dopamine agonist (including the rotigotine patch) might be considered.²⁶ Some clinicians have used amitriptyline (5-40 mg) or quetiapine to reduce sleep-maintenance insomnia.²⁵ However, many specialists recommend formal evaluation in a sleep laboratory to properly diagnose patients with frequent arousals despite treatment for apnea.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) significantly reduces motor symptoms and can provide important benefits on sleep duration and quality.²⁵ However, DBS-STN has minimal or no effect on RBD or RLS.²⁵ Clonazepam and possibly high-dose melatonin may help alleviate RBD. RLS usually is at least partially alleviated by dopamine agonists, such as ropinirole and pramipexole.^{3,25} In patients with clear evidence of nighttime hallucinations that affect sleep, clozapine or quetiapine can be considered (see Psychosis section below).

Continuous positive airway pressure (CPAP) is routinely used in non-PD patients with obstructive sleep apnea. CPAP or bilevel positive airway pressure has also benefited PD patients, although many patients have difficulty with the airway masks, often removing them if uncomfortable. This emphasizes the importance of having access to a sleep laboratory, which can work with the patient to find a mask that is comfortable. A caveat in the patient with sleep apnea is that treatment of the sleep disorder with a benzodiazepine (eg, clonazepam) can exacerbate sleep apnea, and other approaches should be considered.

Nocturia in some patients may be related to lower-extremity edema from hypokinesia and effects of dopamine agonists or amantadine during the waking hours; edema frequently subsides overnight, leading to nocturia.²⁶ Physical activity and the use of tight stockings during the day may help prevent edema and nocturia. Pharmacologic treatment with tolterodine or oxybutynin is another option, the latter being less expensive. In males, nocturia may be a result of benign prostatic hypertrophy. An indwelling catheter or Penrose drain is an option in selected patients with severe nocturia²⁶; alternatively, urologic consultation can be considered.

Excessive Daytime Sleepiness. Daytime sleepiness in PD occurs in up to 50% of patients. It may be the result of: (1) underlying neuropathophysiology, such as depletion of dopamine or other neurotransmitters²⁵ (eg, hypocretin); (2) sleep lost as a result of insomnia²⁵; and/or (3) excessive sleepiness caused by dopaminergic medications, including dopamine agonists and levodopa.^{2,3,26} Dopamine agonists tend to produce more sleepiness than levodopa.³ Although dopamine agonist-induced daytime somnolence and daytime sleep would seem to

reduce the need for nighttime sleep, this has not been formally established.²⁶

The major concern of patients with daytime sleepiness is the potential for sudden sleep episodes or sudden-onset sleep (SOS), carrying the risk of driving accidents.^{3,25} SOS has been reported to occur without warning, but more commonly appears to occur in the context of excessive daytime sleepiness. The true frequency of SOS is unknown, although falling asleep behind the wheel has been reported in 4% to 8% of patients.^{2,25} The primary risk factors for SOS are dopamine agonist and levodopa therapy.^{3,25} The Epworth Sleepiness Scale has been shown to be useful to screen for SOS, with a sensitivity of 52% to 72%.^{3,25}

Treatment. Treatments for daytime somnolence in PD are limited. Reducing the dopamine agonist dose or switching to a different dopamine agonist may be helpful. The nonstimulant, wake-promoting agent modafinil may benefit some patients, although significant improvement has not been observed in all clinical trials. This agent is also expensive (\$275 for 30-day course of 200 mg once daily).²³ In some patients, use of oral selegiline may be useful because of its metabolism into an amphetamine-like chemical. Stimulants (eg, methylphenidate) are also used in clinical practice. Focusing on the treatment of nocturnal insomnia—if this is a significant problem for the patient—can also have the added benefit of minimizing daytime drowsiness in many cases.

A cardinal rule for the clinician is to warn the patient with PD not to drive if sleepy. Moreover, if the patient elicits a history of dozing off during the day or if the Epworth Sleepiness Scale is abnormal (ie, score >10), the patient is at risk of SOS. The at-risk patient should be educated on the possibility of SOS and warned not to drive at all if the risk is deemed to be high. Patients with moderate-to-severe motor symptoms or moderate-to-severe cognitive dysfunction should also be warned against driving if at all possible.

Psychosis

Psychosis in PD is associated with an increase in functional disability, greater caregiver burden often resulting in nursing home placement, and a higher risk of mortality.^{2,8,10,29} Psychosis in the form of hallucinations or illusions, typically visual, occur in

10% to 40% of patients who are receiving PD pharmacotherapy; delusions are seen less commonly in the subset of patients with hallucinations.^{2,8,10} These data point to a major role of dopaminergic therapy in the etiology of PD-associated psychosis, and this has been demonstrated.^{10,16} In this regard, evidence to date is insufficient to suggest that one type of medication is more likely than another to induce psychosis. In contrast, psychotic symptomatology has been observed in 5% to 10% of patients with PD who were not receiving dopaminergic medications, including the time prior to development of levodopa.^{10,16}

Given the percentage of cases occurring in the absence of medications, other factors appear to play a role. A complex interaction of drug therapy, underlying neuropathology, and comorbidities (eg, cognitive or visual impairment) likely contribute to psychosis.^{10,30} This is supported by the documented risk factors for psychosis in PD; that, in addition to medication exposure, include greater cognitive dysfunction, older age, longer duration of PD, visual disturbances, comorbid depression and anxiety, and sleep disorders, such as RBD.^{10,16,25}

Auditory hallucinations occur less commonly than visual hallucinations.² In general, patients with psychosis related to PD may be divided into 2 groups. In the first, hallucinations are the only abnormality and are often benign, in that they are untroubling to the patient. These patients may not require treatment.¹⁰ The second group experiences more complex and disturbing symptoms, such as hallucinations with concomitant delusions or in the context of delirium.^{2,10} Delirium can occur in the context of advanced dementia or be induced by concurrent medical conditions or dopaminergic therapy.² Patients with more complex or severe psychosis usually require treatment. Patients with relatively benign psychosis can advance to the more severe form as the disease progresses.²

Dementia with Lewy bodies (DLB) is also characterized by hallucinations, often with fluctuations in cognition.¹⁶ In general, the presence of psychosis early in the course of parkinsonism or prior to the introduction of dopaminergic therapy suggests a diagnosis of DLB.¹⁰ Intolerance of antipsychotic medications is also a feature supporting a diagnosis of DLB.³¹

A valid screening instrument for psychosis in PD

is lacking. However, the Parkinson Psychosis Rating Scale has shown some usefulness and is relatively easy to administer.^{7,10} The Neuropsychiatric Inventory, which includes psychosis subscales, is another instrument that can be clinically useful and can be self-administered by a family member or caregiver. As insight is often retrained, simply asking the patient a few relevant questions during a routine clinic visit may also uncover psychotic symptoms.

Treatment. Treatment of psychosis in PD is complicated by the desire to balance dopaminergic therapy (which can aggravate psychosis) and antipsychotic medications, many of which can aggravate parkinsonism. A review of medications taken by the patients is necessary to eliminate those that might be contributing to psychosis. Nonessential drugs not being taken for PD are the first consideration, especially central nervous system active drugs. This should be followed by a risk–benefit analysis of antiparkinson medications, any of which can contribute to the development of psychotic symptoms.^{10,32} A risk–benefit model based on expert opinion has been developed for the latter step, which suggests reducing or discontinuing medications in the following order^{16,32}: anticholinergic agents; selegiline (deprenyl); amantadine; dopamine agonists; cathechol-O-methyltransferase inhibitors; controlled-release levodopa; and immediate-release levodopa.

A point will be reached in this process where further reduction in medications will significantly jeopardize motor-function control, and if psychosis is persistent and problematic at this point, then an antipsychotic agent should be added.^{10,16,32}

Typical (or first-generation) antipsychotic agents, such as haloperidol, are not indicated because of their propensity to worsen symptoms of PD.¹⁶ The currently recommended agents are the atypical (or second-generation) antipsychotic agents quetiapine and clozapine.^{7,10,19} While only clozapine has clearly demonstrated efficacy for psychosis in PD, both agents appear to be well tolerated from a motor standpoint.^{7,19} Except for olanzapine, the other atypical antipsychotic agents have not been well studied in this setting. In available studies, olanzapine did not improve PD psychosis and worsened motor symptoms.⁷

Quetiapine has been shown effective in treating PD psychosis in open-label studies, but 2 placebo-

controlled studies have been negative.^{15,29,33} Although mild worsening of motor symptoms may occur with quetiapine, it is considered the agent of choice for psychosis in PD, based on the results of open-label studies and the clinical experience of movement disorders specialists.¹⁰

Clozapine has demonstrated effectiveness in the treatment of psychosis in placebo-controlled studies and does not aggravate motor symptoms.^{10,16,32,34} However, it can rarely induce agranulocytosis and requires weekly blood counts during the first 6 months of therapy, bimonthly for the next 6 months, and then monthly thereafter.¹⁹ This additional clinical surveillance greatly increases cost of care, and this side effect of the medication places the patient at risk for a potentially serious adverse event. This is not required for quetiapine, although atypical antipsychotics have warnings for increased morbidity (cerebrovascular events) and mortality when used in patients with dementia. In general, clozapine is recommended as an alternative agent in patients unresponsive to or unable to tolerate quetiapine.¹⁰

Cholinesterase inhibitors (eg, rivastigmine) also may have antipsychotic properties in PD dementia and DLB; therefore, they might be considered for use in psychotic patients with comorbid cognitive impairment (see below).¹⁰

Cognitive Dysfunction and Dementia

Dementia in PD is as common or more common than depression or psychosis. The cross-sectional prevalence of dementia has ranged from 20% to 40%, which is up to 6-fold higher than that seen in healthy individuals.^{2,3,10} However, this range may be an underestimate of the cumulative prevalence of dementia in PD, as noted in one prospective study found an 8-year cumulative prevalence rate of 78%.¹⁰ A substantial proportion of PD patients without dementia have varying degrees of cognitive impairment; this impairment can occur early on, even in newly diagnosed patients.¹⁰ Cognitive impairment contributes significantly to disability and poor HRQOL in PD.⁸

Cognitive dysfunction associated with PD classically has been termed a dysexecutive or subcortical syndrome, characterized by psychomotor slowing and impaired executive, attention, and visuospatial abilities.^{3,16,35} Memory impairment is variable¹⁷; if

impaired, this typically involves poor retrieval, as opposed to the encoding memory deficits of Alzheimer's disease (AD). For example, cueing by a family member may aid recall in the patient with PD, whereas cueing is not usually helpful in the patient with AD.¹⁶

Early executive impairment and memory deficits in PD are risk factors for subsequent development of dementia.¹⁰ Other risk factors for dementia include older age, possibly older age at onset of PD, increasing severity of PD, and psychosis or depression.^{3,10}

Cognitive changes and ultimately dementia are associated with the underlying neurodegenerative processes in PD.^{16,36} Multiple neurotransmitter deficits are evident, including acetylcholine, dopamine, serotonin, and norepinephrine.^{10,16} Cholinergic (acetylcholine) and dopaminergic (dopamine) deficits have been linked to memory dysfunction and dysexecutive syndrome,^{10,16} and noradrenergic deficits to inattention.

Provisional diagnostic criteria for dementia in PD were recently published. Compared with the diagnostic criteria for AD, the PD dementia criteria deemphasize memory impairment and emphasize the range of cognitive domains that are affected in PD. Hopefully this will increase the recognition of cognitive impairment in PD, as the stages of cognitive impairment leading up to eventual dementia are underdiagnosed. Cognitive deficiencies are often not reported by the patient in a clinical interview, and the patient may appear cognitively intact on a superficial interview. More detailed interviewing and screening with a sensitive instrument, with follow-up neuropsychologic testing if indicated, may be necessary to detect cognitive dysfunction. Clinical querying and cognitive screening should be performed regularly in PD.

In the clinical interview, the patient should be questioned about difficulties in memory (eg, details of recent events) and other areas of cognition, such as ability to balance a checkbook or complete other complex tasks, visuospatial problems, and attentional impairment.^{10,16} This will often reveal an underlying problem. Neuropsychologic screening instruments typically used to detect pre-AD cognitive impairment may not be sensitive in PD,¹⁶ and no test has been specifically validated for this purpose.¹⁰ The AAN recommends use of the Cambridge Cognitive Examination or Mini-Mental State

Table 2. Comparison of Clinical Features of Lewy-body Dementia, PD Dementia, and Alzheimer's Disease

	Lewy-body Dementia	PD Dementia	Alzheimer's Disease
Clinical features			
Common presentation	Psychotic symptoms and/or parkinsonian features	Parkinsonian features	Memory decline
Psychotic symptoms	Early visual hallucinations with or without delusions	Associated with exposure to PD pharmacotherapy	Usually later in disease process
Memory decline	As disease progresses, particularly in accessing memories	Difficulty accessing memories	Earlier, global, and progressive difficulty in forming memories
Speech impairment	Usually late	Hypophonia, dysarthria	Aphasia, paraphasia
Parkinsonian features			
Tremors at rest	Present in 20%-50%	Present in 75%	Only late in disease
Rigidity	Common	Common	Only late in disease
Gait abnormality	Early in disease	Early or late in disease	Late in disease
Response to levodopa	Variable	Common	NA
Antipsychotic sensitivity			
	Can be extreme	Variable, increased parkinsonism at higher dosages	Development of parkinsonism at higher dosages
Efficacy of cholinesterase inhibitors			
	One positive efficacy study	One positive efficacy study	Established

PD indicates Parkinson's disease; NA, not applicable. From reference 10, with permission.

Examination (MMSE) to screen for dementia in patients with PD.⁷

Those involved in routine clinical care of patients with PD have found the Montreal Cognitive Assessment (MoCA) useful to screen for early cognitive changes; the MoCA assesses a wider range of cognitive domains than the MMSE, takes less than 10 minutes to complete, with a possible score of 30 points (normal, ≥ 26 points).³⁷ Alternatively, other screening tools recommended by specialists include¹⁰:

- *The Hopkins Verbal Learning Test-Revised.* Assesses verbal memory abilities, including both free and recognition recall, and can be completed in about 15 minutes.
- *The Clock Drawing Test (CDT).* Commonly used for screening in AD, the CDT is sensitive for assessing visuospatial and executive abilities. However, interpretation may be limited by the presence of micrographia or tremor.

It is of importance to distinguish PD from AD and DLB, as the symptom profile, course, and management of each disorder differs (Table 2). The presence of dementia and psychosis early in the disease course (ie, within the first year) is highly uncharacteristic in PD and favors a diagnosis of DLB.

Patient referral to a neuropsychologist should be

considered if uncertainty arises regarding the presence of cognitive impairment at any point during the course of the disease.

Treatment. Rivastigmine was found to be moderately effective in PD dementia in a large placebo-controlled study^{16,38} and is US Food and Drug Administration approved for this indication. In small studies, the cholinesterase inhibitor donepezil has improved cognitive function in PD patients with dementia,^{16,39} and also in patients with dysexecutive syndrome in the absence of dementia.³⁵ The response to rivastigmine and donepezil in these studies supports the contention that dysexecutive syndrome and dementia in PD are, at least in part, related to a cholinergic deficit. Rarely, treatment with cholinesterase inhibitors has caused a worsening of parkinsonism.¹⁰

Doses, cost of therapy, and principal adverse effects of these 2 agents in patients with PD are shown Table 3.^{16,19,22,23,39} Although somewhat expensive, to the extent that successful treatment is associated with improved functionality and HRQOL, the cost may be offset by reductions in both indirect and direct healthcare costs by minimizing disability, medical resource needs, poor work productivity, and extra caregiver assistance.

Table 3. Drugs for Cognitive Dysfunction and Dementia in Parkinson's Disease

Drug	Usual Initial Dose	Usual Maintenance Dose	Cost of Therapy (\$)*	Primary Adverse Effect
Donepezil [†] (Aricept [®])	5 mg daily	10 mg/day	160	Headache, insomnia, nausea, diarrhea, anorexia, vomiting, muscle cramps
Rivastigmine [‡] (Exelon [®])	1.5 mg bid	3-6 mg bid	195	Headache, dizziness, nausea, vomiting, diarrhea, abdominal pain

*Approximate cost of treatment for 30 days with the lowest usual maintenance dose.

[†]Donepezil has been effective in small dementia studies, and in executive dysfunction without dementia, in patients with Parkinson's disease.

It is not FDA approved for these indications.

[‡]Rivastigmine has shown efficacy in dementia in patients with Parkinson's disease. It is FDA approved for this indication.

Adapted from references 16, 19, 22, 23, 39.

A recent cost-effectiveness study⁴⁰ was based on results of the rivastigmine trial mentioned above.³⁸ Overall, no significant difference between rivastigmine and placebo groups was observed with respect to total costs. The clinical benefits derived by use of rivastigmine, and attendant reduction in caregiver costs, were offset by an increase in direct costs (mainly those related to drug acquisition). This precluded a conclusion regarding cost-effectiveness, despite evidence of improved patient care with rivastigmine. However, the time horizon was limited to 6 months, and the authors concluded that cost reductions secondary to improved clinical outcomes with rivastigmine would probably increase over a longer time frame.

Impulse Control Disorders

In recent years, there has been increased recognition of impulse control disorders (ICDs) in patients with PD.^{31,41,42} ICDs are defined as failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or others.^{3,42} Manifestations include compulsive gambling, hypersexuality, shopping, and binge eating.^{3,42}

ICDs are thought to occur in about 1.5% of the general population.³ In patients with PD, a total, cumulative prevalence of an ICD sometime during PD of 6.6% was reported in one study,⁴² although unpublished preliminary results of a large-scale study suggest that ICDs may affect 10% to 15% of patients with PD.

The primary etiology of ICDs appears to be dopamine agonist therapy.^{31,41,42} A class effect has

been observed, with no one agent more likely than another to induce ICDs, and higher doses of any dopamine agonist predict a greater risk.⁴² However, a history of ICD symptoms—before onset of PD—may be an additional risk factor for occurrence of ICDs during therapy with these agents.⁴² There is some evidence that ICDs may be related in some way to underlying PD pathology,³ although this requires further study.

When prescribing dopamine agonists, patients should be informed of the potential risk for developing an ICD. Clinical monitoring is indicated. The Minnesota Impulsive Disorders Interview is useful for detecting a range of ICDs, although it is not a self-assessment tool and is somewhat time-consuming and confusing to administer. Other screening instruments for ICD are under development.

Symptom improvement or disappearance of ICD symptoms may be seen with dose reduction or discontinuation of dopamine agonists, or switching to a different dopamine agonist.⁴² Regarding psychiatric medications, antidepressants (eg, SSRIs) have been reported to be effective for ICDs in some studies of non-PD patients, and there are also case reports of atypical antipsychotics being effective in PD.

Conclusion

Neuropsychiatric symptoms and cognitive impairment in PD are associated with significant disability and poor HRQOL. In particular, depression and cognitive impairment may be more disabling to the patient than motor symptoms, and controlling motor symptoms is no longer the only consideration

in patient management. Effective management of neuropsychiatric symptoms can potentially minimize disability, improve HRQOL, reduce caregiver burden, and reduce healthcare resource utilization/healthcare costs, including a reduced or delayed need for long-term care placement. Long-term cost-effectiveness analyses, incorporating an HRQOL component, are needed to confirm these speculations.

Deficiencies cited in the recognition and treatment of neuropsychiatric symptoms suggest the need for improvement in managing these comorbidities. The best available methods for screening and diagnosing neuropsychiatric features, and proper and cost-conscious use of the most effective treatment modalities, must be imparted to clinicians to enable their use in everyday practice. This can be greatly facilitated through educational programs sponsored by managed care, which can update clinicians on current treatment practices and guidelines to improve outcomes in PD.

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REFERENCES

1. Poewe W. The natural history of Parkinson's disease. *J Neurol*. 2006;253:VII2-VII6.
2. Chaudhuri KR, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*. 2006;5:235-245.
3. Simuni T. Diagnosis and management of Parkinson's disease. *Medscape Neurology*, August 30, 2007. www.medscape.com. Accessed December 14, 2007.
4. Leibson CL, Long KH, Maraganore DM; National Institute for Clinical Excellence. Direct medical costs associated with Parkinson's disease: a population-based study. *Mov Disord*. 2006;21:1864-1871.
5. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. *J Neurol Neurosurg Psychiatry*. 2007;78:1304-1309.
6. Huse DM, Schulman K, Orsini L, Castelli-Haley J, Kennedy S, Lenhart G. Burden of illness in Parkinson's disease. *Mov Disord*. 2005;20:1449-1454.
7. Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66:996-1002.
8. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc*. 2004;52:784-788.
9. Jeffrey S. Psychiatric symptoms have greater impact in early vs late PD. *Medscape Medical News*, October 10, 2007. www.medscape.com/viewarticle. Accessed December 12, 2007.
10. Weintraub D, Stern MB. Psychiatric complications in Parkinson disease. *Am J Geriatr Psychiatry*. 2005;13:844-851.
11. Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson disease. *Neurology*. 2007;69:342-347.
12. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. 2002;8:193-197.
13. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2003;16:178-183.
14. Reese SL. Psychosocial factors in Parkinson's disease. *Dis Mon*. 2007;53:291-295.
15. Brandt-Christensen M, Kvist K, Nilsson FM, Andersen PK, Kessing LV. Treatment with antiparkinson and antidepressant drugs: a register-based, pharmaco-epidemiological study. *Mov Disord*. 2007;22:2037-2042.
16. Barbas NR. Cognitive, affective, and psychiatric features of Parkinson's disease. *Clin Geriatr Med*. 2006;22:773-796.
17. Weintraub D, Morales KH, Duda JE, Moberg PJ, Stern MB. Frequency and correlates of co-morbid psychosis and depression in Parkinson's disease. *Parkinsonism Relat Disord*. 2006;12:427-431.
18. Weintraub D, Comella CL, Horn S. Parkinson's disease—Part 1: pathophysiology, symptoms, burden, diagnosis, and assessment. *Am J Manag Care*. 2008;14:S40-S48.
19. Drugs for Parkinson's disease. *Treat Guidel Med Lett*. 2007;5:89-94.
20. Weintraub D, Taraborelli D, Moreales KH, Duda JE, Katz IR, Stern MB. Escitalopram for major depression in Parkinson's disease: an open-label, flexible-dosage study. *J Neuropsychiatry Clin Neurosci*. 2006;18:377-383.
21. Weintraub D, Morales KH, Moberg PJ, et al. Antidepressant studies in Parkinson's disease: a review and meta-analysis. *Mov Disord*. 2005;20:1161-1169.
22. Drugs for psychiatric disorders. *Treat Guidel Med Lett*. 2006;4:35-46.
23. *Red Book*. Montvale, NJ: Thomson Healthcare; 2007.
24. Maia AF, Pinto AS, Barbosa ER, Menezes PR, Miguel EC. Obsessive-compulsive symptoms, obsessive-compulsive disorder, and related disorders in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 2003;15:371-374.
25. Arnulf I. Sleep and wakefulness disturbances in Parkinson's disease. *J Neural Transm*. 2006;70:357-360.

26. **Korczyn AD.** Management of sleep problems in Parkinson's disease. *J Neurol Sci.* 2006;248:163-166.
27. **Garcia-Borreguero D, Odin P, Serrano C.** Restless legs syndrome and PD: a review of the evidence for a possible association. *Neurology.* 2003;61:S49-S55.
28. **Tan EK.** Restless legs syndrome and Parkinson's disease: is there an etiologic link? *J Neurol.* 2006;253:VII33-VII37.
29. **Fenelon G, Mahieux F, Huon R, Ziegler M.** Hallucinations in Parkinson's disease: prevalence, phenomenology, and risk factors. *Brain.* 2000;123:733-745.
30. **Wolters ECh.** PD-related psychosis: pathophysiology with therapeutical strategies. *J Neural Transm Suppl.* 2006;71:31-37.
31. **Rao SS, Hofmann LA, Shakil A.** Parkinson's disease: diagnosis and treatment. *Am Fam Physician.* 2006;74:2046-2054.
32. **Friedman JH, Factor SA.** Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord.* 2000;15:201-211.
33. **Morgante L, Epifanio A, Spina E, et al.** Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol.* 2004;27:153-156.
34. **The 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.
35. **Linazasoro G, Lasa A, Van Blercom N.** Efficacy and safety of donepezil in the treatment of executive dysfunction in Parkinson disease: a pilot study. *Clin Neuropharmacol.* 2005;28:176-178.
36. **Haugarvoll K, Aarsland D, Wentzel-Larsen T, Larsen JP.** The influence of cerebrovascular risk factors on incident dementia in patients with Parkinson's disease. *Acta Neurol Scand.* 2005;112:386-390.
37. **The Montreal Cognitive Assessment (MoCA).** www.mocatest.org. Accessed February 4, 2008.
38. **Emre M, Aarsland D, Albanese A, et al.** Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med.* 2004;351:2509-2518.
39. **Aarsland D, Laake K, Larsen JP, Janvin C.** Donepezil for cognitive impairment in Parkinson's disease: a randomized controlled study. *J Neurol Neurosurg Psychiatry.* 2002;72:708-712.
40. **Willan AR, Goeree R, Pullenayegum EM, McBurney C, Blackhouse G.** Economic evaluation of rivastigmine in patients with Parkinson's disease dementia. *Pharmacoeconomics.* 2006;24:93-106.
41. **Pontone G, Williams JR, Bassett SS, Marsh L.** Clinical features associated with impulse control disorders in Parkinson disease. *Neurology.* 2006;67:1258-1261.
42. **Weintraub D, Siderowf AD, Potenza MN, et al.** Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol.* 2006;63:969-973.