Clinical manifestations of Parkinson disease

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Literature review current through: **Jul 2024.**
This topic last updated: **Mar 14, 2024.**

INTRODUCTION

Parkinson disease (PD) is an adult-onset progressive neurodegenerative disorder, first described as "Shaking palsy" over 200 years ago by James Parkinson [1]. While traditionally considered a motor system disorder based on the hallmark features of tremor, rigidity, and bradykinesia, PD is now recognized to be a complex disorder involving a wide range of nonmotor manifestations that contribute to disability.

This topic will review the clinical manifestations of PD. The epidemiology, pathophysiology, diagnosis, differential diagnosis, and initial management of PD are reviewed in separate topics:

- (See "Epidemiology, pathogenesis, and genetics of Parkinson disease".)
- (See "Diagnosis and differential diagnosis of Parkinson disease".)
- (See "Initial pharmacologic treatment of Parkinson disease".)

AGE OF ONSET

PD is an adult-onset neurodegenerative disease. The incidence of disease rises rapidly over 60 years of age, with a mean age at diagnosis of 70.5 years [2]. Monogenetic forms

of PD, which account for less than 10 percent of PD cases, tend to have a younger age of onset than sporadic PD. (See "Epidemiology, pathogenesis, and genetics of Parkinson disease", section on 'Genetics'.)

PRODROMAL SYMPTOMS

Several nonmotor symptoms of PD are commonly reported by patients before the onset of classic motor symptoms. Such prodromal symptoms can precede motor manifestations by years or even decades [3]. Symptoms that have received the most attention as sensitive prodromal markers of PD are:

- Rapid eye movement (REM) sleep behavior disorder (RBD) (see 'Sleep disorders' below)
- Constipation (see 'Autonomic dysfunction' below)
- Hyposmia/olfactory dysfunction (see 'Olfactory dysfunction' below)

Many other nonmotor symptoms discussed below have also been reported as early symptoms, including urinary urgency, sexual dysfunction, depression, anxiety, color vision impairment, and neurocognitive dysfunction. (See 'Nonmotor symptoms' below.)

Prodromal symptoms correspond to early neurodegenerative changes and alpha-synuclein deposition in extranigral sites, such as the lower brainstem, the olfactory bulb and tracts, and the peripheral autonomic nervous system [3]. They are not specific to PD and can also be seen with other synucleinopathies, such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Alpha-synuclein aggregation can be detected in peripheral tissues and blood using a variety of techniques. (See "Diagnosis and differential diagnosis of Parkinson disease", section on 'Alpha-synuclein testing'.)

As early markers of neurodegeneration, such prodromal symptoms are seen as a possible window of opportunity for disease-modifying and preventive strategies targeting alpha-synuclein as well as other pathways. In some cases, it may be possible for patients to participate in clinical trials based on isolated symptoms that do not fulfill criteria for clinical disease but that may indicate increased risk for future phenoconversion to PD or other synucleinopathies. One resource for patients is the North American Prodromal Synucleinopathy (NAPS) Consortium.

CARDINAL FEATURES

PD is characterized by three main motor features: tremor, bradykinesia, and rigidity (table 1). Although postural instability is often mentioned as a fourth feature, it typically occurs much later in the disease and is thus not included as a core motor feature in diagnostic criteria for PD [4].

Tremor

- **Clinical characteristics** – The tremor in PD is a type of rest tremor, meaning that it is most noticeable when the affected body part is supported against gravity and not engaged in purposeful activities. Other conditions like essential tremor more commonly cause action tremor, which occurs with voluntary muscle contraction and movement. (See "Overview of tremor".)

  The tremor in the upper extremity is called "pill-rolling" because of the way the thumb and fingers appear to be rolling a small object between them. The frequency is moderate, ranging from 3 to 7 oscillations per second (Hz) and most commonly 4 to 5 Hz [5].

  Patients with PD may have tremor with postural maneuvers or with action, but tremor severity usually decreases with purposeful action and is most severe at rest. As a result, tremor tends to be the least physically disabling of the cardinal manifestations of PD. Self-consciousness and social disability associated with rest tremor should not be overlooked, however. When the tremor is severe, it can be difficult to distinguish a primary resting tremor from a primary action tremor.

  Some patients with PD have a re-emergent tremor: a postural tremor that manifests after a latency of several seconds and has a frequency typical of the rest tremor in PD [6,7]. This distinction is important, as patients with PD who have a re-emergent postural tremor may be misdiagnosed as having essential tremor [8].

- **Evolution and distribution** – Tremor is the presenting symptom in approximately 70 to 80 percent of patients with PD and affects 80 to 100 percent of patients at some point in the course of the disease [9].

  In the early stages of PD, tremor is usually intermittent and may not be noticeable to

others. In fact, approximately half of patients with PD report feeling a sensation of internal tremulousness in the limbs or body, even in the absence of observable tremor. However, as the disease progresses, the tremor usually becomes more apparent.

Tremor usually starts unilaterally in the hand and then spreads contralaterally several years after the onset of symptoms. The side that is initially affected tends to be the more affected side throughout the course of the disease. The tremor can also involve the legs, lips, jaw, and tongue but rarely involves the head. Anxiety, emotional excitement, or stressful situations can exacerbate the tremor.

- **Examination** – Tremor in the limbs is best appreciated when the patient is relaxed with the hands resting quietly on the lap. Distractions in the form of mental calculations or voluntary repetitive movements of the contralateral limb often accentuate a mild tremor and may uncover a latent tremor. A resting hand tremor may be detected only if the examiner pays careful attention to the patient's hands during the gait evaluation.

Bradykinesia

- **Clinical characteristics** – Bradykinesia means generalized slowness of movement but also refers to decreased amplitude of movements. While it is the most common feature in PD, it is also the most difficult symptom for patients to describe. "Weakness," "incoordination," and "tiredness" are often used to describe the decreased ability to initiate voluntary movement.

  In the arms, bradykinesia typically starts distally with decreased manual dexterity of the fingers. Patients often complain of difficulty performing simple tasks, such as buttoning clothes, tying shoelaces, double clicking a computer mouse, typing, or lifting coins from a pocket or purse.

  In the legs, common complaints related to bradykinesia when walking include dragging the legs, shorter (shuffling) steps, or a feeling of unsteadiness. Patients may also have difficulty standing up from a chair or getting out of a car.

- **Evolution and distribution** – Bradykinesia is an early symptom of PD and is present in approximately 80 percent of patients at the onset of disease [9]. It is arguably the

major cause of disability in PD and is eventually seen in almost all patients.

Bradykinesia often begins distally on the same side as tremor, then progresses to involve both sides and more proximal and axial movement. Similar to tremor, one side of the body is more affected than the other throughout the disease course. As the disease progresses, worsening bradykinesia may lead to gait freezing and festination. Festination refers to an irresistible impulse to take much quicker and shorter steps [1].

- **Examination** – To assess bradykinesia, limb movements on both sides of the body should be examined. Clinicians should carefully observe speed, amplitude, and rhythm of finger tapping, hand opening-closing, pronation-supination hand movements, and heel or toe tapping. It is important to examine these tasks for more than a few seconds, as in mild PD it takes some time for slowing and decreased amplitude to become apparent. As the disease progresses, movements become less coordinated, with frequent hesitations and/or arrests.

  Bradykinesia may also be observed when the patient stands up from a seated position and during a gait examination. Arm swing may be diminished on one side more than the other, and step length may be shorter than expected. Clinicians should also pay close attention to whether there is a decrease in global spontaneous movements, such as gesturing.

Rigidity

- **Clinical characteristics** – Rigidity is an increased resistance to passive movement about a joint. Rigidity can affect any part of the body and may contribute to complaints of stiffness and pain. Features of PD that result from rigidity, at least in part, include the striatal hand (extension of the proximal and distal interphalangeal joints with flexion at the metacarpophalangeal joints), decreased arm swing with walking, and the typical stooped posture.

  Patients may have cogwheel rigidity, which refers to a ratchety pattern of resistance and relaxation as the examiner moves the limb through its full range of motion [10]. This phenomenon is thought to be a manifestation of tremor superimposed on increased tone [11]. However, not all patients with PD have cogwheel rigidity; many instead will have lead-pipe rigidity, a tonic resistance that is smooth throughout the

entire range of passive movement.

- **Evolution and distribution** – Rigidity occurs in approximately 75 to 90 percent of patients with PD [9]. Rigidity, like tremor and bradykinesia, often begins unilaterally and typically on the same side as the tremor if one is present. Rigidity eventually progresses to the contralateral side and remains asymmetric throughout the disease [12].

- **Examination** – Rigidity is tested by passively manipulating the limbs. It can be brought out by having the patient perform repetitive maneuvers using the contralateral limb (eg, opening and closing a fist, throwing an imaginary ball) or by performing mental arithmetic.

Postural instability

- **Clinical characteristics** – Postural instability refers to a decreased ability to prevent falling and is caused by impairment of centrally-mediated postural reflexes. Among the primary motor features of PD, postural instability is the least responsive to dopaminergic therapies [13]. In addition, postural instability and gait difficulty are major contributors to disability in patients with PD [14].

- **Evolution** – Postural instability usually does not appear until later in the course of PD. Patients with parkinsonian signs who fall early in the course of the illness most likely have another parkinsonian syndrome, such as progressive supranuclear palsy or multiple system atrophy (MSA), rather than PD. (See "Diagnosis and differential diagnosis of Parkinson disease", section on 'Differential diagnosis'.)

  Initially, a positive pull test on examination may be the only sign of balance impairment. However, as postural instability progresses, patients may fall with less and less provocation, and the gait may show signs of freezing or festination. Once postural reflexes are lost, patients generally require a wheelchair for safety.

- **Examination** – Postural instability is tested with the pull test, where the examiner stands behind the patient and firmly pulls the patient backwards by the shoulders. Patients with normal postural reflexes should be able to maintain balance and retropulse (step backward) no more than two steps. The pull test is not valid unless the patient takes at least one step backward. Patients with PD and postural

instability, on the other hand, are likely to fall or take multiple steps backward before stabilizing themselves.

Clinical subtypes — Three major clinical subtypes of PD have been described based on the predominant feature [15-17]:

- Tremor-dominant
- Akinetic-rigid
- Postural instability and gait difficulty

Several studies have compared the tremor-dominant subtype with either the akinetic-rigid or the postural instability and gait difficulty subtypes, and most have found that the tremor-dominant subtype is associated with slower progression and less neuropsychologic impairment than the other two groups [18-24].

While some clinicians may find these groupings useful, clinical PD progression is highly variable among individuals, and assignment of patients to subtypes can change as the disease progresses [24,25]. Thus, there are no symptoms or signs in idiopathic PD that allow a practitioner to accurately predict the future course of PD for any given individual.

OTHER MOTOR FEATURES

Additional motor features of PD include (table 1):

- **Craniofacial**
  - Hypomimia (masked facial expression)
  - Decreased spontaneous eye blink rate
  - Speech impairment, including hypokinetic dysarthria, hypophonia, and palilalia (repetition of a phrase or word with increasing rapidity)
  - Dysphagia
  - Sialorrhea
- **Visual**
  - Blurred vision
  - Impaired contrast sensitivity
    Hypometric saccades

- Impaired vestibulo-ocular reflex
- Impaired upward gaze and convergence
- Eyelid-opening apraxia

- **Musculoskeletal**

  - Micrographia
  - Dystonia (see 'Pain and sensory disturbances' below)
  - Myoclonus
  - Stooped posture
  - Camptocormia (severe anterior flexion of the thoracolumbar spine) (figure 1) [26]
  - Pisa syndrome (subacute axial dystonia with lateral flexion of the trunk, head, and neck) (figure 2) [27-29]
  - Kyphosis
  - Scoliosis
  - Difficulty turning in bed

- **Gait**

  - Shuffling, short-stepped gait
  - Freezing
  - Festination

Most of these features result from one or more of the cardinal manifestations. As examples, decreases in spontaneous associated movements, such as loss of gestures during conversation, decreased eye blinking, or facial masking, probably result from a combination of bradykinesia and rigidity. Dysphagia is due to bradykinesia of the pharyngeal musculature, which can lead to pooling of saliva in the mouth and drooling (sialorrhea). (See "Swallowing disorders and aspiration in palliative care: Definition, pathophysiology, etiology, and consequences", section on 'Parkinson disease'.)

Clinicians should be aware that functional neurologic symptoms or functional overlay can also occur in some patients with PD [30,31]. This may manifest as excessive retropulsion, astasia-abasia, knee buckling, and incongruent ballistic dyskinesia, which can be confused with levodopa-induced dyskinesia.

NONMOTOR SYMPTOMS

PD is a complex disorder with diverse clinical features that include nonmotor manifestations in addition to motor symptomatology. These features include the following (table 2):

- Cognitive dysfunction and dementia
- Psychotic symptoms (hallucinations and delusions)
- Mood disorders including depression, anxiety, and apathy/abulia
- Sleep disturbances
- Fatigue
- Autonomic dysfunction
- Olfactory dysfunction
- Gastrointestinal dysfunction
- Pain and sensory disturbances
- Dermatologic findings

In a multicenter survey of over 1000 patients with PD, virtually all (97 percent) patients reported nonmotor symptoms, with each patient experiencing an average of approximately eight nonmotor symptoms [32]. Nonmotor symptoms in the psychiatric domain occurred most frequently. Psychiatric symptoms such as psychosis or dementia may cause more disability than the motor features and may be more difficult to treat. In a single-center survey of 265 patients with PD, pain, mood disorders, and sleep problems were the most troublesome nonmotor symptoms occurring in both early- and late-stage PD [33].

The most clinically relevant nonmotor manifestations of PD will be reviewed here individually. The management of nonmotor symptoms of PD is discussed separately. (See "Management of nonmotor symptoms in Parkinson disease".)

Cognitive dysfunction and dementia — Cognitive dysfunction is common in PD and exists on a continuum of severity; prevalence increases with the duration of the movement disorder. When severe, dementia often surpasses the motor features of PD as a major cause of disability and mortality.

Executive and visuospatial functions are often affected early in the disease course, whereas memory impairment is a later feature (table 3). Risk factors, prevalence,

clinical features, and the overlap between PD and dementia with Lewy bodies (DLB) are reviewed in detail separately. (See "Cognitive impairment and dementia in Parkinson disease".)

Psychotic symptoms — Psychosis occurs in 20 to 40 percent of drug-treated patients with PD, and visual hallucinations are the most common psychotic symptom [34-36]. Risk factors for psychosis in PD include the use of high doses of antiparkinson drugs, the presence of dementia, advancing age, impaired vision, depression, presence of sleep disorders, high comorbid disease burden, and longer disease duration.

- **Hallucinations** – Visual hallucinations in PD are usually complex, involving well-formed images of people or animals. The content may or may not arouse fear. Duration and frequency are variable, but most hallucinations last for seconds to minutes. Auditory, olfactory, and tactile hallucinations also occur, although less frequently and generally in conjunction with visual hallucinations [34,37].

  The prevalence and severity of hallucinations increase over time [38]. Most patients retain insight that their hallucinations are not real. However, patients with concomitant dementia or delirium may have decreased insight. Symptoms in such patients tend to be more resistant to treatment.

- **Delusions** – Delusions can also be a prominent feature of psychosis in PD and are usually paranoid in nature. Common delusions include spousal infidelity, people stealing money, intruders living in the house, or nurses planning harmful plots.

Psychosis, not motor dysfunction, is the single greatest risk factor for nursing home placement in patients with PD [39,40]. Psychosis is also associated with increased caregiver burden [41] and an increased risk of mortality [42,43]. (See "Palliative approach to Parkinson disease and parkinsonian disorders", section on 'Caregiver burden'.)

Patients with new or worsening psychosis should also be evaluated for reversible factors and delirium, as not all symptoms are attributable to the disease itself. All medications used to treat motor symptoms of PD, especially dopamine agonists, can cause or aggravate psychotic symptoms (algorithm 1). An approach to evaluation and treatment of psychosis is presented separately. (See "Management of nonmotor symptoms in Parkinson disease", section on 'Psychosis'.)

Mood disorders — Depression, anxiety, abulia, and apathy are among the most troublesome nonmotor symptoms in patients with both early- and late-stage PD [33].

Depression — Depression is the most common psychiatric disturbance seen in PD [44]. Though generally mild to moderate in severity, depressive symptoms in PD are associated with a negative impact on motor disability and decreased quality of life [45-47]. Common symptoms include sadness, anhedonia, and decreased interest in activities.

Estimates for the prevalence of depression in PD vary, but up to 50 percent of patients have depressive symptoms, occasionally as a presenting complaint [44,47-49]. The rates for major depressive disorder in PD are lower, ranging from less than 10 percent in community studies [48,50], to more than 20 percent in specialty movement disorder clinics [51-53]. Despite the high prevalence, however, depression in PD remains undertreated [47,51,54]. (See "Management of nonmotor symptoms in Parkinson disease", section on 'Depression'.)

Recognizing depressive features in PD is a challenge. The psychomotor slowing and blunted affect commonly seen with depression often resemble the bradykinesia and masked facial expression seen in PD. Furthermore, somatic features of depression, such as decreased appetite, difficulty with concentration, and sleep disturbances, are commonly seen in patients with PD who do not have depression.

Depression is a risk factor for suicidality, which is more common in patients with PD compared with the general population. In a meta-analysis that included 28 observational studies and more than 500,000 patients with PD, the prevalence of suicidal ideation in patients with PD was 22 percent [55]. The prevalence of suicidal behavior was low (1.25 percent) but nonetheless elevated relative to the general population or control patients with nonneurologic diseases (hazard ratio 1.73, 95% CI 1.40-2.14). Risk was similar in males and females with PD. Patients with more severe depression, sleep disorders, and feelings of hopelessness appear to be at higher risk [56-58]. Whether treatments for PD, including dopaminergic medications and deep brain stimulation (DBS), contribute to excess risk remains uncertain. (See "Device-assisted and lesioning procedures for Parkinson disease", section on 'Complications and adverse effects'.)

Anxiety — Anxiety is the next most frequent psychiatric disturbance in PD [44] and is estimated to occur in approximately 30 to 40 percent of patients [53,59]. All types of anxiety disorders have been reported in PD, though generalized anxiety disorder and

social phobia appear to be the most common [59-61]. Depression and anxiety are often comorbid conditions in PD [62]; they are also associated with "on-off" fluctuations, with worsened mood and anxiety during "off" periods and with improvement when in the "on" state [63-65].

Apathy and abulia — Apathy is a primary loss of motivation, characterized by diminished speech, motor activity, and emotional expression [66]. This definition of apathy is essentially synonymous with that of abulia, which has been defined as a loss of the impulse, will, or motivation to think, speak, and act. Diminished motivation is the key concept in both apathy and abulia. The neurologic basis of apathy and abulia is most commonly ascribed to frontal lobe and limbic system dysfunction [67-69].

The pooled prevalence of apathy in patients with PD is 40 percent [70]. It is more common with older age, cognitive impairment, depression, increased motor symptoms, and more severe disability. While apathy frequently accompanies depression, it can occur in patients with PD who do not have depression [71,72]. A potentially useful discriminating characteristic is mood, which is neutral in apathy and negative in depression [66].

The presence of apathy has a negative impact on quality of life in patients with PD [32]. Apathy may coexist with impulse control disorders, which also have detrimental effects on quality of life [53]. (See "Initial pharmacologic treatment of Parkinson disease", section on 'Impulse control and related behavioral disorders'.)

Sleep disorders — Up to 80 percent of patients with PD have one or more sleep disorders, including insomnia, restless legs syndrome (RLS), and rapid eye movement (REM) sleep behavior disorder (RBD) [32,73].

- **Insomnia** – Patients with PD frequently have difficult falling asleep (sleep initiation insomnia), difficulty staying asleep (sleep maintenance insomnia), or a combination of the two. Problems with sleep maintenance (sleep fragmentation) are most common. Multiple factors contribute to insomnia, including nocturnal motor symptoms, neuropsychiatric symptoms, nocturia and other autonomic problems, other sleep disorders like RLS, nocturnal leg cramps, dystonia, pain, and medication side effects.

  Clinical features, evaluation, and management of insomnia in patients with PD are reviewed separately. (See "Insomnia, daytime sleepiness, and other sleep disorders

in Parkinson disease", section on 'Insomnia'.)

- **Restless legs syndrome** – RLS is a movement disorder characterized by an urge to move the limbs, associated with an unpleasant sensation that occurs mainly or exclusively at night, emerges or worsens with rest, and improves with movement, especially walking (table 4). RLS is reportedly more common in patients with PD than in the general population, although symptoms overlap with leg restlessness caused by "wearing off" from dopaminergic medications, which may be conflated with RLS. (See "Insomnia, daytime sleepiness, and other sleep disorders in Parkinson disease", section on 'Restless legs syndrome and periodic limb movement disorder'.)

  Periodic limb movements of sleep (PLMS) are frequently but not always associated with RLS. The symptoms of PLMS are typically slow rhythmic movements of the legs, consisting of dorsal flexion of the foot and great toe [74].

- **REM sleep behavior disorder** – RBD is a common prodromal feature of PD and ultimately affects at least 50 percent of patients with clinically established PD. RBD is characterized by dream enactment behaviors (eg, vocalizations, reaching, punching, kicking) that occur because of a loss of the normal atonia (muscle paralysis) of REM sleep. Movements correlate with dream mentation; in other words, patients are acting out their dreams. Patients and bed partners may not recognize movements as abnormal, especially when mild. The disorder is important to recognize and treat, as patients can injure themselves or their bed partners due to the vigor of the movements (algorithm 2). (See "Rapid eye movement sleep behavior disorder".)

  Among patients with PD, RBD has been associated with greater clinical burden with more rapid cognitive impairment, more psychiatric comorbidities, poorer treatment response, and more widespread brain atrophy compared with PD patients without RBD [75-79]. RBD appears to specifically correlate with freezing of gait, and many of the same brainstem regions implicated in the pathophysiology of RBD mediate the pathogenesis of freezing of gait [80]. (See "Rapid eye movement sleep behavior disorder", section on 'Pathogenesis'.)

Excessive daytime sleepiness — Excessive daytime sleepiness (EDS) has long been recognized as a problem in PD. The prevalence of EDS in PD varies according to study methodology, but estimates range from 33 to 76 percent [81-84]. Some patients may just be sleepy, while others have additional unintended sleep episodes or sudden sleep

"attacks" [85]. EDS and sudden somnolence can be a hazard for patients with PD who drive [86].

EDS in PD is likely multifactorial. Possible risk factors include difficulty sleeping at night, depression, dementia, obstructive sleep apnea, dopaminergic treatment, high comorbid disease burden, and male sex [87-92]. It has also been argued that EDS may be intrinsic to the disease process [93]. Evaluation and treatment are reviewed separately. (See "Insomnia, daytime sleepiness, and other sleep disorders in Parkinson disease", section on 'Excessive daytime sleepiness'.)

Fatigue — Fatigue is a common problem in patients with PD, reported by approximately one-third of patients at diagnosis and becoming more prevalent as the disorder progresses [94,95]. Fatigue is associated with longer disease duration, depression, and EDS [94]. It may be persistent or intermittent.

Although fatigue is associated with depression and EDS, several studies have found that patients with PD who do not have depression or EDS nonetheless have a high prevalence of fatigue [94,96,97]. These data support the hypothesis that fatigue is an independent symptom of PD that overlaps with, but is not causally related to, depression and EDS. The pathophysiology of fatigue in PD is not understood.

Autonomic dysfunction — Autonomic problems in PD include orthostasis, constipation, dysphagia, diaphoresis, urinary difficulties, and sexual dysfunction. These problems are also present in multiple system atrophy (MSA), making it difficult to distinguish between the two disorders. The autonomic symptoms in MSA, however, are generally more severe than in PD. Furthermore, MSA tends to be less responsive to levodopa as the disease progresses, and MSA is often associated with cerebellar and pyramidal findings. (See "Multiple system atrophy: Clinical features and diagnosis".)

- **Orthostatic hypotension** – Orthostatic hypotension is very common in patients with PD, even relatively early in the course of disease, with a cumulative prevalence of approximately 60 percent [98-100]. Risk factors include older age, cognitive dysfunction, and longer disease duration [100]. In addition to the disease itself, orthostatic hypotension can be aggravated or caused by antiparkinsonian agents including levodopa, dopamine agonists, and monoamine oxidase type B (MAO-B) inhibitors, and other drugs, particularly alpha-adrenergic blockers such as tamsulosin for prostatism.

- **Urinary dysfunction** – Common urinary symptoms indicative of autonomic dysfunction in patients with PD include frequency, urgency, and urge incontinence [101,102]. The most common abnormality on urodynamic evaluation is reduced bladder capacity because of involuntary detrusor muscle contractions at early stages of bladder filling [103].

- **Sexual dysfunction** – Sexual dysfunction can range from underactivity to hypersexuality and may affect up to 25 percent of patients with PD [104]. Underactive sexual behavior in PD commonly manifests as decreased interest and drive [105,106] and can be due to depression [107], axial rigidity, bradykinesia, or dissatisfaction with relationships [108]. Male patients may have the inability to achieve or maintain an erection, while female patients with PD often report vaginal tightness, dryness, an inability to achieve orgasm, or involuntary micturition during sex [106,109,110].

  A separate issue is that hypersexuality can be associated with antiparkinsonian therapies, both pharmacologic and surgical. (See "Device-assisted and lesioning procedures for Parkinson disease", section on 'Deep brain stimulation' and "Initial pharmacologic treatment of Parkinson disease", section on 'Impulse control and related behavioral disorders'.)

Olfactory dysfunction — Olfactory dysfunction is very common in PD and can manifest as deficits in odor identification, discrimination, and detection [111]. Loss of smell may go unnoticed by patients, even when dysfunction is present on smell testing.

These deficits in olfaction may precede motor symptoms or occur relatively early in the course of PD [102,112,113]. Although nonspecific, olfactory dysfunction on smell testing in community-dwelling older adults is associated with an increased risk of incident PD over 5 to 10 years of follow-up [112-116].

Pain and sensory disturbances — Painful sensory symptoms are reported in up to half of patients with PD [117]. The pain can be lancinating, burning, or tingling, and can be generalized or localized to different areas of the body, including the face, abdomen, genitals, and joints [117-119].

Painful sensations in PD tend to correlate with motor fluctuations.

Dystonia, which is often painful, is a common symptom in PD. Leg/foot dystonia is more common than hand/arm dystonia and may even be the initial manifestation of PD, particularly in patients with young-onset disease. Patients may experience involuntary sustained flexion of the large toe, the smaller toes, or all toes on the more severely affected side. At times, toe dystonia can be associated with foot inversion and plantarflexion, which may impair gait and lead to falls. Dystonia often responds to levodopa, and leg cramps and dystonia affecting the foot are common "off" responses to decreased levodopa levels, especially overnight or in the morning [120]. However, levodopa-induced dyskinesia can be dystonic and painful as well. (See "Medical management of motor fluctuations and dyskinesia in Parkinson disease".)

Peripheral neuropathy is more common in PD than in the general population and contributes to pain as well as gait and balance dysfunction. Underlying causes for peripheral neuropathy in individuals with PD may include peripheral nerve alpha-synuclein aggregation, long-term levodopa exposure with elevated homocysteine levels, B vitamin deficiencies, and comorbidities such as diabetes [121-123]. The estimated prevalence of large fiber neuropathy in PD is 16 percent [124], and small fiber neuropathy may be even more common. In a study of 99 patients with PD with a median age of 67 years and mean disease duration of 6.5 years, comprehensive neurophysiologic testing and skin biopsies revealed a peripheral neuropathy in 40 percent of patients, most commonly small fiber neuropathy (70 percent) [125]. Neuropathy was associated with slower gait speed, shorter stride length, and worse standing balance.

Dermatologic findings — Seborrheic dermatitis is a common, well-recognized skin disorder that affects 20 to 60 percent of patients with PD, often as an early symptom [102,126]. It is unclear why it occurs so frequently in PD. Manifestations include scaly erythematous patches in areas of the skin rich with sebaceous glands, such as the scalp (picture 1), face (picture 2), and chest [127]. Other dermatologic changes include hyperhidrosis and dermatophytosis [102]. (See "Seborrheic dermatitis in adolescents and adults".)

Melanoma occurs with a higher frequency in PD than in the general population. Based on a meta-analysis of 24 observational studies in a total of over 290,000 individuals, the risk of melanoma is nearly twofold higher in patients with PD (odds ratio [OR] 1.83, 95% CI 1.46-2.30) [128]. The exact relationship between PD and melanoma has not been fully elucidated. Although case reports have suggested an association between melanoma and

levodopa therapy due to a shared dopamine biochemical pathway, a review of large cohort studies found that the risk of melanoma is elevated even before exposure to levodopa therapy [129].

DISEASE PROGRESSION AND PROGNOSIS

PD is a progressive neurodegenerative disease that usually shortens life expectancy. Progression of symptoms is highly variable, however, and it is not possible to predict future course of PD for a given individual at the time of diagnosis.

- **Motor complications** – Motor symptoms tend to be highly responsive to dopaminergic therapies early in the disease course, but motor fluctuations and "wearing off" develop in 30 to 40 percent of patients by five years and up to 60 percent by ten years. (See "Medical management of motor fluctuations and dyskinesia in Parkinson disease", section on 'Symptom spectrum'.)

- **Progression of disability** – A transition from disease impairment to disability (loss of independent function) generally occurs between three and seven years after diagnosis [130]. In a study of 142 patients with PD followed from 2000 to 2012, approximately 77 percent had a poor outcome (ie, death, dementia, or postural instability) at 10 years after diagnosis [22]. A small group of patients have a particularly slow rate of disease progression, maintaining balance and postural stability for ≥10 years and lacking severe disability even at ≥20 years.

- **Life expectancy** – Most studies suggest that mortality is modestly increased for patients with PD compared with age-matched controls [22,131-135]. A systematic review and meta-analysis found that mortality ratios varied widely among included studies, but nearly all showed increased mortality in PD, with a pooled mortality ratio of 1.5 [136]. Median survival from diagnosis ranged from 6 to 22 years. Increasing age and presence of dementia were associated with an increased risk of mortality.

  Validated predictive tools for end-of-life prognosis are not available for PD, and it can be difficult to determine the most appropriate timing for hospice referral. An approach to palliative care and decision-making in patients with PD is presented separately. (See "Palliative approach to Parkinson disease and parkinsonian disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Parkinson disease (The Basics)")
- Beyond the Basics topics (see "Patient education: Parkinson disease symptoms and diagnosis (Beyond the Basics)")

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: Parkinson disease".)

SUMMARY AND RECOMMENDATIONS

- **Cardinal features** – The cardinal features of Parkinson disease (PD) are tremor, bradykinesia, and rigidity. Symptoms often begin unilaterally and later spread to involve both sides of the body. Postural instability is another key feature, but it generally occurs later in the course of the disease and is not included in the diagnostic criteria for PD.

- **Tremor** – The tremor of PD is typically described as "pill-rolling" because of the way the thumb and the fingers appear to be rolling a small object between them. It is most noticeable when the affected limb is relaxed or "at rest." Tremor can also involve the legs, lips, and jaw but rarely the head. (See 'Tremor' above.)

- **Bradykinesia** – Bradykinesia is a generalized slowness of movement. In the arms, bradykinesia typically starts distally with decreased manual dexterity of the fingers. In the legs, it manifests as dragging of the feet and shortened, shuffling steps. (See 'Bradykinesia' above.)

- **Rigidity** – Rigidity is an increased resistance to passive movement. In PD, rigidity may have a cogwheel or ratchety quality as the limb is moved through its full range of motion. In other patients, there is tonic resistance that is smooth throughout the entire range (lead-pipe rigidity). (See 'Rigidity' above.)

- **Other motor features** – In addition to the cardinal manifestations, other motor features of PD include craniofacial (eg, masked facial expression, hypophonia), visual (eg, hypometric saccades, eyelid-opening apraxia), musculoskeletal (eg, micrographia, stooped posture), and gait (eg, shuffling, short-stepped gait, freezing) abnormalities (table 1). (See 'Other motor features' above.)

- **Nonmotor features** – PD is a complex disorder with diverse clinical features that include nonmotor manifestations (table 2) in addition to motor symptomatology. These features include the following (see 'Nonmotor symptoms' above):

  - Cognitive dysfunction, most commonly problems with executive function (decision-making or multitasking), memory retrieval, and visuospatial misperception (see 'Cognitive dysfunction and dementia' above)

  - Psychotic symptoms, most commonly visual hallucinations (see 'Psychotic symptoms' above)

  - Mood disorders including depression, anxiety, and apathy/abulia (see 'Mood disorders' above)

  - Sleep disturbances, including frequent awakenings, restless legs syndrome (RLS), and rapid eye movement (REM) sleep behavior disorder (RBD) (see 'Sleep disorders' above)

- Excessive daytime sleepiness (EDS) and fatigue (see 'Excessive daytime sleepiness' above and 'Fatigue' above)
- Autonomic dysfunction, including orthostasis, constipation, dysphagia, diaphoresis, urinary dysfunction, and sexual dysfunction (see 'Autonomic dysfunction' above)
- Olfactory dysfunction (see 'Olfactory dysfunction' above)
- Pain and sensory disturbances (see 'Pain and sensory disturbances' above)
- Dermatologic findings, most commonly seborrheic dermatitis (see 'Dermatologic findings' above)

- **Patient perspective** – A patient perspective on the clinical manifestations of PD is provided separately. (See "Patient perspective: Parkinson disease".)

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Topic 4903 Version 56.0

GRAPHICS

Motor features of Parkinson disease

Cardinal manifestations
Tremor
Bradykinesia
Rigidity
Postural instability
Other motor features
Craniofacial
Hypomimia (masked facial expression)
Decreased eye blinking
Speech disturbances (hypokinetic dysarthria, hypophonia)
Dysphagia
Sialorrhea
Visual
Blurred vision
Impaired contrast sensitivity
Hypometric saccades
Impaired vestibuloocular reflex
Impaired upward gaze and convergence
Lid apraxia
Musculoskeletal
Micrographia
Dystonia
Myoclonus
Stooped posture
Camptocormia (severe anterior flexion of the thoracolumbar spine)
Pisa syndrome (subacute axial dystonia with lateral flexion of the trunk, head, and neck)

Kyphosis
Scoliosis
Difficulty turning in bed
Gait
Shuffling, short-stepped gait
Freezing
Festination

Graphic 81338 Version 5.0

Camptocormia

Severe anterior flexion of the thoracolumbar spine, known as camptocormia or bent spine syndrome.

Graphic 109736 Version 1.0

Pisa syndrome

Lateral flexion of the trunk, head, and neck, known as Pisa syndrome.

Graphic 109738 Version 1.0

Nonmotor symptoms of Parkinson disease

Cognitive dysfunction
Psychosis
Mood disorders (depression, anxiety, apathy/abulia)
Sleep disturbances
Fatigue
Autonomic dysfunction (urinary urgency/frequency, constipation, orthostasis, erectile dysfunction)
Olfactory dysfunction
Pain and sensory disturbances
Dermatologic findings (seborrhea)

Graphic 71879 Version 2.0

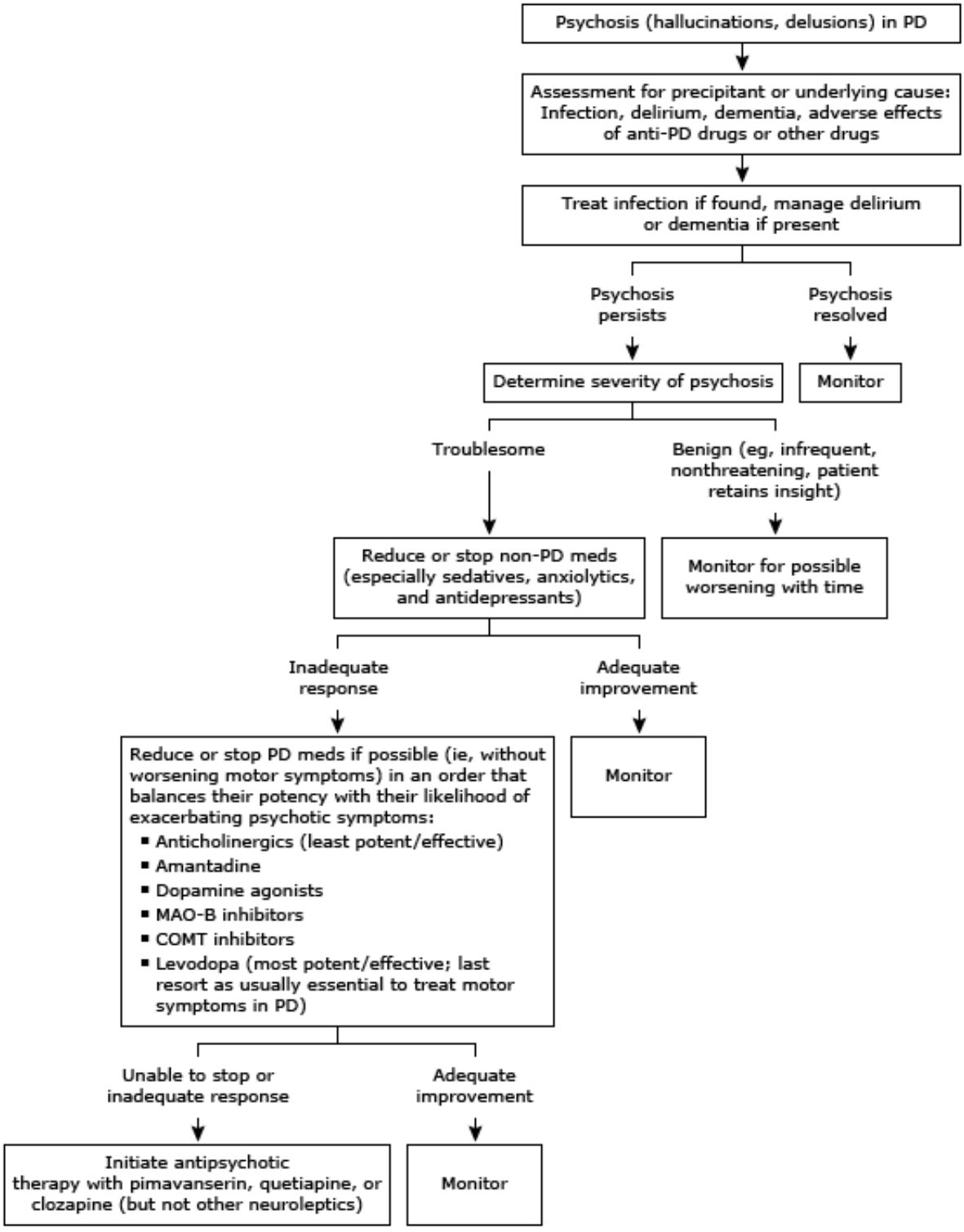
Clinical features of Parkinson disease dementia

Cognitive features	Behavioral features
Impaired attention Executive dysfunction Visuospatial dysfunction Impaired verbal memory	Apathy Changes in mood, including depression or anxiety Visual hallucinations Paranoid delusions Excessive daytime sleepiness Sleep disturbances, including fragmentation, nightmares, and REM sleep behavior disorder

REM: Rapid eye movement.

Graphic 99499 Version 1.0

Management of psychosis in Parkinson disease



PD: Parkinson disease; MAO-B: monoamine oxidase type B; COMT: catechol-O-methyl transferase.

Graphic 110759 Version 3.0

Diagnostic criteria for restless legs syndrome

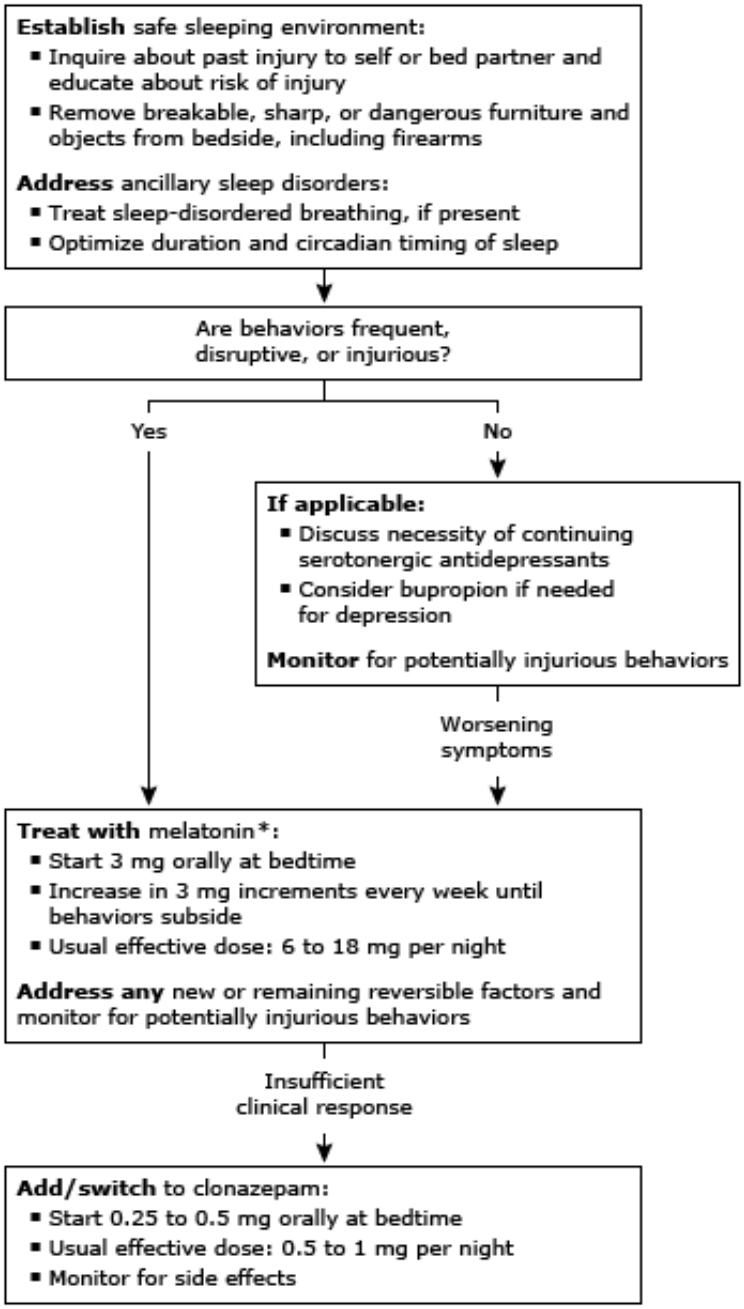
RLS, a neurologic sensorimotor disease often profoundly disturbing sleep and quality of life, has variable expression influenced by genetic, environmental, and medical factors. The symptoms vary considerably in frequency from less than once a month or year to daily and severity from mildly annoying to disabling. Symptoms may also remit for various periods of time. RLS is diagnosed by ascertaining symptom patterns that meet the following 5 essential criteria, adding clinical specifiers where appropriate.
Essential diagnostic criteria (all must be met):
1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs*¶.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues$^{\Delta}$.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day$^{\diamond}$.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)§.
Specifiers for clinical course of RLS:¥
A. Chronic-persistent RLS – Symptoms when not treated would occur on average at least twice weekly for the past year.
B. Intermittent RLS – Symptoms when not treated would occur on average <2/week for the past year, with at least 5 lifetime events.
Specifier for clinical significance of RLS:
The symptoms of RLS cause significant distress or impairment in social, occupational, educational, or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition, or mood.

RLS: restless legs syndrome.
* Sometimes the urge to move the legs is present without the uncomfortable sensations, and sometimes the arms or other parts of the body are involved in addition to the legs.
¶ For children, the description of these symptoms should be in the child's own words.

Δ When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
◇ When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.
§ These conditions, often referred to as "RLS mimics," have been commonly confused with RLS, particularly in surveys, because they produce symptoms that meet or at least come very close to meeting criteria 1 to 4. The list here gives some examples that have been noted as particularly significant in epidemiologic studies and clinical practice. RLS may also occur with any of these conditions, but the RLS symptoms will then be more in degree, conditions of expression, or character than those usually occurring as part of the other condition.
¥ The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS, such as pregnancy or drug-induced RLS, where the frequency may be high but limited to duration of the provocative condition.

Graphic 86837 Version 11.0

Management of rapid eye movement sleep behavior disorder



REM sleep behavior disorder (RBD) occurs commonly in association with Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. In younger adults (<40 years), it may occur in association with serotonergic antidepressants or narcolepsy. Spontaneous RBD in adults is often a prodromal symptom of Parkinson disease or related alpha-synuclein neurodegenerative disorders. Refer to UpToDate clinical content for further details and discussion of prognostic disclosure and counseling.

REM: rapid eye movement.
* Melatonin doses provided are for immediate release. Use of time-release melatonin has a

theoretical but unproven advantage over immediate-release formulations. For time-release melatonin, a suggested starting dose is 5 mg orally at bedtime, titrating by 5 mg every 1 to 2 weeks to a maximum of 15 mg nightly.

Graphic 134977 Version 2.0

Seborrheic dermatitis of the scalp

Diffuse erythema and scaling of the scalp.

Graphic 76985 Version 7.0

Facial seborrheic dermatitis

Intense erythema and scaling involving the central face and nasolabial folds.

Graphic 59104 Version 5.0

Contributor Disclosures

Kelvin L Chou, MD Grant/Research/Clinical Trial Support: Abbott [Deep brain stimulation]; Neuraly [Parkinson disease]. Consultant/Advisory Boards: Neurocrine [Parkinson disease]. All of the relevant financial relationships listed have been mitigated. **Howard I Hurtig, MD** No relevant financial relationship(s) with ineligible companies to disclose. **April F Eichler, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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