

## *Behavioral disturbances in Parkinson's disease*

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*Treatment of Parkinson's disease (PD) is complex and often involves addressing behavioral changes in addition to the movement disorder. Patients with PD are susceptible to any psychiatric condition seen in the general population; some disorders, such as depression and anxiety, may result from PD-related neuropathological changes. Medication-related hallucinations are seen in many PD patients who are treated with dopaminergic agents for motor symptoms. Cognitive impairment is also seen and can be multifactorial. Treatment of behavioral symptoms in PD can greatly improve patients' overall function and quality of life. As surgical interventions to treat motor symptoms, such as deep brain stimulation of the subthalamic nucleus of the substantia nigra, become more prevalent, the behavioral effects of these procedures must also be addressed.*

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**P**arkinson's disease (PD) is now being recognized as a complex illness with numerous behavioral symptoms, in addition to the well-recognized motor symptoms such as tremor, rigidity, postural instability, and bradykinesia. Depression, anxiety, psychosis, and cognitive changes are all extremely common in PD. The magnitude of these symptoms in PD has been revealed by several large studies of patients with PD. Over half of all PD patients experience psychiatric illness at some point in the disease. Depression and hallucinations are the most commonly described psychiatric symptoms, but many others occur. Studies have shown that psychiatric symptoms are often unrecognized in PD patients by their physicians and—when they are recognized—often go undertreated. Specific cognitive deficits have been described in early PD, and at least a third of PD patients develop dementia. Surgical procedures to treat motor symptoms are also increasingly being implicated as a cause of behavioral changes, both positive and negative, in patients with PD.

### **Mood disorders**

Depression has been shown to occur more often in patients with PD than in age-matched samples.<sup>1</sup> Reports of prevalence of depression in PD have varied widely, depending on how the diagnosis of depression is made. Reviews of prior work indicate that about 40% of PD patients are depressed. These studies may not fully represent the frequency of depression, however, since most were based on information gathered from patients in clinics. Scott et al<sup>2</sup> examined a sample of 948 patients and found that 36% of PD patients complained of depression. However, depression was not identified by the patients as the most distressing symptom. A population-based study of 97 PD patients found that 36.1% reported mild depressive symptoms, while another 10% reported moderate and

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severe symptoms.<sup>3</sup> In a small, community-based New Zealand study, the prevalence of major depression was 2.7%; overall prevalence of mood and anxiety disorders was 6.8% in nondemented PD patients. The prevalence of mental illness for these PD patients did not differ significantly from that of age-matched controls with no neurological disease, but similar disability.<sup>4</sup> Rojo et al<sup>5</sup> estimated the prevalence of depressive symptoms, as related to other clinical data, in a series of 350 PD patients over a 9-year period. Mild-to-moderate depressive symptoms and severe depressive symptoms were found in 40.2% and 16.7% of PD patients, respectively. Female gender, advanced disease, and poorer cognitive performance were significantly associated with depressive symptoms. On follow-up, 34% of patients remained stable, 35% showed an improvement in depressive symptoms, and 30.9% worsened.

In addition to reactive mood changes due to loss of function, neurochemical changes in PD probably contribute to the development of mood symptoms. Loss of the dopamine neurons in the ventral tegmental area, the origin of mesolimbic dopaminergic projection, is the most likely neuropathological cause of mood symptoms in PD, since changes in the serotonin and norepinephrine systems are not as extensive. Although one earlier study found lower levels of serotonin metabolites in PD patients with major depression compared to those without,<sup>6</sup> most cerebral spinal fluid (CSF) studies did not concur with this result.<sup>7-9</sup> However, positron emission tomography (PET) has shown hypometabolism in caudate and inferior orbitofrontal cortex in depressed PD patients, possibly indicating damage to the dopaminergic system from the ventral tegmental region.<sup>10</sup> Other blood flow studies of major depression in PD found changes in medial frontal cortex and the anterior cingulate.<sup>11</sup> These

changes seen in PD depression are similar to those seen in some studies of major depression.

A study of major depression and dysthymia in 78 PD patients with classic PD (tremor plus rigidity and/or bradykinesia) compared with 34 akinetic-rigid variant PD patients found that the prevalence of dysthymia was similar in the two groups (31% versus 32%, respectively). However, the finding for major depression was significantly different, with akinetic-rigid variant patients showing a higher prevalence of major depression compared with the classic variant patients (38% versus 15%, respectively). Bradykinesia was the motor symptom most highly correlated with severity of depression. The authors suggest that the pattern of neurodegeneration may differ in akinetic-rigid parkinsonism, such that frontal lobe circuits are more affected compared with classic PD.<sup>12</sup> The effect of “on” and “off” medication fluctuations on mood and anxiety symptoms has also been studied. Maricle et al<sup>13</sup> found improvement in mood and anxiety along with motor function after levodopa administration, compared with placebo.

Treatment of depression in patients with PD is generally the same as that for any elderly person, with lower doses of medication and heightened awareness of medication interactions and side effects (*Table 1*). Work by Shulman et al<sup>14</sup> and Weintraub et al<sup>15</sup> suggests that depression in PD is often unrecognized by physicians, and that when treatment is attempted, it is often suboptimal. Few double-blind, placebo-controlled studies have been conducted on the treatment of depression in PD. A meta-analysis by Klassen et al<sup>16</sup> found a total of 12 well-designed, placebo-controlled, double-blind studies of antidepressant efficacy in PD in the literature, all of which were with tricyclic antidepressants (TCAs). Dry mouth and orthostatic hypoten-

| Class | Example(s)    | Average dose (mg/day) | Starting dose (mg/day) | Comments                                                                                                         |
|-------|---------------|-----------------------|------------------------|------------------------------------------------------------------------------------------------------------------|
| SSRI  | Escitalopram  | 10                    | 10                     | All may also be used for treatment of anxiety; higher doses may be needed if anxiety is the main target symptom. |
|       | Paroxetine    | 20                    | 10                     |                                                                                                                  |
|       | Sertraline    | 50-100                | 25                     |                                                                                                                  |
| SNRI  | Venlafaxine   | 37.5-150              | 37.5                   | Useful for both depression and anxiety                                                                           |
| TCA   | Nortriptyline | 50-150                | 25                     | Monitor blood levels for therapeutic range; nighttime dosing suggested, since can be sedating                    |
| Other | Bupropion     | 100-300               | 100                    | Bupropion may be activating, can worsen anxiety                                                                  |
|       | Mirtazapine   | 15-45                 | 15                     | Mirtazapine can be very sedating, helpful if depression accompanied by insomnia and/or agitation                 |

**Table 1.** Examples of treatment for depressed mood in Parkinson's disease. SSRI, selective serotonin reuptake inhibitor; SNRI, selective noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.

sion were the most commonly seen side effects of TCAs. PD patients may also develop constipation, urinary retention, blurred vision, and unwanted sedation on these medications. In extreme cases, delirium may occur. A placebo-controlled trial of the selective serotonin reuptake inhibitor (SSRI) citalopram for depression in PD found that Hamilton Depression Scale scores decreased in both the citalopram-treated and the placebo-treated groups of PD patients.<sup>17</sup> The authors questioned the use of the Hamilton Depression Scale for evaluation of mood changes in PD. No exacerbation of motor symptoms was seen in the citalopram treatment group compared with the placebo group. Chung et al,<sup>18</sup> in their systematic review of efficacy and safety of antidepressant treatment in PD, concluded that there are insufficient data on the efficacy and safety of antidepressant therapies in PD, and that treatment recommendations could not be definitively made at this time. One particular potential drug interaction should be noted. The manufacturer of selegiline has advised against its use with antidepressants, due to concern regarding the possible overstimulation of the serotonin system, leading to the serotonin syndrome. However, the risk of serotonin syndrome has been very low in clinical experience with these medications.

Noncontrolled studies and case reports suggest that SSRIs are helpful in treatment of depression and other psychiatric conditions in PD, and have no adverse effects on motor symptoms<sup>19</sup>; other reports indicate that motor symptoms may worsen with SSRI use, although this effect is reversible with discontinuation of the SSRI.<sup>20</sup> Dell'Agnello et al<sup>21</sup> used an open-label study to assess the efficacy of four SSRIs (citalopram, fluoxetine, fluvoxamine, and sertraline) for treatment of depression in PD patients. In their study of 62 patients, all four SSRI treatment groups showed significant improvement in depressive symptoms without worsening motor symptoms. Bupropion, an antidepressant with dopamine agonist effects, has received little study in PD to date. It produced dose-limiting side effects in some subjects in the limited investigations that have been conducted with PD patients.<sup>22</sup> There are currently no studies on the efficacy of psychotherapy for treatment of depression in PD.

### Anxiety disorders

Anxiety disorders (including generalized anxiety, social phobia, obsessive-compulsive disorder, and panic disorder) are probably increased in PD, although there has been lit-

tle research in this area. Many PD patients have anxiety symptoms due to legitimate concern about their chronic, progressive illness. In the small studies that have been conducted to date, PD patients also had higher rates of anxiety disorders compared with other neurological<sup>23,24</sup> and medical illnesses.<sup>25</sup> One study found actual anxiety disorders, separate from simple anxiety symptoms, interfered with normal function in 40% of patients with PD.<sup>26</sup> Anxiety disorders are often seen in conjunction with depression in PD, a common comorbidity in the general population.<sup>27</sup> Anxiety symptoms may occur with "on-off" fluctuations in medication treatment of motor symptoms.<sup>28,29</sup>

There is some evidence that anxiety disorders in PD are linked to the underlying neurobiology of the illness. Noradrenergic dysfunction is implicated most strongly in studies of anxiety disorders in the general population, and noradrenergic dysfunction may play a role in development of anxiety symptoms in PD. Neuropathological changes in the noradrenergic system, including cell loss in the locus ceruleus, have been seen in PD brain autopsy studies.<sup>30</sup> In a preliminary yohimbine challenge study, Richard et al<sup>31</sup> administered oral yohimbine, an  $\alpha_2$ -adrenergic autoreceptor blocker, to 6 PD patients with anxiety or depression, 2 PD patients with no psychiatric symptoms, and 2 normal controls. The patients with a history of anxiety showed precipitation of panic attacks following the challenge at a rate similar to that seen in anxiety disorder patients given yohimbine. All the PD patients showed increased sensitivity to development of somatic symptoms following yohimbine challenge. This study, while too small to offer any conclusive evidence, does suggest that there are noradrenergic system alterations in PD mimicking those thought to occur in primary anxiety disorders. Further work is obviously needed to investigate noradrenergic dysfunction in PD. Deficits in both the serotonergic and GABAergic (GABA,  $\gamma$ -aminobutyric acid) systems have also been implicated in the development of anxiety disorders, and PD has been reported to affect both systems.<sup>32,33</sup>

Some characteristics of anxiety disorders seen in PD are different from those seen in the general population, further suggesting a link to the neuropathology of PD. There is no gender discrepancy in anxiety disorders in PD,<sup>28</sup> unlike the higher prevalence of female anxiety disorder patients in the general population. Development of anxiety disorders in PD typically occurs after onset of motor symptoms.<sup>28,34</sup> This is also in contrast to anxiety disorders in the general population, which usually begin early in life.

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Lauterbach et al<sup>35</sup> examined the prevalence of generalized anxiety, generalized anxiety disorder, panic attacks, and panic disorder in PD and in primary dystonia. Generalized anxiety disorder was more common in dystonia patients, while panic disorder was more common in those with PD. Generalized anxiety developed more commonly after dystonia onset, while panic attacks developed more commonly after onset of PD. The authors suggest relationships between generalized anxiety and reduced pallidal inhibition of thalamofrontotemporal projections, and between panic attacks and pathological changes in locus ceruleus function.

Obsessive-compulsive disorder has been linked to basal ganglia pathology,<sup>36</sup> which may also produce disruption of frontal circuitry. It would thus be expected that increased rates of obsessive and compulsive symptoms may occur at increased rates in PD. In a study of 30 PD patients, Tomer et al<sup>37</sup> found that severity of left-sided motor symptoms correlated significantly with increases in overconscientiousness, repetition, disturbing thoughts, and cleanliness obsessions. Increases in concern regarding routine and orderliness were the only obsessive and compulsive symptoms highly correlated with right-sided motor symptom severity. Severity of depressive symptoms did not show a correlation with side of motor symptom presence. Since greater deficiencies in striatal dopamine function have been seen contralateral to the side of worse motor function in PD, the authors suggest that neurodegeneration of the dopamine system may contribute to development of obsessive and compulsive symptoms in PD. Alegret et al<sup>38</sup> found that PD patients with more severe motor symptoms showed more obsessive traits and admitted to more checking, doubting, and cleaning behaviors than age-matched normal controls, as opposed to those with milder disease, suggesting that a certain degree of basal ganglia pathology is needed to generate these symptoms.

There have been no studies to date on treatment of anxiety disorders in PD. As with depression in PD, treatment generally proceeds as it would for any elderly person with an anxiety disorder, with extra caution regarding side effects and drug interactions. SSRIs are generally the first type of medication administered. Benzodiazepines may be helpful for treatment of anxiety symptoms, especially until another medication, eg, an SSRI, has time to take effect. However, benzodiazepines may impair cognition, especially in PD patients with dementia, and benzodiazepine withdrawal may precipitate anxiety.

## Hallucinations and psychosis

Psychosis in PD that requires antipsychotic therapy is frequently associated with severe morbidity, including nursing home placement and persistent psychotic symptoms. The prevalence of hallucinations and psychosis in PD has increased substantially with the use of levodopa treatment for motor symptoms. Their presence has also been found to increase the risk of death in PD. Factor et al report that the use of atypical antipsychotic therapy has apparently reduced some of morbidity and mortality associated with PD psychosis, on the basis of the finding that 28% of nursing home patients died within 2 years of admission compared with 100% in a study conducted prior to availability of atypicals; however, psychosis remains a significant problem in the treatment of PD.<sup>39</sup> Between 20% and 40% of PD patients will experience these symptoms at some point during the course of the illness.<sup>40</sup>

Hallucinations in PD can be very vivid, and accompanied by either preserved insight, which is not a state of psychosis, or diminished insight, constituting actual psychosis. In clinical practice, a continuum of insight is seen, a finding that is supported by research.<sup>41</sup> Visual hallucinations are the most common type of hallucination in PD patients.<sup>42,43</sup> People, animals, or objects are often reported, and some patients are amused by these manifestations. The figures disappear when the patient attempts to touch them. A study of 102 consecutive clinic patients diagnosed with PD using strict criteria found that almost 30% had visual hallucinations or delusions. Symptoms in four of the patients were found to be secondary to delirium.<sup>41</sup> Some data suggest that the presence of visual hallucinations is stable over time.<sup>44</sup> A large, community-based study of PD patients found certain features associated with increased risk for hallucinations, including advanced age, later stage of PD, cognitive impairment, and depression.<sup>45</sup>

The causal role of dopaminergic treatment agents with respect to these symptoms is somewhat controversial. Psychosis and hallucinations were seen in PD prior to the development of dopaminergic agents, but the prevalence of these symptoms has increased dramatically with the use of such treatments. Most groups feel that dopaminergic therapy for the motor symptoms of PD causes the majority of hallucinations and psychosis seen in PD, perhaps by overstimulation of the mesocorticolimbic dopamine system, which may be oversensitive in PD.<sup>46</sup> Friedman and Sienkiewicz<sup>47</sup> found that patients who have an earlier onset of PD have more complex psychotic



complications from dopaminergic therapy and are more likely to develop dyskinesias as a side effect of treatment. The authors suggest that this may be due to the more focal nature of the pathology in young-onset PD patients, where neuropathological change may be primarily in the dopaminergic system.<sup>48</sup>

Some investigators feel the underlying disarray of the dopaminergic system in PD itself contributes more to development of hallucinations and psychosis. Two large studies did not find an association between the use of antiparkinsonian medications and the presence of hallucinations, suggesting the underlying disease pathology is the more important factor.<sup>41,45</sup> Holroyd et al<sup>41</sup> proposed that visual system abnormalities may play a role in development of hallucinations in many patients.

If the patient is not disturbed by the hallucinations and has preserved insight, no treatment may be needed. Treatment of hallucinations and psychosis generally begins with a careful evaluation of the patient to ensure that underlying infection or interaction of medications is not producing delirium with psychosis. Once delirium has been ruled out, antiparkinsonian medication dosage should be reduced, if this is possible without significant worsening of motor function, since this may reduce the severity of hallucinations. Many patients develop their own coping strategies for these symptoms. Diederich et al<sup>49</sup> found that almost 80% of PD patients with hallucinations used coping strategies including cognitive techniques, interactive techniques, and visual techniques (69%, 62%, and 33% of patients used these strategies, respectively).

If pharmacotherapy is required, atypical antipsychotics are most commonly used, since they are the least likely to cause side effects or worsen motor symptoms. At this time, the atypical neuroleptic quetiapine is the first-line treatment used by most clinicians to treat hallucinations or psychosis in PD. Dewey and O'Suilleabhain<sup>50</sup> reported an overall favorable response rate of 66% in 61 PD patients with drug-induced psychosis in a retrospective study. Targum and Abbot<sup>51</sup> found quetiapine to be efficacious and well tolerated in an open-label study of 11 PD patients with hallucinations and psychosis. Low doses (12.5 mg/day quetiapine may be sufficient in some patients) should be tried to minimize side effects, since there have been case reports of motor symptom exacerbation with quetiapine treatment.<sup>52</sup>

Clozapine, an atypical antipsychotic agent, is the most widely studied medication used for treatment of hallucinations and delusions in PD. In a large, randomized, dou-

ble-blind, placebo-controlled study of low-dose clozapine for hallucinations and psychosis, patients in the medication group showed significant improvement in psychiatric symptoms. Clozapine was also found in this study to improve tremor, and did not worsen parkinsonian symptoms.<sup>53</sup> The main drawback of clozapine use is the need for frequent blood draws, due to the risk of medication-induced leukopenia, which can be fatal.

Two other atypical neuroleptics, olanzapine and risperidone, have shown some efficacy in treatment of hallucinations and psychosis in PD. However, both have also been reported to worsen motor symptoms.<sup>54-56</sup> The one double-blind, randomized study comparing olanzapine and clozapine in hallucinating PD patients was stopped after a significant decline in motor function was seen in the olanzapine-treated patients. The authors of this study recommended that olanzapine not be used for PD patients.<sup>57</sup> A single case report by Connemann and Schonfeldt-Lecuona<sup>58</sup> found remission of psychosis and improvement of motor symptoms in a PD patient treated with ziprasidone, a new atypical antipsychotic. However, another report described development of neuroleptic malignant syndrome in a PD patient who was being treated with ziprasidone.<sup>59</sup> These are the only reports of ziprasidone use in patients with PD to date; further study is needed to determine its safety and efficacy in this population.

### Cognitive impairment and dementia

Specific cognitive deficits have been described in early PD. Studies using strict criteria for dementia show prevalence estimates ranging from approximately 18% to 41% in community-based samples.<sup>60-64</sup> Dementia in PD is different from that seen in Alzheimer's disease (AD) in several ways. PD patients have more pronounced executive deficits (such as difficulties in planning and set-switching) and motivational decline than in early AD patients.<sup>65</sup> Many patients with PD have slowed thinking and mild impairment of executive function, but do not develop actual dementia, even in advanced stages of PD.<sup>66</sup> Even in cases where cognitive impairment does not lead to dementia, these changes in the ability to plan and execute tasks can be extremely disabling to many patients, especially if they wish to continue to work despite progression of motor symptoms. Family members and other caregivers may become frustrated with a patient's lack of motivation and inability to follow through on plans. Education of patients and families as to what apathy and impaired executive

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function entail, and why they develop in a condition such as PD, which is regarded by the general public as simply a disorder of motor function, can be a meaningful intervention in many cases. Formal neuropsychological tests of cognitive function can help differentiate dementia due to PD from other dementias, such as AD, in a patient who has PD and cognitive changes.

When evaluating a PD patient with possible dementia, there are numerous factors that may contribute to worsening of cognition. These include factors specific to PD, such as toxicity of PD medications for the movement disorder. Other causes are seen throughout the geriatric population, including polypharmacy and delirium (*Table II*). Addressing these issues may help reduce the severity of dementia and lessen disability due to cognitive factors in the patient. The most commonly cited risk factors for development of dementia in PD include advancing age and severity of extrapyramidal signs. Recent work suggests that this may be due to a combination of the effect of age and extrapyramidal signs, rather than separate effects.<sup>67</sup> The neuropathology underlying dementia in PD is unclear. Neuronal dysfunction due to PD itself may cause memory loss. However, some patients with PD and memory decline also have changes that are more consistent with neuropathological findings seen in AD. Many PD patients have a mix of the two types of pathology.<sup>68,69</sup> Deficits in the dopaminergic system contribute to cognitive decline, but involvement of the cholinergic and adrenergic systems is also likely. PD autopsy studies have shown significant reductions in neocortical cholinergic neurons.<sup>70</sup>

## Factors specific to PD

- Toxicity of dopaminergic agents
- Hallucinations, psychosis, or delirium secondary to antiparkinsonian medications
- Exacerbation of cognitive dysfunction during medication "off" periods
- Sleep deprivation (due to sleep fragmentation in PD, REM sleep disorder, vivid nightmares)

## Factors common in geriatric patients in general

- Medication interactions
- Use of anticholinergic agents, or agents with high levels of anticholinergic activity
- Undiagnosed depression or other mood disorder
- Other psychiatric symptoms (eg, anxiety)

**Table II.** Factors that may contribute to cognitive impairment and dementia in patients with Parkinson's disease (PD). REM, rapid eye movement.

Although functional imaging has been used to study motor changes in PD, little work has been done to examine cognitive deficits, despite the high frequency of this symptom in PD. As discussed above, executive dysfunction, including problems with planning and set switching, are common in PD. Some groups have used modified versions of the Tower of London, a planning task, to examine executive performance with functional imaging, and found variable dorsolateral prefrontal activation changes in PD.<sup>71,72</sup> Lewis et al<sup>73</sup> examined early cognitive changes in PD and found reduced activity in frontostriatal circuits during performance of a working memory task.

Cholinesterase inhibitors have received the most attention as potential agents to treat PD dementia. The medications discussed below, donepezil, rivastigmine, galantamine, and memantine (an *N*-methyl-D-aspartate [NMDA] antagonist), are all approved for use in treatment of AD in the US, but not for use in other types of dementia, including that associated with PD. Donepezil has received the most extensive study as a potential therapeutic agent for dementia in PD. Aarsland et al<sup>74</sup> performed a double-blind, placebo-controlled, crossover study and found that this medication was well tolerated in PD patients and did not worsen motor symptoms. Significant positive effects of donepezil treatment on cognition were seen on objective memory testing and on clinician and caregiver ratings. Open-label studies also suggest donepezil may be useful in the treatment of hallucinations in PD, but worsening of motor symptoms and delusions have been reported in these studies.<sup>75,76</sup> In addition to possibly improving cognition, rivastigmine has also been found to ameliorate hallucinations and improve behavioral problems.<sup>77,78</sup> Galantamine, a cholinesterase inhibitor with additional nicotinic activity approved for use in AD, has been investigated for use in PD dementia, with some positive preliminary results, but variable effects on motor function.<sup>79</sup> Donepezil, rivastigmine, and galantamine may all potentially worsen motor function in PD.

Behavioral symptoms, such as hallucinations, may improve with cholinesterase inhibitor treatment, as has been reported in some AD cases treated with these agents. Contraindications to acetylcholinesterase inhibitor use include a history of bleeding gastric ulcers, since these medications will increase gastric secretions. Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of peptic ulcer or gastrointestinal bleeding when taken with cholinesterase inhibitors. Gastrointestinal side effects, such as nausea and diarrhea, are common, but often tran-

sient side effects. Cardiac conduction abnormalities may occur, due to vagotonic effects on the sinoatrial and atrioventricular nodes. Cholinesterase inhibitors are likely to exaggerate succinylcholine-type muscle relaxation during anesthesia due to anticholinesterase properties.

Three studies have used memantine, a moderate-affinity NMDA antagonist, to treat motor symptoms in PD, including an early study of intravenous administration.<sup>80-82</sup> These results suggest there are some beneficial effects with respect to PD motor symptoms; however, there were side effects, including behavioral changes. Further work is needed to determine safety and efficacy of this agent for treatment of both cognitive and motor symptoms in PD. Neuroprotective agents, which are being studied for prevention of dementia in various neurodegenerative illnesses, are being tested for use in PD.<sup>83,84</sup>

### DBS and behavioral changes

There is increasing recognition that deep brain stimulation (DBS) and other surgical interventions for motor symptoms of PD may have additional effects on behavior. The basic premise of DBS is that neuropathological change in PD leads to abnormal neural transmission from several structures, including the subthalamic nucleus and globus pallidus internus. DBS interrupts this aberrant activity, and ameliorates motor symptoms of PD. Given that frontal-subcortical circuits are known to affect behavior,<sup>85</sup> in addition to their modulation of movement, it is important that patients are evaluated for behavioral symptoms prior to surgery, and that potential postoperative changes in psychiatric or cognitive status are addressed quickly. Possible negative effects of DBS on a patient's emotional state and cognition should be considered along with other potential surgical complications of DBS.

Depression and depressed mood, the most commonly seen psychiatric symptoms in PD, have received the most study in DBS patients. Other behavioral changes, including euphoric mood and frank mania, hallucinations, anxiety, and sleep disorders have also received some limited study.<sup>86</sup> The efficacy of DBS is being evaluated in refractory cases of obsessive-compulsive disorder, an approach that may help illuminate the neurobiology underlying both disorders, since similar frontostriatal circuitry may be involved.

Rates of depressed mood associated with DBS vary widely, from less than 10% to over 30% of patients experiencing these symptoms.<sup>87-91</sup> The role of past psychiatric

history as a predictor of psychiatric outcome after DBS is not definitive at this time, but there is some indication from existing reports that patients with a prior history of mood symptoms may be more likely to develop depressed mood following DBS.<sup>87,88,91</sup> Suicidal ideation and suicide have also been reported.<sup>87,88,91</sup> It should be noted that many patients with prior history of depression do not develop depressed mood associated with DBS. It is thus advisable that patients receive psychiatric evaluation prior to DBS, and that psychiatric conditions such as depression and anxiety receive adequate treatment preoperatively.

As with psychiatric symptoms, the reported effects of DBS on cognition are variable. It is generally agreed that patients should receive cognitive screening as part of preoperative evaluation, since there have been reports of patients with poor cognitive function who became demented following DBS.<sup>92-94</sup> In addition, DBS may be particularly likely to contribute to cognitive deficits in patients over age 69.<sup>95</sup> Thus, the risks and benefits of the procedure should be weighed with particular care in these patients, for whom any further decline in cognition could greatly offset improvement of motor symptoms with DBS.

### Conclusion

As we further our understanding of the neuropsychiatric symptoms in PD, treatment of these patients has become more challenging. Although many agents are now available to treat motor symptoms in PD, less is known about safety and efficacy of treatment for behavioral symptoms, despite the fact that they affect large numbers of patients and significantly contribute to morbidity and mortality in many cases. A multitude of psychiatric symptoms is seen in PD, including mood changes, anxiety disorders, hallucinations, and frank psychosis. Changes in cognitive function are also seen, and, in some cases, progress to development of dementia. Treatment of these behavioral symptoms can greatly improve patients' overall function and reduce the burden placed on caregivers. Thus, despite the lack of formal treatment studies, clinicians should make efforts to treat behavioral disturbances. Surgical interventions, such as DBS, are extremely beneficial for treatment of motor symptoms, but may worsen or cause behavioral symptoms. Patients should be evaluated carefully before DBS procedures and should also be monitored postoperatively for development of behavioral changes. □

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## Trastornos de conducta en la enfermedad de Parkinson

El tratamiento de la enfermedad de Parkinson (EP) es complejo y a menudo requiere evaluar los cambios conductuales además de los trastornos del movimiento. Los pacientes con EP pueden presentar cualquier trastorno psiquiátrico que se dé en la población general; y algunas enfermedades como la depresión y los trastornos ansiosos pueden producirse a partir de cambios neuropatológicos relacionados con la EP. En muchos pacientes que son tratados con agentes dopaminérgicos para los síntomas motores se observan alucinaciones en relación con la medicación. También se ha observado deterioro cognitivo el cual puede ser multifactorial. El tratamiento de los síntomas conductuales en la EP puede mejorar significativamente el funcionamiento general del paciente y la calidad de vida. A medida que las intervenciones quirúrgicas y la estimulación cerebral profunda de los núcleos subtalámicos de la sustancia nigra están siendo aplicados con mayor frecuencia para tratar los síntomas motores, resulta necesario evaluar los efectos sobre la conducta de estos procedimientos.

## Troubles du comportement dans la maladie de Parkinson

Le traitement de la maladie de Parkinson (MP) est complexe et se doit souvent d'aborder les troubles du comportement en plus des dyskinésies. Les Parkinsoniens sont sujets aux mêmes troubles psychiatriques que ceux observés dans la population générale ; certains d'entre eux, comme la dépression ou l'anxiété, peuvent résulter de modifications neuropathologiques liées à la MP. Des hallucinations liées au traitement surviennent chez de nombreux patients parkinsoniens qui prennent un traitement dopaminergique prescrit pour les troubles moteurs. Un déficit cognitif est également observé et peut être multifactoriel. Le traitement des troubles du comportement dans la MP peut améliorer de façon importante l'état général et la qualité de vie des patients. Certaines interventions chirurgicales réalisées pour traiter les troubles moteurs, telle la stimulation cérébrale profonde du noyau sous-thalamique de la substance noire, sont de plus en plus fréquentes et leurs effets sur le comportement doivent être abordés.

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