



**EDUCATIONAL OBJECTIVE:** To advise physicians on how to recognize and treat the many nonmotor symptoms of Parkinson disease

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# Parkinson disease: Not just a movement disorder

## ■ ABSTRACT

Nonmotor symptoms are common in Parkinson disease and can significantly worsen the health and quality of life of the patient and family members. These symptoms can be broadly categorized as sensory, autonomic, cognitive-behavioral, and sleep-related. Clinicians can improve the care of these patients by recognizing and addressing these problems.

## ■ KEY POINTS

Nonmotor symptoms can be due to the disease itself, to its treatment, or to on-off fluctuations in motor status as doses of medication wear off.

Impaired sense of smell, depression, anxiety, fatigue, and constipation can precede the motor symptoms of Parkinson disease and may be symptoms of the disease itself.

Orthostatic hypotension, sedation, psychosis, confusion, and impulsiveness may be adverse effects of medical therapy or may worsen with it.

Depression occurs in up to 50% of patients with Parkinson disease, although it may be difficult to recognize because many of its physical features can also be manifestations of Parkinson disease itself.

**P**ARKINSON DISEASE is characterized by tremor, rigidity, bradykinesia, and postural instability, but if we focus on these easily identified motor signs we risk overlooking the many nonmotor symptoms that coexist with them (TABLE 1).

These nonmotor symptoms—sensory, autonomic, and behavioral—are important to recognize, as they can lead to even more serious complications and impair quality of life.

## ■ COMMON, TROUBLESOME, AND UNDERDIAGNOSED

Nonmotor symptoms are very common. In fact, up to 60% of patients suffer from more than one nonmotor symptom, and 25% have four or more,<sup>1</sup> including autonomic dysfunction, sensory symptoms, and cognitive and behavioral problems.<sup>2</sup>

Nonmotor symptoms can be primary complaints and, for some patients and family members, can cause greater disability than motor symptoms.<sup>3,4</sup> For instance, depression and cognitive problems contribute to a decline in quality of life regardless of the degree of motor impairment.

Yet these symptoms are often underdiagnosed.<sup>5</sup> A delay in diagnosis may reflect the tendency of clinicians, patients, and family members to focus on the more apparent motor features of Parkinson disease, a lack of awareness of the nonmotor symptoms, or both. Consequently, patient education is essential. Identifying and treating these symptoms requires a multidisciplinary clinical team approach and an ongoing dialogue with the patient and family.

## ■ VARIOUS SYMPTOMS, VARIOUS CAUSES

Some nonmotor symptoms (eg, impaired sense of smell, depression, anxiety, fatigue, and con-

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TABLE 1

**Nonmotor symptoms in Parkinson disease: Management strategies**

SYMPTOM	MANAGEMENT
<b>Sensory</b>	
Pain, paresthesia	Treat motor fluctuations and musculoskeletal problems
Visual problems	Correct visual acuity
Impaired sense of smell	No treatment
<b>Autonomic</b>	
Orthostatic hypotension	Fluids, salt intake, mineralocorticoids, pyridostigmine (Mestinon), midodrine (Proamatine)
Drenching sweats	Treat related "off periods" or dyskinesia
Drooling	Botulinum toxin injection
Dysphagia	Swallowing evaluation and training
Constipation	Fluids, dietary changes, exercise, stool softeners, laxatives, botulinum toxin injection
Urinary frequency, urgency	Behavioral management, bladder antispasmodics
Sexual dysfunction	Phosphodiesterase inhibitors; treat contributing factors
<b>Cognitive-behavioral</b>	
Depression	Supportive psychotherapy, selective serotonin reuptake inhibitors, venlafaxine (Effexor), mirtazapine (Remeron), electroconvulsive therapy
Apathy	Methylphenidate (Ritalin), bupropion (Wellbutrin)
Anxiety	Selective serotonin reuptake inhibitors, benzodiazepines
Impulsive behavior	Assess contribution of dopaminergic agents
Psychosis	Search for systemic illness, reduce medications active in the central nervous system (CNS), assess contribution of antiparkinsonian or other CNS-active medications, give quetiapine (Seroquel) or clozapine (Clozaril)
Dementia	Cholinesterase inhibitors
<b>Sleep disorders</b>	
Daytime sleepiness	Review medications; modafinil (Provigil) may help; consider obstructive sleep apnea
Insomnia	Consider possible causes
Restless legs syndrome	Dopaminergic agents, opiates, clonazepam (Klonopin), gabapentin (Gabarone); iron in iron-deficient patients
Vivid dreams	Clonazepam

stipation) can precede the motor symptoms of Parkinson disease and may be symptoms of the disease itself. Perhaps accounting for these observations, recent pathologic studies described diffuse Lewy body deposition in areas outside of nigral dopaminergic neurons,<sup>6,7</sup> and the olfactory bulb, medulla, and pontine tegmentum may be involved before the substantia nigra.

Other symptoms, such as orthostatic hypotension, sedation, psychosis, confusion, and impulsiveness, may be adverse effects of medical therapy or may worsen with it.

Nonmotor symptoms can also emerge as a "wearing-off" phenomenon with standard treatment.<sup>2,8</sup> The "off period" is a term primarily used to describe the reemergence of mo-

tor symptoms as a dose of levodopa wears off and before the patient receives the next dose. However, nonmotor symptoms, in particular depression and anxiety, can also occur in this period.

To treat nonmotor symptoms, one needs to identify and treat the primary symptom or the comorbid illnesses that may worsen it (eg, confusion in the setting of dehydration and infection), assess the possibility of adverse drug effects (a particular problem with many anti-Parkinson drugs), and try to reduce off periods with changes in dopaminergic therapy.

### ■ SENSORY SYMPTOMS

#### Off-period pain, paresthesia

Pain that cannot be attributed to muscle spasms, dystonia, somatic disease, autonomic dysfunction, or peripheral nerve disease occurs in up to 38% of patients with Parkinson disease.<sup>9,10</sup> The pain is often diffuse and aching. Paresthesia-like complaints include numbness, tingling, and change in temperature.

Some sensory symptoms occur mostly during off periods and may respond to dopaminergic therapy. Examples are limb paresthesia, truncal pain, trigeminal neuralgia-like pain, and vaginal or perineal pain.<sup>9-11</sup>

#### Impaired sense of smell, vision

Impaired sense of smell can precede motor symptoms and is being investigated as a possible screening symptom for early diagnosis.<sup>12,13</sup>

Altered vision is a less recognized symptom of Parkinson disease. Many patients have difficulty reading even if they have normal visual acuity. Part of their difficulty stems from oculomotor defects such as impairment in visual saccadic movements and muscle rigidity.<sup>14</sup> Visual pathways can be affected, as evidenced by abnormal visual evoked potentials that correlate with disease severity and by impairment in contrast sensitivity, color perception, and judgment of line orientation.<sup>15</sup>

It is unclear how these visual abnormalities contribute to everyday symptoms in Parkinson disease. Certainly, visual scanning activities such as reading are impaired.

Patients also suffer from drug-induced visual illusions and hallucinations, which are often colorful. Diederich et al<sup>16</sup> found that

contrast discrimination and color perception were significantly more impaired in Parkinson patients who have visual hallucinations, which suggests that it is important to correct visual abnormalities.

### ■ AUTONOMIC SYMPTOMS

In general, autonomic problems increase with age, disease severity, medication use, postural instability, cognitive decline, and visual hallucinations.<sup>17,18</sup>

#### Orthostatic hypotension

Almost half of patients with Parkinson disease have orthostatic hypotension.<sup>19</sup> Of concern, patients with postural instability are at greater risk of orthostatic hypotension, thereby further increasing their risk of falling and injuring themselves.<sup>20</sup>

Postprandial hypotension is more common in Parkinson disease and is more often associated with midday meals, perhaps owing to a higher carbohydrate content and its effect on insulin release<sup>21</sup> (many patients reserve high-protein meals for the evening and eat a greater proportion of carbohydrates during the day).

Home blood pressure monitoring is especially helpful, since blood pressure can fluctuate significantly and office readings may not reveal the problem.

Orthostatic hypotension can be both a drug side effect and a manifestation of the disease. Although all dopaminergic drugs can worsen orthostatic hypotension, the motor benefits of these drugs should be reviewed in relation to this risk. Dopaminergic agonists and amantadine (Symmetrel) should be used with caution in patients with significant orthostatic hypotension.

Treatment should include fluids, a high-salt diet, elastic stockings, fludrocortisone (Florinef), pyridostigmine (Mestinon), and perhaps the selective alpha 1 agonist midodrine (Proamatine). However, midodrine can cause supine hypertension and must be used cautiously in patients with advanced disease who take daytime naps because of fatigue. If postprandial hypotension is a problem, altering the patient's diet to include smaller but more frequent meals may help.

Impaired sense of smell may be an early symptom of Parkinson disease

### Cold limbs, sweating

Complaints related to temperature regulation include cold limbs and excessive sweating. Off-period drenching sweats occur as an end-of-dose symptom thought to be related to subtherapeutic plasma dopamine levels and may respond to dopaminergic therapy aimed at reducing motor fluctuations and off periods.<sup>22</sup>

### Gastrointestinal symptoms

Dysphagia (difficulty swallowing), sialorrhea (excessive salivation), nausea, constipation, and defecatory dysfunction are more common in patients with Parkinson disease than in age-matched controls, even after controlling for factors such as drugs, autonomic dysfunction, diet, and exercise.<sup>23</sup> These problems can cause malnutrition (necessitating a gastrostomy tube), aspiration pneumonia, and difficulty in swallowing and retaining pills,<sup>24</sup> all of which can lead to problems that are even more serious. Although gastrointestinal symptoms occur in all stages of Parkinson disease, patients with advanced disease are at greater risk.

**Dysphagia.** James Parkinson described dysphagia and sialorrhea in his original 1816 monograph.<sup>25</sup> The prevalence of dysphagia increases with severity of disease.<sup>23</sup> Dysphagia is usually due to altered pharyngeal contraction, resulting in difficulty propelling food into the pharynx and retention of food in the pyriform sinuses and valleculae, but esophageal dilatation and dysmotility, spasms, gastroesophageal reflux, and increased transit time also contribute.<sup>24,26,27</sup>

**Constipation** may affect more than half of patients.<sup>28</sup> One study reported a higher risk of developing Parkinson disease in men with infrequent bowel movements.<sup>29</sup>

Constipation and defecatory dysfunction can be severe enough to result in colonic dilatation and pseudo-obstruction.<sup>30</sup> Altered gastrointestinal transit time may contribute to erratic absorption of medications.

Causes of constipation include slow colonic transit, weak abdominal muscles, decreased phasic contraction, and a paradoxical increase in puborectalis muscle and anal sphincter activity with straining, consistent with pelvic muscle dystonia.<sup>31</sup>

Treatment includes reducing off periods, limiting anticholinergic agents, prescribing a

proper bowel regimen, and encouraging fluids and exercise. In addition, daily stool softeners, fiber, and polyethylene glycol are effective. Botulinum toxin injection into the puborectalis muscle may improve outlet obstruction.<sup>32</sup>

**Risk of aspiration.** Dysphagia, in association with respiratory symptoms, should prompt an evaluation for aspiration. Thickening liquids and early referral to a swallowing specialist may lessen the risk of aspiration.

**Drooling** is bothersome and embarrassing for many patients. Treatment historically included antimuscarinic agents, but these can cause constipation and confusion in patients with advanced disease. More recently, botulinum toxin injections into the parotid and submandibular glands have been shown to be effective in patients with excessive drooling.<sup>33</sup>

### Urinary problems

Urologic abnormalities can be divided into dysfunction of the bladder, dysfunction of the urethral sphincter, and other causes of outflow obstruction such as prostate enlargement in men. The most common complaint is nocturia, followed by frequency and urgency.<sup>34</sup>

Nocturnal polyuria and urinary hesitancy and urgency are embarrassing but treatable. Urinary incontinence is a common reason for nursing home placement, and nocturia is a common cause of falls, as patients attempt to get up to urinate.<sup>35,36</sup>

Treatment of urinary incontinence should begin with an assessment for urinary tract infection, stress incontinence in women, and prostate enlargement in men. Urinary urgency due to detrusor hyperreflexia or spastic bladder can improve with anticholinergic antispasmodic agents. However, these should be used with caution in patients who are experiencing hallucinations or cognitive problems.

### Sexual dysfunction

Sexual dysfunction, including decreased libido and erectile dysfunction, is in part related to autonomic dysfunction.

Treatment is complex, as these problems are multifactorial. Contributing factors include physical disability, the stress of living with a progressive illness, drug effects, depression, pain, difficulty in communication, caregiver stress, and impact on intimacy. The

**Almost half of Parkinson patients have orthostatic hypotension**

phosphodiesterase inhibitor sildenafil (Viagra) can improve erectile dysfunction, but must be used cautiously in patients with orthostatic hypotension.<sup>37</sup> Other drugs of this class are available but have not been tested in this population.

### ■ COGNITIVE-BEHAVIORAL PROBLEMS

Neuropsychiatric disorders are common in Parkinson disease and at times can be more distressing to the patient and family than the motor symptoms. These include mood disorders, apathy, anxiety, impulse control disorders, psychosis, and dementia.

Dopaminergic medications used to treat movement can precipitate or exacerbate these neuropsychiatric problems. Therefore, treatment requires a balance between motor and neuropsychiatric benefits, with close dialogue with the patient and family about primary goals of treatment.

#### Depression

Depression is among the most common neuropsychiatric symptoms in Parkinson disease, occurring to some degree in up to 50% of patients.<sup>38</sup> Diagnosing it is critical, because it can worsen physical symptoms, cognitive status, quality of life, and caregiver distress.<sup>39</sup>

However, depression can be difficult to recognize, because many of its features (eg, fatigue, psychomotor slowing, flattened affect, sleep difficulties) can also be manifestations of Parkinson disease. One should specifically ascertain whether the patient has a depressed mood or loss of interest in pleasurable activities. The Beck Depression Inventory is sensitive for depression in Parkinson disease and thus may be a reasonable screening tool.<sup>40</sup>

**Treatment.** Psychotherapy may help and may even be a first-line treatment in patients who cannot tolerate antidepressant drugs. Practical recommendations include relaxation techniques, a sleep hygiene regimen, engaging in meaningful activities to achieve a sense of purpose, and caregiver education.<sup>41</sup>

We have little evidence-based guidance on drug treatment of depression in patients with Parkinson disease. A recent meta-analysis found only two placebo-controlled studies in the past 40 years that monitored outcome

based on a standardized rating scale of depression in patients with Parkinson disease.<sup>42</sup>

In preliminary studies, dopamine agonists have shown some efficacy in treating depression without Parkinson disease.<sup>43</sup> However, the antidepressant contributions of anti-Parkinson drugs have not been well established.

Selective serotonin reuptake inhibitors (SSRIs) appear to be safe and well tolerated.<sup>44</sup> Venlafaxine (Effexor) and mirtazapine (Remeron) are also reasonable initial options. Tricyclic antidepressants should be used with caution because they can cause anticholinergic side effects, especially confusion, in this population.

All serotonergic agents should be used with caution when given in combination with monoamine oxidase inhibitors, which are often used to treat motor symptoms in Parkinson disease, because of the risk of serotonin syndrome, which is characterized by fever, altered mental status, myoclonus, tremor, hyperreflexia, and diaphoresis and may be fatal.

Electroconvulsive therapy can be reserved for the treatment of severe refractory depression in patients with Parkinson disease without complex medical issues.<sup>45</sup>

#### Apathy

Apathy is present in approximately 30% of patients with Parkinson disease.<sup>46</sup>

Apathy can be very difficult to differentiate from depression, as the two disorders can occur together. Apathy can also be present without signs or symptoms of depressed mood. Apathy is commonly conceptualized as involving three domains: cognitive (lack of interest), behavioral (lack of initiation and drive), and affective (lack of emotion). The possibility of a primary apathy syndrome should be considered if the patient does not respond to standard treatments for depression. This is critical, as the treatment of the two syndromes may differ.<sup>47</sup>

Although efficacy data are limited, bupropion (Wellbutrin) and methylphenidate (Ritalin)<sup>48</sup> can be tried for their activating or stimulant properties.

#### Anxiety disorders

Anxiety disorders commonly accompany depression in Parkinson disease, but they can

Many symptoms are worse during end-of-dose 'off periods'

also occur independently. They most often present in the setting of wearing-off or on-off fluctuations associated with medication status. Anxiety disorders in patients with Parkinson disease include generalized anxiety and panic attacks, which are responsive to SSRIs and benzodiazepines.<sup>49</sup> Benzodiazepines are effective, and clonazepam (Klonopin) may be preferred because it has a long half-life, thereby minimizing anxiety associated with wearing-off or unpredictable off periods. Conversely, a long half-life and depressive effects may limit its use in advanced age.

**Classic obsessive-compulsive disorder** is less common, but obsessive behaviors and impulse control difficulties can occur in up to 7% of patients with Parkinson disease and presumably reflect dopamine dysregulation, most often associated with dopamine agonists.<sup>50</sup> Impulsive behavior can include gambling, hypersexuality, and bingeing.

One form of obsessive-compulsive disorder is punding, a behavior characterized by intense fascination with repetitive handling and examining of objects, most often mechanical objects.<sup>51</sup> Behaviors can include assembling and disassembling, collecting, or sorting of objects.

### Visual hallucinations

Many patients with Parkinson disease have visual hallucinations as a side effect of dopaminergic drugs. At first, the patient realizes that they are hallucinations, but this insight may be lost as the disease progresses. The clinician should also consider other potential causes such as dementia, systemic illness, or psychosocial stress.

If visual hallucinations present early in the course of the disease and are accompanied by loss of insight and by cognitive fluctuations, the patient may actually have Lewy body dementia.<sup>52</sup> Its features include parkinsonian symptoms, visual hallucinations, a fluctuating level of consciousness, and neuroleptic sensitivity.

### Psychosis

The first-line treatment for psychosis in patients with Parkinson disease should involve:

- Searching for a systemic illness such as urinary tract infection, aspiration pneumonia, or dehydration;

- Stopping or lowering the dose of drugs that act on the central nervous system; and
- If possible, stopping or lowering the dose of anti-Parkinson drugs that have the greatest risk of cognitive side effects. In many cases, this is not a realistic option, and adding an antipsychotic drug may be necessary.

Monitoring and treating psychosis is paramount, as it is a major risk factor for nursing home placement.<sup>53</sup>

Conventional neuroleptics such as haloperidol (Haldol) should be avoided because they can exacerbate parkinsonian symptoms.

Two atypical neuroleptics, clozapine (Clozaril) and quetiapine (Seroquel), appear to be the best tolerated in Parkinson disease patients. Clozapine is the only neuroleptic found to be more efficacious than placebo in patients with Parkinson disease.<sup>54</sup> However, of the two, clozapine has a higher risk of side effects and requires frequent blood monitoring, making it difficult to use. Quetiapine has been shown to be as efficacious as clozapine,<sup>55</sup> but it failed to show efficacy in a recent controlled study.<sup>56</sup> Nevertheless, it is considered the first-line treatment option, since it is safer.<sup>40</sup>

Other atypical antipsychotics appear to exacerbate Parkinson disease or have not been adequately studied and should therefore be used with caution.

### Dementia

Estimates of the prevalence of dementia in patients with Parkinson disease vary widely, most likely reflecting differences in populations studied and methods used. The best estimates indicate that 20% to 30% of patients with Parkinson disease develop dementia.<sup>57</sup>

Parkinson dementia is one of the classic subcortical dementias, characterized by slow thinking and by difficulties in working memory and problem-solving due to disruption of frontal-subcortical circuits.<sup>58</sup> Its most common neuropsychiatric symptoms are hallucinations and depression, with less agitation, disinhibition, and irritability than in Alzheimer dementia.<sup>59</sup>

Anti-Parkinson drugs, especially anticholinergics, can exacerbate cognitive impairments in patients with Parkinson disease. An acute change in cognitive abilities or visual hallucinations is often associated with an un-

**If the mental status changes acutely, look for infection, aspiration pneumonia, dehydration**

derlying medical illness such as infection (eg, a urinary tract infection or aspiration pneumonia) or dehydration.

Anticholinesterase inhibitors such as rivastigmine (Exelon) are indicated in patients with Parkinson dementia but may provide only a modest benefit.<sup>60</sup>

### ■ SLEEP DISORDERS

#### Excessive daytime sleepiness

Fatigue and hypersomnolence often impair quality of life.<sup>61</sup> Daytime hypersomnolence is often multifactorial: it can be caused by the disease itself,<sup>62</sup> by dopaminergic therapy,<sup>63,64</sup> by a comorbid illness, or by nighttime sleep problems.

Sudden and uncontrollable episodes of sleep are an extreme form of hypersomnolence and are worrisome, especially with activities such as driving.<sup>65</sup> Greater sleepiness (measured by the Epworth Sleepiness Scale), longer duration of Parkinson disease, and use of dopaminergic agonists increase the risk of such attacks.<sup>66</sup> In general, very few patients experience such attacks without warning signs of sedation.

Treatment must include a comprehensive evaluation of current medications, the effect of dopaminergic agents (especially agonists), and nighttime factors that influence sleep (some of which are described below). Modafinil (Provigil), effective in narcolepsy, helped in some studies<sup>67</sup> but not in others<sup>68</sup>; it could be tried in moderate to severe cases of excessive daytime sleepiness.

Sleep apnea contributes to daytime hypersomnolence. An evaluation for sleep apnea should be considered even in patients who are not overweight, as some evidence suggests that this disorder is common in Parkinson disease and correlates with disease severity.<sup>69</sup>

#### Insomnia

Sleep is impaired in up to 74% of Parkinson patients.<sup>70,71</sup> A sleep study may show a low total sleep time, many awakenings, a short rapid-eye movement (REM) latency, and short slow-wave sleep (stages III and IV); the patient experiences the problem as light sleep with frequent awakenings.<sup>72</sup> A variety

of problems related to Parkinson disease can directly affect sleep patterns: eg, pain, stiffness, tremor, problems turning over in bed, dystonia, dementia, nocturia,<sup>73</sup> depression, and anxiety.<sup>74</sup>

#### Restless legs syndrome

Restless legs syndrome is an uncomfortable, sometimes painful feeling in the legs or other body parts during rest (especially at night) that improves with movement.<sup>75</sup> It may be more common in patients with Parkinson disease than in the general population<sup>76,77</sup> and can precede the diagnosis of Parkinson disease.<sup>78</sup>

Iron supplementation with ferrous sulfate can help if iron deficiency (ferritin < 50 µg/L or iron saturation < 16%) is present but is ineffective in its absence. Levodopa and the dopaminergic agonists ropinirole (Requip)<sup>79</sup> and pramipexole (Mirapex)<sup>80</sup> are effective Parkinson disease treatments that also treat restless legs syndrome. In addition, opioids, clonazepam, and gabapentin (Gabarone) may help.<sup>81</sup>

#### Vivid dreams

Parkinson patients often describe very vivid, intense, frightening, and unpleasant dreams,<sup>73</sup> which may be a precursor to psychosis.<sup>82</sup>

REM sleep behavior disorder is characterized by sustained phasic muscle activity in place of normal atonia during REM or dream sleep. The patient's bed partner may describe him or her behaving in an aggressive way as if acting out his or her dreams, ie, hitting, yelling, or kicking. Upon awakening, the patient's recall of the dream content is consistent with the nocturnal behavior.

REM sleep behavior disorder may actually precede the motor symptoms of Parkinson disease,<sup>83,84</sup> and as many as 20% of patients with REM sleep behavior disorder eventually develop Parkinson disease.<sup>85</sup> The possible link between the two disorders is strengthened by a case report describing a patient with REM sleep behavior disorder, no signs of Parkinson disease on examination, but brain pathology similar to that found in Parkinson disease.<sup>86</sup>

Clonazepam is an effective treatment for REM sleep behavior disorder and should be considered if sleep is disrupted or patient safety becomes a concern.<sup>87</sup> ■

**Beware  
of serotonin  
syndrome  
if combining  
SSRIs and MAO  
inhibitors**

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