

An **Update** on **Parkinson's Disease** and Its **Psychiatric** **Complications**

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A symposium entitled "An Update on Parkinson's Disease and Its Psychiatric Complications" was held on February 24, 2004, at the 17th Annual Meeting of the American Association for Geriatric Psychiatry in Baltimore, MD. The presentations addressed the complex association between Parkinson's disease, depression, and anxiety; the prevalence of cognitive impairment, dementia, and sleep disorders among patients with Parkinson's disease; and the challenge of treating these patients in the context of drug–drug and drug–symptom interactions.

CME Certified

Educational Objectives

Upon completion of this activity, participants should be able to:

- Describe current trends in the diagnosis and treatment of Parkinson's disease.
- Discuss treatment options for depression in Parkinson's disease, and evaluate their utility in this patient population.
- Identify treatment options for psychosis in Parkinson's disease, and summarize the role of various agents in this context.
- Review the diagnosis and clinical management of cognitive impairment and dementia in patients with Parkinson's disease.
- Describe the management of fatigue, sleep problems, and anxiety in patients with Parkinson's disease.

CME ACCREDITATION

AN UPDATE ON PARKINSON'S DISEASE AND ITS PSYCHIATRIC COMPLICATIONS

This activity was developed for primary care physicians and geriatric psychiatrists.

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Sponsorship

This activity is sponsored by the American Association for Geriatric Psychiatry.



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This CME activity was planned and produced in accordance with the ACCME Essentials.

Based upon trials, the estimated time to complete this program is 1 hour.

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Faculty Disclosure

The American Association for Geriatric Psychiatry requires that the authors participating in a continuing medical education activity disclose to participants any significant financial interest or other relationship (1) with the manufacturers of any commercial service discussed in an educational presentation, and (2) with any commercial supporters of the activity.

Dr. Aarsland reported that he is a consultant for Pfizer Inc., Lundbeck, and Janssen-Cilag.

Dr. Lyketsos reported that he has received grant/research support from Abbott Laboratories, Bayer, Bristol-Myers Squibb, Eisai-Pfizer, Eli Lilly and Company, Forest Laboratories, Janssen Pharmaceutica, NeuroLogic, and Parke-Davis. He has served as a consultant for AstraZeneca, Bristol-Myers Squibb, DuPont, Eli Lilly, Forest, Janssen, NeuroLogic, Organon, and Pfizer Inc. Dr. Lyketsos has served on the speakers' bureau for Abbott Laboratories, Bayer, Bristol-Myers Squibb, DuPont, Eisai, Eli Lilly, Forest, Janssen, Lundbeck, Novartis, Parke-Davis (Warner-Lambert), and Pfizer.

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Dr. Marsh reported that she has received grant/ research support from Eli Lilly and Company and Pfizer Inc.

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PARKINSON'S DISEASE: UPDATE ON DIAGNOSIS AND TREATMENT

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Parkinson's disease (PD) affects approximately 0.5-1 million people in the United States; the annual incidence is 50,000 to 60,000. The average age at onset is 55-60 years, and 85% of patients with PD are more than 65 years old; indeed, Alzheimer's disease (AD) and PD are the most significant geriatric neurodegenerative disorders. In the past 10 years, great strides have been made in the understanding and treatment of PD, which is now recognized to involve cognition, behavior, and mood as well as the nigrostriatal dopamine system.

There is a very complex interaction between the neurological and the psychiatric aspects of PD. The motor symptoms can influence the psychiatric presentation and vice versa. Similarly, some of the medications used to treat PD can affect psychiatric issues, and the converse is true as well. Therefore, it is important for psychiatrists to be familiar with the symptoms and treatments of PD as they address the psychiatric complications that so often accompany this disease.

Signs and Symptoms

Parkinson's disease typically starts unilaterally and gradually involves both sides of the body, but it usually remains worse on the initial side. There are three cardinal motor features of PD. The first is the classic, rhythmic rest tremor, which is seen in very few conditions other than PD. The second, akinesia or bradykinesia, is a lack of movement or slow movement, often accompanied by decreased facial expression, slow, shuffling gait, and start-hesitation. The third is limb rigidity. For a diagnosis of typical, idiopathic PD, at least two of the three features of the cardinal triad must be present.¹

Slow progression and response to levodopa are also typical of PD, as are dementia, cognitive

dysfunction, and depression/anxiety. Orthostatic hypotension is usually asymptomatic; significant early symptomatic orthostatic hypotension or postural instability should raise a red flag indicating that the diagnosis may not be typical PD. Patients with PD commonly have mild urologic problems and sweating abnormalities. Gastrointestinal dysfunction, primarily constipation, is caused by both the disease and the medications used to treat it.¹ Dyskinesias are abnormal, involuntary movements, usually associated with high or peak levodopa levels, but also frequently occurring when plasma levodopa levels drop.

The significant cognitive dysfunction and dementia as well as drug-induced psychosis that occur in PD may develop any time in the course of the illness. Generally, younger-onset patients and those with tremor-predominant symptoms may remain cognitively intact for many years (even decades), while older-onset patients (over 60) and those with a primarily akinetic syndrome with earlier involvement of gait and balance are more likely to develop cognitive dysfunction, even within a few years.

Treatment

Nothing has yet been proven to be neuroprotective for PD. Once patients develop functionally disabling symptoms, they need to start symptomatic therapy. Generally, if patients are young and their symptoms are very mild, they may start treatment with a dopamine agonist. With older patients, one would worry more about cognitive side effects; those patients might be started on levodopa, which is still the most effective treatment for bradykinesia, rigidity, and tremor. Immediate- and controlled-release levodopa preparations can be used individually or in combination. In the last decade, the option of adding a catechol-O-methyltransferase (COMT) inhibitor, which can prolong levodopa action, has been available as well.

Early in treatment, patients do well, but as time goes on, the therapeutic window narrows, and they start to cycle and have "on" and "off" periods and dyskinesias. For more advanced PD, the levodopa is adjusted by increasing the dose or narrowing the dosing interval, and/or switching between or combining controlled- and immediate-release levodopa. This may also be the time to start peripheral COMT inhibition—

with either entacapone, which is fairly mild, or tolcapone, which is much more potent—or to introduce a dopamine agonist if the patient is not already on one. Amantadine, a mild antiparkinsonian agent, has recently been found to be helpful in reducing dyskinesias.²

There is no single right choice of treatment for patients with PD. The major principles are to treat the chief complaint first; start low and go slow, adding one new medication at a time and adjusting one medication at a time; focus on the dosing interval, not just the dose; and stay alert for red flags, particularly older age, confusion, and psychosis.

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DEPRESSION IN PARKINSON'S DISEASE

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Patients with PD have a wide range of psychiatric symptoms (Figure 1).¹ The most common is depression, but hallucinations, apathy, and anxiety are very common as well. The relationship between PD and depression is multifaceted and bidirectional, with many aspects common to both. Patients with previous depression are at increased risk for developing PD later in life.^{2,3} Also, patients with PD have a higher incidence and prevalence of depression than do individuals without PD.^{4,5} One possible modulator of this commonality is dopamine, which in addition to influencing motor symptoms, also affects mood, motivation, and cognition. There is commonality between therapeutic strategies; antidepressants influence motor symptoms,

and dopaminergic drugs may influence mood.

In 1992, Cummings⁶ concluded that approximately 40% of patients with PD had clinical depression, and recent community-based studies support this prevalence for minor depression, with major depression being estimated at 10% or less.⁵

Diagnosis

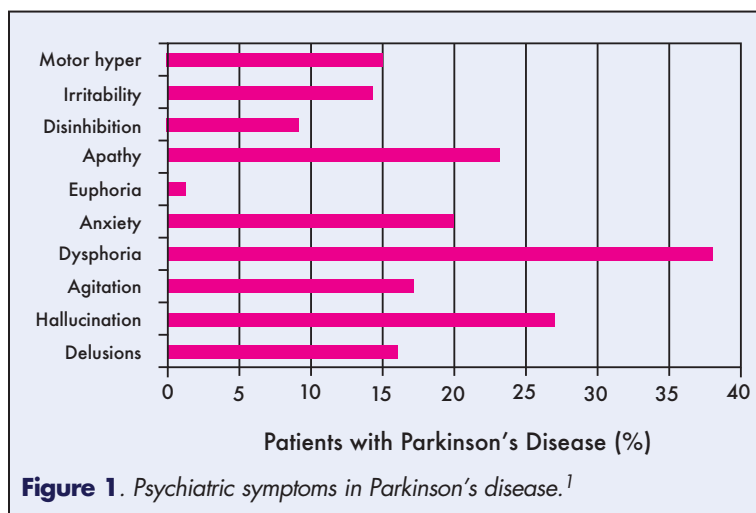
Diagnostic challenges exist in assessing depression in patients with PD because of the common symptoms. There is a risk of overdiagnosing depression since parkinsonian symptoms, such as cognitive impairment and apathy, can resemble depression. There is also a danger of underdiagnosing depression because of masking by motor symptoms, age bias, or lack of attention to emotional problems.

Although there is debate as to the specific depressive pattern in PD, some commonly accepted key features include reported and apparent sadness, anhedonia, increased pessimism, irritability, and comorbid anxiety.

Mechanism and Effects

There are several potential mechanisms of depression in PD. The most commonly reported factor is right-sided onset of symptoms. Structural and functional brain changes, genetics, drug treatment, general psychosocial stress, and the psychological reaction to having the disease and its functional impairment may contribute, as may latent or previous psychiatric disease.

Of the underlying neurochemical changes in



PD related to depression, those related to serotonin, noradrenaline, and dopamine are probably the most relevant. These three neurotransmitters, which are changed and decreased in PD,⁷⁻⁹ have been associated with depression in non-PD populations, and drugs that affect them may relieve depression.¹⁰⁻¹²

Depression accounts for 40% of the variation in quality of life of patients with PD and their caregivers versus less than 20% being explained by motor symptoms.^{13,14} In addition, depression exacerbates cognitive and functional impairment.

Treatment

There is some evidence that nortriptyline might be efficacious in treating depression in PD, whereas data are insufficient for other antidepressants.^{15,16} Clinical experience indicates that selective serotonin reuptake inhibitors (SSRIs) may be beneficial, but there is an inherent risk for worsening parkinsonism with these agents, since serotonin has an inhibitory effect on nigrostriatal dopamine output. However, in clinical practice, worsening of parkinsonism is rarely observed.

Electroconvulsive therapy, the best treatment for depression available, increases dopaminergic activity and may improve parkinsonism as well.¹⁷ Results of a recent study suggest that dopaminergic agents such as methylphenidate may improve depression and apathy.¹⁸ Bupropion could be particularly useful for depression and extrapyramidal symptoms in PD.¹⁹ Finally, another recent study indicated that pramipexole, a dopamine agonist, may improve depression and apathy in PD.²⁰

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PSYCHOSIS IN PARKINSON'S DISEASE

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Parkinson's disease is frequently complicated by psychosis. The prevalence of psychosis in PD is reported as ranging from 8-40% depending on definitions used and the sample. When there is no significant dementia, the rates are lower, 5-17%; with significant dementia they are much higher, up to 81%.^{1,2} Psychosis in PD is the number one factor in nursing home placement and it is associated with increased mortality.³ Fortunately, with the advent of the atypical

antipsychotics, the prognosis is improved for these patients.

Features

Often, by the time patients with PD are referred to geriatric psychiatrists, they have associated behavioral disturbances, frequently of a quite marked and disruptive nature. In addition, these patients commonly have advanced PD with dyskinesias and on-off motor fluctuations, so clinical management is complex. Psychosis is generally divided into three categories: (1) visual hallucinations with insight, (2) hallucinations and/or delusions without insight, and (3) hallucinations and/or delusions with delirium (altered consciousness from baseline).

Minor hallucinations, found in one study to occur in approximately 26% of patients with PD,⁴ are categorized as presence hallucinations, passage hallucinations, and illusions. About 22% of individuals will have complex visual hallucinations, which can occur at any time but often occur at night. Auditory hallucinations occur in about 10% of patients. Overall, patients have about a 46% lifetime rate of hallucinations, with most having more than one type.⁴

Delusions are reported as occurring in up to 30% of patients. They often accompany hallucinations. Delusions manifest variously, including delusions of spousal infidelity (which are very difficult for caregivers who devote themselves to taking care of patients), persecutory delusions, and delusions of influence.⁵

In a longitudinal study with 116 patients at the Johns Hopkins Parkinson's Disease Research Center, about 22% of the patients had psychotic symptoms, and visual hallucinations were the most common (84%).⁶ A high percentage (60%) also had auditory hallucinations, 12% had olfactory hallucinations, 12% tactile, and 4% visceral; 64% had delusions.⁶ Especially important is the high likelihood that a patient with psychosis may have another psychiatric problem. Among the patients with psychosis, 56% had additional psychiatric problems, particularly depression (71%), anxiety (21%), and apathy (14%).⁶

In addition to the psychotic symptoms, patients with psychosis may also exhibit non-

motor fluctuations, disinhibition, agitation, aggression, or combativeness. Caregiver strain is also a major issue.⁷ The psychotic symptoms and associated agitation frequently are so severe that they must be managed with antipsychotic medications.

Etiology/Risk Factors

There is no single explanation for psychosis in PD. It is advisable to consider patients' medication regimen since development of psychosis in idiopathic PD is virtually always associated with use of dopaminergic agents. There is also a role for nondopaminergic factors. For example, the anti-acetylcholine medications also induce psychosis. Other nondopaminergic factors are cognitive impairment and dementia, which is a strong certain risk factor for the development of psychosis, as well as various PD-related factors such as severity, age at onset, duration, and rate of progression.⁸ Spontaneous (ie, non-drug-induced) psychosis has been observed in diseases with shared pathology, such as Alzheimer's disease, dementia with Lewy bodies (DLB), and Huntington's disease; whether this is also the case for idiopathic PD is unclear.

Dementia With Lewy Bodies

The clinical and neuropathological distinctions and similarities between advanced PD with dementia and psychosis and DLB are not completely understood; both are synucleinopathies and they may represent part of the same disease spectrum. The main criteria currently available for diagnosing DLB are progressive cognitive decline, fluctuating cognition, recurrent visual hallucinations, and/or spontaneous parkinsonism. The presence of two symptoms indicates a diagnosis of probable DLB, and one symptom indicates possible DLB.⁹ There are several common symptoms between DLB and PD with dementia including frequent depression, sleep disorders, and hallucinations. Management issues are also often the same, and patients with DLB respond motorically to dopaminergic drugs, although there is usually greater sensitivity to their psychotogenic effects. Dementia with Lewy bodies is further distinguished from idiopathic PD by the clinical history, with psychosis and cognitive problems occurring early in DLB,

and occurring later in the course of PD. The neuropathology is also different. In DLB, there are diffuse cortical Lewy bodies, which may or may not be seen in PD with dementia. In particular, in PD there is nigral neuronal loss, which is not a requisite feature for DLB.¹⁰⁻¹²

Treatment

The Table lists steps in the treatment of psychosis.^{13,14} These steps are not necessarily taken consecutively—sometimes they may all be taken at once—nor must they all be taken. Medications for Parkinson's disease should be eliminated, as most patients with advanced PD ultimately only tolerate levodopa.¹⁵ Use of antipsychotic medications can facilitate an increase in antiparkinsonian medications. The typical antipsychotics are not recommended because of the risk of medical complications and increased parkinsonism. Susceptibility to neuroleptic malignant syndrome and other complications may be caused by the use of antipsychotics, as well as by withdrawing PD medications.¹⁶⁻¹⁸ The atypical agents have proven useful in several clinical trials. Risperidone and olanzapine have relatively poor tolerance as they aggravate parkinsonism. Quetiapine is fairly well tolerated, but it should be started at low dosages (< 25 mg), which are often therapeutic, to avoid or limit motor complications or other side effects such as orthostasis or sedation. Evidence regarding ziprasidone and aripiprazole is anecdotal. Likewise, there are reports that ondansetron, a 5HT-3 inhibitor indicated for treatment of nausea in chemotherapy patients, can also be useful for psychosis without causing motor side effects, especially in acute postoperative states. The gold standard is

TABLE

Treatment of Psychosis^{13,14}

Step	Action
1	Primary prevention
2	Treat medical illnesses (eliminate medications that cause delirium or confusion and psychosis)
3	Eliminate psychoactive medications (eg, benzodiazepines, opiates, tricyclics)
4	Treat comorbid psychiatric illnesses
5	Use nonpharmacologic strategies (eg, education, reassurance, activities)
6	Eliminate antiparkinsonian medications (order: anticholinergics, selegiline, amantadine, dopamine agonists, COMT inhibitors)
7	Address disrupted sleep
8	Try cholinesterase inhibitors
9	Try neuroleptic agents

COMT = catechol-O-methyltransferase.

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clozapine, which is particularly effective in PD, although dosage must be monitored to avoid adverse effects that include sedation, confusion, and possible agranulocytosis and seizures.¹⁹ Patients with DLB seem to respond differently to clozapine, and there have been reports of confusion and comatose states.

There is some evidence that cholinesterase inhibitors can improve cognition in PD and DLB, and that might subsequently help psy-

chosis. However, tolerance is variable, and patient responses must be monitored cautiously. Electroconvulsive therapy is especially helpful in treating psychotic depression.²⁰⁻²³

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COGNITIVE IMPAIRMENT, DEMENTIA, AND PARKINSON'S DISEASE

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Studies have estimated the prevalence of dementia and “cognitive impairment no dementia” in PD to be between 15% and 35%.^{1,2} In studies with longer follow-up, estimates have been as high as 80% in the later stages of PD.³⁻⁵ Cognitive impairment without dementia, which typically does not affect day-to-day functioning significantly, can be specific to one cognitive domain, such as executive dysfunction or forgetfulness, but is not global as is dementia. *Dementia* by definition is global, affecting several cognitive domains, and has clear functional effects on daily living activities. Dementia of PD is a specific syndrome in the same way that dementia of AD is. Cognitive changes in PD usually have subcortical features characterized by the four **Ds**: dysmnnesia, delay, dysexecutive, and depletion, as opposed to the four **As** of a cortical dementia as seen in AD (amnesia, agnosia, aphasia, and apraxia).⁶

The causes of cognitive decline are not known; it is possible that PD itself might be a cause. Dementia due to PD itself typically occurs many years after the onset of motor impairment and has subcortical features. In addition, many patients with PD also have DLB, which may be causing the clinical disturbance. When dementia begins close to the onset of motor symptoms and seems to fluctuate, then DLB should be suspected. Pathologically, Alzheimer's disease is found in 30-50% of patients; therefore, it is probable that a patient who may have had PD will also have Alzheimer's pathology in his or her brain, which may account for some specific clinical changes. In patients with PD who develop cortical dementia in later stages of the motor disease, AD should be considered as a contributing cause.

Treatment

The primary goals are to treat the disease causing the dementia, if possible, and to target the dementia-related symptoms empirically.⁶ This must be done in the context of good supportive care for patients and caregivers. Patients with Parkinson's disease have much more insight than do patients with Alzheimer's disease.⁶ Structure and safety issues must be addressed, since dementia impairs an individual's ability to drive, live alone, etc.⁶ The effect of the primary disease therapies on cognition must be considered; for example, in PD levodopa seems to confer relatively little benefit to cognition,⁷ and pallidotomy may worsen it.⁸

Several symptom-targeted therapies are available, such as cognitive rehabilitation, but they have been poorly studied. Treating depression may be beneficial, but this does not improve cognition in AD, and that may also be true in PD. Therapies that target cognitive symptoms in other settings might be helpful in PD. Small improvements have been detected with donepezil, although gastrointestinal adverse effects and other side effects may be a problem.^{9,10} Results of a placebo-controlled, double-blind trial suggest that rivastigmine may improve neuropsychiatric symptoms, especially those associated with DLB, with little motor cost.¹¹ These studies suggest that there may be a beneficial class effect of cholinesterase inhibitors in PD.

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SLEEP, ANXIETY, AND FATIGUE IN PATIENTS WITH PARKINSON'S DISEASE

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Sleep Problems and Fatigue

Sleep problems are more common in PD than would be expected as a function of age alone. The sleep quality of patients with PD is much lower than that of comparable controls (Figure 2).¹ Approximately 60% of people with PD complain of sleep disturbance, and one-quarter of those consider it a serious problem.² The kinds of disturbances vary widely and include nighttime muscle and movement problems (eg, restless legs), unrefreshing sleep, morning headaches, and sleep apnea.

Approximately half of patients with PD complain of excessive daytime sleepiness (EDS), which is different from fatigue and is associated with severity and length of illness. The drugs used to treat PD can cause either EDS or nighttime awakening. An issue related to EDS is sudden sleep attacks, which are

reported by approximately 4% of patients with PD (about 1% of whom had no warning) and which can be dangerous if, for instance, the patient is driving.³ Another common sleep problem for people with PD is rapid eye movement (REM) behavior disorder, in which the normal muscle atonia that occurs during REM sleep is missing, and patients may act out their dreams, which can be dangerous.

The variability of sleep problems in PD may be due to a corresponding variability in the effects of PD on the neurotransmitters that regulate sleep. Depression is a major risk factor for sleep disturbance. The rigidity of PD also plays a role. When most people get into an uncomfortable position in the middle of the night, they will just change position and will not wake up. People with PD, however, may become stuck in that position and be awakened.

Fatigue is another common complication of PD, affecting approximately 40% of patients with Parkinson's disease.⁴ It is very difficult to separate fatigue from sleepiness. Unlike EDS, fatigue occurs early in the disease course and is not correlated with disease severity.

Treatment

The first step is to rule out treatable causes of insomnia and EDS. If a patient has sleep apnea, a lot of nighttime movement, or any unusual symptoms, referral for a formal sleep study is in order, followed by specific treatment based on the results.

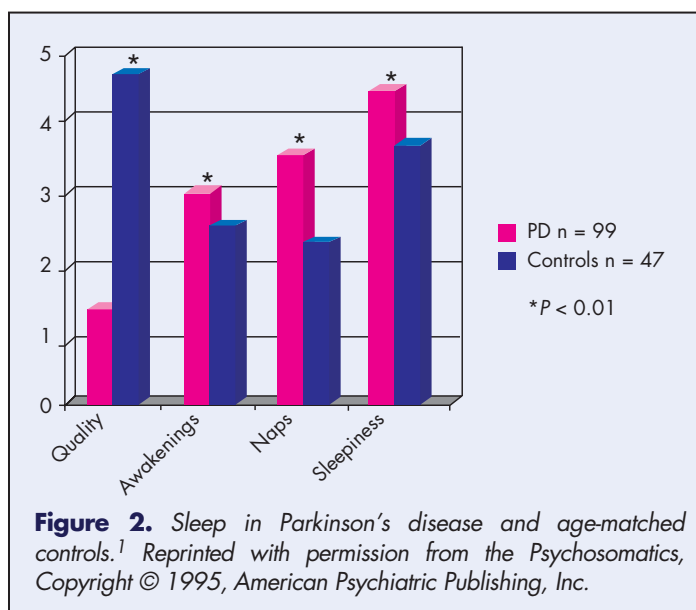


Figure 2. Sleep in Parkinson's disease and age-matched controls.¹ Reprinted with permission from the Psychosomatics, Copyright © 1995, American Psychiatric Publishing, Inc.

The PD regimen should be optimized; some patients may do well with long-acting, controlled-release compounds, whereas others may need shorter-acting agents. Psychiatric treatment should also be optimized; a patient whose depression or anxiety is not adequately controlled will not sleep well.

Beyond disease- or symptom-specific changes, one might try nonbenzodiazepine hypnotics, which work reasonably well and are well tolerated in this population. For fatigue, multimodal treatment is usually most effective; this should include exercise, which is very helpful to patients with PD for several reasons including fatigue. Cognitive behavioral therapy is very useful as well.

Anxiety

As many as 65% of patients with PD complain of some degree of anxiety, and their complaints do not always correlate with categories in the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition*. Anxiety and depression often go hand in hand.⁵ In a 12-year study following 38,000 individuals who developed PD, baseline anxiety was a significant risk factor for developing PD.⁶ Many of these individuals probably have anxiety prior to PD onset; whether it actually contributes to the development of PD is not known.

Treatment

Selective serotonin reuptake inhibitors are first-line treatment for anxiety. Clinical experience indicates that antidepressants work for anxiety in PD as well.⁷ The benzodiazepines clearly work, but the same limitations to their

use exist here as in other chronic anxiety disorders. The atypical antipsychotics are of interest in this area. For instance, quetiapine, which may be effective in treating PD, may help with sleep problems and psychosis. Cognitive behavioral therapy may also be of use.

The state of the art in surgical treatment of PD is bilateral deep-brain stimulation (DBS), most commonly of the subthalamic nucleus. One study showed that anxiety decreased significantly after DBS.⁸ Deep-brain stimulation is much safer than pallidotomy. Thalamotomy is used exclusively for tremor and does not help the other symptoms of PD. It is critical that patients be evaluated properly before surgery, both neurologically and cognitively. If patients have significant cognitive dysfunction before surgery, their outcomes will be worse. The surgery is more appropriate for patients who are relatively young, healthy, and cognitively intact, with a lot of fluctuations and dyskinesias.

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CME EXAMINATION & EVALUATION

AN UPDATE ON PARKINSON'S DISEASE AND ITS PSYCHIATRIC COMPLICATIONS

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CME EXAMINATION

- The cardinal features of PD are:
 - Rhythmic rest tremor
 - Akinesia/bradykinesia
 - Rigidity
 - a + b
 - a + b + c
- Patients with PD are at higher risk for depression, but patients with depression are not at higher risk for PD.
 - True
 - False
- Clinical depression occurs in approximately _____% of PD patients.
 - 30
 - 40
 - 50
 - 60
- The most commonly reported predictive factor for depression in PD is:
 - Left-sided symptom onset
 - Right-sided symptom onset
 - Any unilateral symptom onset
 - Bilateral symptom onset
- PD patients have about a _____% lifetime rate of hallucinations.
 - 28
 - 37
 - 46
 - 55
- The atypical, but not the typical, antipsychotics are useful for treating psychosis in PD.
 - True
 - False
- There may be a class effect of _____ in dementia of PD.
 - Typical antipsychotics
 - Benzodiazepines
 - MAO inhibitors
 - Cholinesterase inhibitors
- Excessive daytime sleepiness is associated with the duration and severity of PD.
 - True
 - False
- _____ is/are first-line treatment for anxiety.
 - MAO inhibitors
 - Surgery
 - SSRIs
 - Levodopa
- Probable dementia with Lewy bodies can be diagnosed based on the following:
 - Progressive cognitive decline
 - Fluctuating cognition
 - Recurrent visual hallucinations
 - Spontaneous parkinsonism
 - All of the above

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Please circle the number that best reflects your opinions on the following statements, using the following rating scale:

1 = Strongly Agree; 2 = Agree; 3 = Disagree; 4 = Strongly Disagree

- | | | | | |
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