psychotropics. 64% and 71% of residents treated with psychotropics had not received psychopharmacologic treatment or a psychiatric diagnosis, respectively, for the 6 months preceding admission. Medications are widely used empirically based on similarities to other psychiatric conditions, such as depression, anxiety, or psychosis. Furthermore, psychotropics may be used without systematic identification of potential underlying causes of behaviors. NPS in dementia are the result of responses to stressors in individuals with increased vulnerability due to brain circuitry disruptions. Nonpharmacologic strategies targeted at mitigating or eliminating these triggers should be used and evaluated for effect first. Most dementias are progressive in nature and NPS can fluctuate over time. Thus, clinicians and caregivers may find themselves trying to manage several evolving behaviors simultaneously, often with multiple medications, leading to increased risks of adverse effects from medications and unpredictable results. Further complicating this matter is that psychotropics can cause side effects that exacerbate other domains of NPS. For example, antipsychotic medications may contribute to sedation, reversal in sleep-wake cycle, and delirium. If medications are indicated, it is important to follow several guidelines as listed in **Table 60-7**.

TABLE 60-7 ■ GENERAL GUIDELINES FOR STARTING PSYCHOTROPIC MEDICATIONS FOR NEUROPSYCHIATRIC SYMPTOMS

- Explore potential contributing factors for neuropsychiatric symptoms. Consider the need for a medical work-up.
- Define specific targets for intervention
- Implement nonpharmacologic interventions concomitantly
- Be mindful that isolated neuropsychiatric disturbances are unlikely to respond to medications
- Use medications sparingly, starting at a low dose, monitoring for adverse effects (particularly delirium, sedation, orthostasis, falls), and using the lowest effective dose
- Change one medication at a time to allow for a clearer picture of how it affects target symptoms and to minimize adverse effects
- Be aware of potential drug–drug interactions
- Consider timing doses around difficult behaviors (eg, administering a dose half an hour prior to morning care)
- Psychotropic use (particularly antipsychotics) should be time-limited, as symptoms may resolve
- Obtain informed consent prior to starting medications. Routinely review the risk–benefit ratio of treatment with patients and caregivers
- Have a plan in place to manage after-hours crisis

Antipsychotics

Antipsychotics provide (at times considerable) benefit to some patients with psychosis and agitation in dementia but have been associated with higher risk of death, cardiovascular disease, and cerebrovascular disease in this population. The use of antipsychotics in patients with dementia remains controversial because their efficacy is modest and they have been associated with adverse effects, including weight gain, parkinsonism, rapid cognitive decline, a higher risk of cerebrovascular or cardiovascular events, QTc prolongation, and mortality. The DART-AD trial reported an increased long-term risk of mortality in patients with AD prescribed antipsychotics. As a result, the FDA issued a “black box warning” for the use of atypical and conventional antipsychotics in treating patients with dementia-related

psychosis. Retrospective cohort studies evaluating all-cause mortality in older individuals have found higher mortality risk with haloperidol than with risperidone, olanzapine, aripiprazole, ziprasidone, or quetiapine. The highest risk of mortality occurs soon after therapy is initiated, and there appears to be a dose-dependent relationship to mortality. Given these risks, the American Psychiatric Association (APA) has published practice guidelines on the use of antipsychotics to treat agitation or psychosis in patients with dementia, emphasizing judicious use and reserving antipsychotics for when nonpharmacologic approaches have been tried, and when symptoms are severe and dangerous. They also recommend that if there is no significant response after a 4-week period, the medication should be tapered and withdrawn. In patients whose antipsychotic medications are being tapered, symptoms should be assessed at least every month during tapering and for at least 4 months after the medication is discontinued. Long-acting injectable antipsychotics should not be used unless administered for a co-occurring chronic psychotic disorder.

If a risk/benefit assessment favors the use of an antipsychotic for NPS in patients with dementia, treatment should be initiated at a low dose and titrated to the minimum effective dose as tolerated. The choice of antipsychotic should be guided by the target symptoms, side-effect profile, and formulation (eg, consider using medications that have solution or dissolving forms). The recommended dosing in patients with dementia and side effects of atypical antipsychotics discussed in this section are summarized in **Table 60-8**.

TABLE 60-8 ■ SELECT ANTIPSYCHOTIC DOSAGES AND SIDE EFFECTS

MEDICATION	FORMULATIONS[a]	RECOMMENDED DAILY DOSE FOR TREATING NPS IN DEMENTIA	SIDE EFFECTS[b]
Risperidone	Oral tablet Oral solution Oral disintegrating tablets	0.25–1 mg	Orthostatic hypotension, dose-dependent EPS, tardive dyskinesia, hyperprolactinemia, risk of cerebrovascular events, weight gain, moderate risk of diabetes mellitus and dyslipidemia, sedation, cognitive effects
Olanzapine	Tablet Disintegrating tablets IM	2.5–10 mg	Sedation, anticholinergic effects at higher doses, gait disturbance, orthostatic hypotension, high risk of weight gain, hyperglycemia, diabetes mellitus, risk of cerebrovascular events, dose-dependent EPS
Quetiapine	Tablet	12.5–150 mg	Sedation, orthostatic hypotension, moderate risk of weight gain, diabetes mellitus, and dyslipidemia, anticholinergic effects at higher doses
Aripiprazole	Oral tablet Oral solution Oral disintegrating tablets	5–10 mg	Sedation, nausea, lower risk of EPS, weight gain
Haloperidol	Oral tablet Oral solution IM IV	0.5–5	High risk of EPS, sedation, orthostatic hypotension, seizure
Clozapine	Oral tablet	6.25–75 mg	Excessive sedation, sialorrhea, seizure, anticholinergic effects, agranulocytosis, orthostatic hypotension, sustained tachycardia, weight gain, diabetes mellitus, dyslipidemia. Requires weekly blood draws to monitor for agranulocytosis in the first 6 months of treatment.
Pimavanserin	Oral tablet	34 mg	Confusion, peripheral edema, GI distress, hypotension, weight gain

[a]Only short-acting formulations are listed. Long-acting injectable formulations are available for some antipsychotics, but are not recommended for use of neuropsychiatric symptoms in dementia.
[b]All antipsychotics have a black-box warning for increased mortality in individuals with dementia and can cause QT prolongation.
EPS, extrapyramidal symptoms; IM, intramuscular injection; IV, intravenous.

The Clinical Antipsychotic Trial of International Effectiveness—Alzheimer's Disease (CATIE-AD) was designed to compare the efficacy of antipsychotics to placebo in reducing psychotic symptoms or behaviors of agitation/aggression in outpatients with AD. Olanzapine and risperidone showed the most benefit in NPS reduction. However, the magnitude of improvement was modest, and use of atypical antipsychotics over 36 weeks was associated with worsening cognitive function at a magnitude consistent with 1 year's cognitive deterioration on placebo, and there were no observable improvements in functional measures. Similarly, an Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review found that the most effective antipsychotics include risperidone (for psychosis and agitation), olanzapine (for agitation), and aripiprazole (for overall NPS). A meta-analysis of studies examining antipsychotic discontinuation in patients with dementia found that although the proportion of patients with NPS severity worsening was higher than those who

continued on antipsychotics, no statistically significant difference in NPS severity was observed.

Due to the elevated risk of extrapyramidal side effects, typical antipsychotics, such as haloperidol, should not be used as a first-line neuroleptic in nonemergent situations. Extrapyramidal symptoms (EPS) include parkinsonism, tardive dyskinesia, akathisia, and dystonias. Particular care should be taken when considering the use of antipsychotics in patients with DLB and Parkinson disease, as they are extremely sensitive to extrapyramidal side effects, with the exception of clozapine. Extrapyramidal side effects can include parkinsonian symptoms, acute dystonia, and neuroleptic malignant syndrome. Due to its low risk for causing EPS, clozapine is a good option for psychotic symptoms in DLB. However, the potential for serious adverse effects, particularly neutropenia, and the need for close laboratory monitoring makes it more challenging to use in routine clinical practice. Pimavanserin was approved by the FDA in 2016 for treatment of hallucinations and delusions associated with Parkinson disease psychosis. Clozapine and quetiapine, though not specifically approved for use in Parkinson disease, are less likely than other antipsychotics to worsen parkinsonian symptoms.

Antidepressants

Aside from depression, antidepressants are also used to treat other NPS, including anxiety, agitation, and apathy. Up to 50% of community dwelling older adults with dementia in the United States are prescribed antidepressants. Although systematic reviews of the literature have found limited evidence to support the efficacy of antidepressants in the treatment of depression, anxiety, and apathy in dementia, there is emerging evidence for their use in agitation. A summary of dosing and side effects of antidepressants is in **Table 60-9**.

TABLE 60-9 ■ ANTIDEPRESSANT ORAL DOSAGES AND SIDE EFFECTS

	INITIAL DAILY DOSE (mg)	MAX DAILY DOSE (mg)	SIDE EFFECTS
SELECTIVE SEROTONIN REUPTAKE INHIBITORS			
Citalopram	5–10	20	GI distress, sexual dysfunction, slight weight gain, QTc prolongation at doses > 20 mg, hyponatremia, SIADH
Escitalopram	5	10	GI distress, sexual dysfunction, slight weight gain, hyponatremia, SIADH, insomnia, fatigue
Fluoxetine	10	80	GI distress, sexual dysfunction, slight weight gain, abnormal dreams, hyponatremia, SIADH, insomnia, fatigue
Sertraline	25	200	GI distress, sexual dysfunction, slight weight gain, hyponatremia, SIADH, headache
Paroxetine Paroxetine CR	10 12.5	40 50	Anticholinergic effects may increase risk of delirium, may cause withdrawal effects due to short half life, GI distress, hyponatremia, SIADH
SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS			
Duloxetine	30	120	GI distress, dry mouth, urinary hesitancy, headaches, fatigue, sedation, hyponatremia, hepatitis
Venlafaxine XR Venlafaxine IR	37.5 25–50	225 375	GI distress, minimal sedation, headaches, sexual dysfunction, weight loss, withdrawal symptoms, anxiety, dose-dependent hypertension, hyponatremia, mild anticholinergic effects
Desvenlafaxine	50	100	Dizziness, dry mouth, insomnia, decreased appetite, GI distress, dose-dependent hypertension, elevated cholesterol and triglycerides, hyponatremia
OTHER			
Mirtazapine	7.5	30–45	Dry mouth, GI distress, dizziness, QT prolongation, elevated cholesterol and triglycerides, weight gain, increased appetite, sedation
Bupropion XL Bupropion SR Bupropion IR	150 100 75	450 150 BID 150 TID	Mild anticholinergic effects, hypotension, high sedation, slight sexual dysfunction, serotonin syndrome, increased appetite, dry mouth
PREFERRED TRICYCLIC ANTIDEPRESSANTS			
Nortriptyline	10–25	75–150	Therapeutic window 50–150 ng/mL; anticholinergic effects, hypotension, sedation, sexual dysfunction, slight weight gain
Desipramine	10–25	50–150	Therapeutic window 150–300 ng/mL; mild anticholinergic effects, hypotension, slight GI distress, sedation, sexual dysfunction, slight weight gain

Maximum recommended dosage for patients greater than 60 years of age. BID, twice daily; CR, controlled release; GI distress, gastrointestinal distress (eg, nausea, vomiting, diarrhea, constipation); IR, immediate release; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TID, three times a day.

Selective serotonin reuptake inhibitors Selective serotonin reuptake inhibitors (SSRIs) act on the serotonergic system by blocking its presynaptic reuptake. They are considered first-line therapy for late-life depression and are generally well tolerated compared to other classes of antidepressants such as TCAs. In the context of dementia, however, systematic reviews and meta-analysis have found little or no difference between groups treated with SSRIs and placebo in depressive symptoms. Fluoxetine has not been associated with improvements in NPS. Though initial findings for sertraline reported promising effects for depression, subsequent larger studies have not found evidence that sertraline is superior to placebo in the treatment of depression in dementia. There is growing evidence, though, for a role of SSRIs in the management of agitation in dementia. The Citalopram for Agitation in

Alzheimer's Disease (CitAD) study, a randomized placebo-controlled trial, found that participants in the citalopram group had significant improvement in agitation, measures of caregiver stress, improved performance on ADLs, and reduced use of emergency medications for agitation (lorazepam) compared to placebo. However, citalopram was associated with side effects including QT prolongation and worsened cognition, which may limit its use. Further analysis found that cognitive and cardiac changes were primarily associated with the R-enantiomer, whereas clinical improvements were primarily associated with the S-enantiomer, escitalopram. The effectiveness of escitalopram for agitation in AD is now being studied in the Escitalopram for agitation in Alzheimer's disease (S-CitAD) trial.

Though SSRIs are generally well tolerated, common side effects include nausea, diarrhea, anorexia, drowsiness, lethargy, sleep disturbance, tremor, and anxiety. These side effects usually improve after 1 to 2 weeks. Hyponatremia may occur with SSRI treatment and should be assessed particularly in older adults. Some SSRIs, such as paroxetine, have anticholinergic properties and should be avoided in older adults.

Serotonin norepinephrine reuptake inhibitors Serotonin norepinephrine reuptake inhibitors (SNRIs) include duloxetine, venlafaxine, and desvenlafaxine. While they are used in late-life depression, evidence for their efficacy in NPS in dementia is limited. A small 6-week randomized placebo-controlled trial of venlafaxine (14 in venlafaxine group, 17 placebo) did not find a significant difference in depressive symptoms between groups. A longer 12-week randomized double blind trial of 20 patients with moderate AD did not find any benefit in venlafaxine for symptoms of depression compared to baseline, though statistically significant change in cognitive and functioning scales were observed. Common side effects of SNRIs include gastrointestinal (GI) distress, headaches, sexual dysfunction, and hyponatremia.

Mirtazapine Mirtazapine is a nonadrenergic and specific serotonergic antidepressant. In the Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial, there was no difference between mirtazapine and placebo, or mirtazapine and sertraline on depressive symptoms. Subsequent subgroup analysis found that mirtazapine reduced depressive symptoms over placebo in participants with primarily affective symptoms and severe endorsement of psychological symptoms, and an absence of sleep problems. A small, open-label study with

16 patients found a significant reduction of agitation. Mirtazapine can be sedating at lower doses and is sometimes used as a sleep aid. However, a more recent randomized placebo-controlled trial of mirtazapine in patients with dementia and sleep disturbances (24 in mirtazapine group vs 16 placebo) found no benefit over placebo in improving sleep duration of efficiency. The group receiving mirtazapine experienced increased daytime sleepiness, limiting its use.

Bupropion Bupropion is a dual inhibitor of norepinephrine and dopamine reuptake. Though it has been shown to be effective in depressed older adults, its use specifically for NPS has not been extensively studied. One RCT reported it was ineffective for the treatment of apathy in Huntington disease. Buproprion should be avoided in individuals with a history of seizures or psychotic symptoms.

Tricyclic antidepressants A number of older and smaller studies have investigated the use of TCAs in dementia. Two RCTs explored the effects of imipramine on depression in dementia reported no benefit over placebo. A RCT of clomipramine reported that participants receiving the treatment of significantly improved depressive symptoms on the Hamilton Depression Scale and rate of remission. A small RCT of desipramine in individuals with moderate AD found improvement in measures of function in the treatment group, but no differences in symptoms of depression. The use of TCAs is limited by their high risk of adverse events, relative to previously discussed classes of antidepressants.

Monoamine oxidase inhibitors The monoamine oxidase inhibitor (MAOI) moclobemide was found to be superior to placebo for depressive symptoms in one multisite, double-blinded, placebo-controlled trial of 649 older adults with symptoms of depression and cognitive decline. However, this antidepressant is not marketed in the United States. The use of MAOIs is limited by the required adherence to a low-tyramine diet and the risk of serotonin syndrome with concomitant use of other serotonergic antidepressants.

Anticonvulsants and "mood stabilizers" Many anticonvulsants are approved for used as so-called mood stabilizers in bipolar disorder. However, there is limited evidence for efficacy in treating NPS in dementia, with more evidence that their use can be harmful. Though initial case studies of valproic acid suggested possible efficacy for treatment of agitation in dementia, recent

trials and a recent Cochrane meta-analysis suggested that valproate, when used solely for "organic brain disorders," is ineffective for treating agitation in people with dementia. Furthermore, valproic acid is poorly tolerated with numerous adverse effects such as sedation, diarrhea, ataxia, and thrombocytopenia.

Carbamezapine has been shown to improve NPS in one small (n=51), randomized trial in patients who were resistant to treatment with antipsychotics. Other trials have reported no benefit over placebo, but increased adverse effects including sedation, disorientation, confusion, and ataxia. Further limiting its use in older adults, carbamazepine is a potent hepatic enzyme inducer, with high potential for drug–drug interactions, is an auto-inducer (making its titration challenging), and is also associated with bone marrow toxicity and hyponatremia.

Studies examining the use of oxcarbazepine and topiramate for behavioral disturbances in dementia are limited. There has only been one randomized controlled study of oxcarbazepine in this context, where no difference was observed compared to placebo for aggression or agitation, while adverse events such as sedation, fainting, and ataxia occurred more frequently in the treatment group. No placebo-controlled trials involving topiramate for NPS in dementia have been conducted. One randomized study found it to have superior efficacy compared to risperidone.

The efficacy of gabapentin in treating NPS has been described in several case reports and open-label trials, including for treating behaviors of sexual inappropriateness. However, despite its frequent off-label use, there are no current randomized controlled trials evaluating the use of gabapentin.

Case reports, retrospective chart reviews, and one open-label trial (which allowed for concomitant use of other psychotropic drugs) have reported modest clinical improvement in NPS using lamotrigine. No randomized-controlled trials have been conducted to date. The need for a slow titration schedule due to the risk of Stevens-Johnson syndrome may limit its use in the acute setting.

Lithium The use of lithium, an established treatment for bipolar and other mood disorders with symptoms of agitation, has been limited in dementia by its narrow therapeutic window, leading to adverse effects including toxicity, increased falls, and confusion in prior case reports and trials. There are currently no randomized controlled trials evaluating the use of lithium. However, the Lithium Treatment for Agitation in Alzheimer's disease (Lit-

AD) clinical trial, which uses low-dose lithium, has recently completed recruitment. Though study results are not yet published, this study will serve as the first randomized, double-blind, placebo-controlled trial to assess the efficacy of lithium for symptoms of agitation and aggression, with or without psychosis, in older adults with AD.

Cholinesterase inhibitors and memantine Cholinesterase inhibitors (AChI), such as donepezil, galantamine, and rivastigmine, and memantine, a noncompetitive N-methyl-aspartate (NMDA) antagonist, are symptomatic therapies for cognitive symptoms in Alzheimer dementia. They are approved for treatment of mild to moderate AD, while memantine is approved for treatment of moderate to severe AD. Evidence for their efficacy in treating NPS is limited. Meta-analyses of randomized controlled trials have found that donepezil, galantamine, and memantine are superior to placebo in reducing emergence of NPS, though the effects are modest compared to that of neuroleptics. Combination therapy of AChI and memantine, which is sometimes used in moderate to severe AD, has been shown in meta-analysis to have superior outcomes in reducing NPS compared to monotherapy and placebo. In general, AChI and memantine should not be considered first-line pharmacologic agents in the management of acute NPS of moderate or greater severity. Given their potential benefit in delaying cognitive symptom progression and modest improvement of NPS, however, they remain reasonable options for treating chronic NPS in dementia.

Both AChI and memantine are generally well tolerated. Common side effects of AChIs include vomiting, diarrhea, dyspepsia, anorexia, eight loss, dyspepsia, headache, dizziness, insomnia, and vagotonic effects leading to bradycardia and heart block. Common side effects of memantine include dizziness, headache, confusion, constipation, and fatigue.

Stimulants Modafinil, a wakefulness-promoting medication, and methylphenidate, a stimulant, have both been evaluated as possible treatments for apathy associated with AD. Modafinil is FDA-approved to treat narcolepsy, shift work sleep disorder, and obstructive sleep apnea. One small randomized controlled trial in people with mild to moderate AD and clinically significant apathy at baseline did not observe statistically significant benefit over placebo for improving apathy or caregiver burden. Common side effects include headaches, nausea, diarrhea, anxiety, dyspepsia, and insomnia.

Methylphenidate is a dopamine reuptake inhibitor which is FDA-approved for treatment of attention deficit/hyperactivity disorder. Methylphenidate has been associated with significant reductions in apathy symptoms in AD in a 6-week and 12-week randomized, double-blind, placebo-controlled trial. Though generally well tolerated, side effects of methylphedniate include cardiovascular effects, insomnia, headaches, and decreased appetite. Psychiatric side effects may include increased impulsivity, hallucinations, and affect lability. As a result, methylphenidate and other stimulants should be avoided in individuals with a history of schizophrenia, bipolar disease, or impulse control disorders.

Benzodiazepines Benzodiazepines are used in 8.5% to 20% of patients with AD, despite limited evidence for their efficacy in reducing agitation or improving sleep quality. A systematic review reported few randomized-controlled trials comparing benzodiazepines to other medications in managing NPS in dementia, and that of the few that are available none have found evidence benzodiazepines are more effective in reducing NPS than antipsychotics. They should be avoided due to their cognitive and deliriogenic effects increasing the likelihood of falls and fractures. The exception is use in emergency situations in which severely agitated patients are at risk of harming themselves or others, or in situations where patients have not responded to alternative pharmacologic interventions. If used, benzodiazepines should be utilized sparingly, with short-acting preparations preferred as they do not accumulate with repeated dosing compared to long-acting. Many benzodiazepines are metabolized through the liver, and benzodiazepines metabolized through glucuronidation (eg, oxazepam, temazepam, or lorazepam) are preferable in individuals with complex medical comorbidities. They have no active metabolites and are less susceptible to drug–drug interactions.

Melatonin Circadian rhythm disturbances such as sleep disturbances and sundowning are common in dementia. Due to its role in maintaining the circadian rhythm, melatonin has been of interest as a pharmacologic therapy for NPS in dementia. A 2020 Cochrane review of pharmacotherapies for sleep disturbance in dementia reported five randomized controlled trials that examined the use of melatonin for sleep disturbances in dementia and found that there was low-certainty evidence that melatonin doses up to 10 mg may have little or no effect on sleep efficacy, time awake after sleep onset, number of nighttime awakenings, or mean duration of sleep. Of studies that

have examined melatonin versus placebo in the context of agitation or sundowning behaviors, one RCT of 20 patients treated for 4 weeks with melatonin 3 mg reported benefits over placebo. One randomized controlled trial of ramelteon, a melatonin-receptor agonist, did not find any evidence of effect on sleep outcomes.

Newer medications Pimavanserin, an atypical antipsychotic with a novel mechanism of action as a selective inverse agonist at the serotonin receptor, was approved in 2016 by the US FDA for treatment of Parkinson disease psychosis. Although it has low risk of EPS due to its lack of dopamine blockade, it carries a similar side effect profile to other atypical antipsychotics, including QT prolongation and the black box warning for increased mortality in patients with dementia. There has been one phase 2, single-center study of nursing home residents using pimavanserin in the treatment of behavioral disturbances in AD. Participants treated with pimavanserin had reduced NPI scores at 6 weeks, but improvements were not sustained at 12 weeks compared to placebo.

Dextromethorphan-quinidine was approved by the US FDA in 2010 for the treatment of pseudobulbar affect. Dextromethorphan is a low-affinity, uncompetitive N-methyl-D-aspartate receptor antagonist, σ_1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic $\alpha_3\beta_4$ receptor antagonist. Off-label use in AD for agitation has been examined in one phase 2 randomized, multicenter, double-blind, placebo-controlled study, which reported a significant reduction in symptoms, though significant adverse events were observed in the treatment group, including falls, diarrhea, and urinary tract infection.

Evidence for the effectiveness and safety of psychoactive cannabinoids, such as dronabinol and tetrahydrocannabinol (THC), has been varied. While some studies have reported significant improvements of NPS, two recent systematic reviews found a high risk of bias in studies with considerable variability with respect to study design, and that higher quality trials did not find evidence of improvement in NPS. Most adverse drug events reported were mild, and the most common adverse drug event was sedation. Further large, randomized controlled trials are needed.

CONCLUSION

NPS are common throughout the range of dementia severity. They can be disabling to the patient, onerous to the caregiver, and at times dangerous. The differential diagnosis of NPSs in dementia is wide, including underlying medical causes, delirium, medication effect, and primary psychiatric disorders. These differentials should be considered prior to implementing a treatment plan. A multidisciplinary dementia care team can be invaluable to delivering effective, personalized care to patients with dementia. Nonpharmacologic interventions should be considered first-line therapy, prior to implementing medications. Pharmacotherapy is appropriate when nonpharmacologic approaches have been unsuccessful, when symptoms are distressing or disruptive to the patient or caregiver, and in emergent situations. All psychotropic medications for behavioral symptoms are associated with adverse effects. Individuals with dementia and multiple medical comorbidities requiring many medications are at elevated risk of adverse effects and drug–drug interactions. When starting new medications, it is best to "start low and go slow," use the lowest possible dose, and frequently reassess the risk/benefit ratio of the medication.

FURTHER READING

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Chapter 61

Parkinson Disease and Related Disorders

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DEFINITION AND TERMINOLOGY

Parkinsonism is the unifying term that describes a constellation of motor and nonmotor neurologic features. Parkinsonism can be defined as a variable combination of six specific, independent motor features: bradykinesia (slowness of movement), tremor at rest, rigidity, loss of postural reflexes, flexed posture, and freezing of gait (where the feet are transiently "glued" to the ground). Of these features, bradykinesia—either affecting the arms or legs ("appendicular bradykinesia") or midline structures including the trunk, head and neck, oropharynx, or eyes ("axial bradykinesia")—is the most central element of parkinsonism and is caused by loss of dopaminergic neurons in a midbrain structure called the substantia nigra pars compacta (SNpc) responsible for innervating a group of critical motor nuclei within the deep portions of the brain collectively labeled the basal ganglia.

There are multiple causes of parkinsonism. The most common and extensively studied is idiopathic Parkinson disease (PD), which is estimated to affect approximately 1% to 2% of people older than age 60. PD is a complex disorder with a wide variety of clinical presentations whose exact pathogenesis is incompletely understood. The eponymous name "Parkinson disease" was coined following the publication of "An Essay on the Shaking Palsy" by the British surgeon James Parkinson in 1817. In more recent years, the term "Parkinson disease" has been favored over "Parkinson's disease" given that Dr. Parkinson neither personally contracted nor "owned" the disease that over time has been associated with his surname.

There are numerous causes of parkinsonism, almost all of which becoming increasingly common with advancing age. These include (a)

secondary parkinsonism caused by toxins, medications, or structural lesions in the brain; (b) atypical parkinsonian conditions including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal syndrome (CBS), and dementia with Lewy bodies (DLB); and (c) more rare neurodegenerative conditions with heterogeneous manifestations that can include parkinsonism such as juvenile Huntington disease, spinocerebellar ataxia type 3, and Wilson disease (**Table 61-1**).

TABLE 61-1 ■ CLASSIFICATION OF THE PARKINSONIAN STATES

Primary parkinsonism (Parkinson disease)
Sporadic
Known genetic etiology (see **Table 61-2**)
Secondary parkinsonism (environmental etiology)
Drugs
Dopamine receptor blockers (most commonly antipsychotic medications)
Dopamine storage depletors (reserpine)
Postencephalitic
Toxins—Mn, CO, MPTP, cyanide
Vascular
Brain tumors
Head trauma
Normal pressure hydrocephalus
Parkinsonism-plus syndromes
Progressive supranuclear palsy (PSP)
Multiple system atrophy (MSA)
Corticobasal syndrome (CBS)
Dementia with Lewy bodies (DLB)
Heterodegenerative disorders
Alzheimer disease
Wilson disease
Huntington disease
Frontotemporal dementia on chromosome 17
X-linked dystonia parkinsonism

Learning Objectives

- Learn the epidemiology, pathobiology, clinical manifestations, and genetics of Parkinson disease (PD).
- Understand the latest terminology and major clinical differences between parkinsonism and PD.

- Learn the common presenting features of diseases, such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and MSA that mimic and require differentiation from PD.
- Acquire new knowledge about the latest tests to diagnose PD and indications and adverse effects of cutting-edge therapies, including dopaminergic and nondopaminergic agents and surgical treatments for PD.
- Understand the significance of exercise, physical activity, and supportive care for management of patients with PD.

Key Clinical Points

1. **Parkinsonism includes a constellation of motor and nonmotor features. Parkinson disease (PD) is he most common neurodegenerative cause of parkinsonism. Other causes include medications, structural lesions of the brain, and diseases that present with extrapyramidal manifestations**
2. **The gold standard of making a diagnosis of PD remains an autopsy that shows Lewy bodies in substantia nigra.**
3. **PD affects more than 1 out of every 100 individuals older than age 60 and is more common in men.**
4. **Patients with PD almost always respond to dopaminergic medications, while those with parkinsonism generally do not. The symptoms most responsive to treatment include bradykinesia and rigidity.**
5. **Besides symptoms, dopamine transporter single-photon emission computed tomography (SPECT) imaging helps to diagnose PD and differentiate it from essential tremor.**
6. **Deep brain stimulation (DBS) surgery is typically indicated for patients with difficult motor complications and medication-refractory tremors.**

It should be noted that there are a variety of overlapping and often outdated names frequently used to describe certain parkinsonian conditions

that can be confusing to the nonspecialist. For example, the term olivopontocerebellar atrophy was formerly used to describe a collection of neurodegenerative conditions including MSA and some other progressive neurodegenerative cerebellar disorders. Similarly, the terms Lewy body dementia (LBD) and DLB are used interchangeably to refer to the same disorder. Finally, the term "diffuse Lewy body disease" is also used loosely by both clinicians and pathologists to describe the topographical distribution of postmortem findings that can be seen in DLB.

EPIDEMIOLOGY

Like other insidiously developing progressive disorders of aging, there are inherent challenges in identifying the true prevalence of PD. The diagnosis of PD is typically made on the basis of clinical examination. There are numerous adjunctive clinical diagnostic measures, including a documented favorable response to a trial of dopaminergic medications, that can enhance certainty in the diagnosis of PD but these may not be used in large epidemiologic studies. The gold standard for making the diagnosis of PD remains autopsy where characteristic intracellular cytoplasmic inclusions of α-synuclein called Lewy bodies are seen in the SNpc and other brain and nervous system regions. Longitudinal clinical postmortem studies suggest that 10% to 20% of patients thought to have PD in life will have alternative diagnoses on autopsy. Interestingly, midbrain Lewy bodies are also seen on autopsy in about 20% of older individuals without a known history of parkinsonism suggesting that PD may be either underdiagnosed or not yet have manifested the typical motor features of the disease during life. Alternatively, these individuals may have so-called prodromal DLB.

Many epidemiologic studies of PD identify cases through medical records rather than through door-to-door examinations of well-defined populations. Incidence rates of PD vary not only by age but also by gender. Estimates across all possible ages and genders tend to range from 4.5 to 19/100,000 person-years reflecting differences in ascertainment methods and biological susceptibility. Among individuals older than age 60, incidence rates range from 27.2 to 107.2 cases/100,000 person-years. The median age of onset is in the early sixties and there is increasing risk for PD seen with each successive decade of life.

Since most people with PD live many years before death, prevalence rates of PD are higher than the incidence rates. Across all age ranges and

genders, PD is thought to affect between 100 and 200 out of every 100,000 people. For people older than age 60, PD is thought to affect slightly more than 1 out of every 100 individuals. Parkinson disease is about 1.5 times more common in men than in women for reasons that may reflect differences in underlying biological susceptibility.

In most cases, PD is not a direct cause of death and frequently goes unmentioned on death certificates. Death in individuals with PD is occasionally due to secondary acute comorbidities seen in patients with mobility restrictions including aspiration pneumonia, traumatic falls, deep vein thrombosis, and pulmonary embolus. Mortality rates in PD are slightly higher in comparison to age- and gender-matched populations, although differences in life expectancy are most profound in individuals with early-onset PD. Individuals with PD and dementia also have a higher risk of death. PD patients who follow with a neurologist have a lower likelihood of death compared to those whose PD is managed exclusively by primary care physicians.

PD is caused by a complex interaction between genetic and environmental risk factors. Nevertheless, to date, relatively few environmental risk factors for sporadic PD have been identified. Exposure to pesticides containing the pyridine compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyradine (MPTP), industrial solvents, and heavy metals including manganese have all been suggested to associate with a higher risk of incident PD. Higher incidence in rural areas has been associated with farming-related exposures to pesticides and/or drinking from well water. There are several factors that have been consistently demonstrated to have an inverse relationship with PD risk including cigarette smoking, caffeinated coffee consumption, high plasma levels of uric acid, and endogenous estrogen exposure. The biological principles that mediate these associations are incompletely understood.

Although over 90% of cases of PD are considered sporadic, there is a growing understanding of the influence of primary monogenetic genetic causes of PD. Mendelian inheritance is implicated in several PD risk factor genes, all of which share a common naming schema as *PARK* genetic loci. To date, there are 20 *PARK* genes (**Table 61-2**). The most notable of these include *PARK1* or α-synuclein mutations, which were the first genetic variant identified to cause familial parkinsonism. There are now several identified autosomal-dominant and autosomal-recessive causes of PD some of which

show variable penetrance depending on the underlying mutation. More recently, common haplotypes of genes known to play a role in other neurodegenerative conditions have been recognized as incremental risk factors for PD. These include the *MAPT* gene encoding the tau protein implicated in neurofibrillary tangles of Alzheimer disease (AD). Allelic variations including point mutations and deletions in the *GBA* gene, whose loss of function is implicated in causing impaired lysosomal activity in Gaucher's disease, have also been linked to cases of early-onset PD, particularly among individuals of Ashkenazi Jewish ancestry.

TABLE 61-2 ■ GENETIC FORMS OF PRIMARY PARKINSONISM

NAME	GENE SYMBOL	PROTEIN	CHROMOSOME
AUTOSOMAL DOMINANT TRANSMISSION			
PARK1/PARK4	*SNCA*	α-Synuclein	4q21.3
PARK3	Unknown	Unknown	2p13
PARK5	*UCH-L1*	Ubiquitin C-terminal hydrolase-L1	4p14
PARK8	*LRRK2*	Leucine-rich repeat kinase 2	12p12
Dopa-responsive dystonia		GTP cyclohydrolase 1	14q22.1–q22.2
PARK13	*HTRA2*	High-temperature requirement protein	2p13
PARK17	*VPS35*	Vacuolar protein sorting 35	16q11
PARK18	*EIF4G1*	Eukaryotic translation initiating factor 4 gamma	3q27
AUTOSOMAL RECESSIVE TRANSMISSION			
PARK2	*PRKN*	Parkin (ubiquitin ligase)	6q25
PARK6	*PINK1*	PTEN-induced kinase 1 (PINK1)	1p36
PARK7	*DJ-1*	DJ-1	1p36
PARK9	*ATP13A2*	ATPase	1p36
PARK10			1p32
PARK14	*PLA2G6*	Phospholipase A2, group 6	22q13
PARK15	*FBX07*	F-box protein 7	22q12
PARK19	*DNAJC6*	DNAJC6	1p32
PARK20	*SYNJ1*	Synaptojanin 1	21q22
OTHER PD-ASSOCIATED GENES			
GBA	*GBA1*	β-Glucocerebrosidase	1q21
VPS35	*VPS35*	Vacuolar protein sorting 35	16p12.1-q12.1
PARK10	Unknown	Unknown	1p32
PARK11	*GIGYF2*	Unknown	2q36
PARK12	Unknown	Unknown	Xq21
PARK16	Unknown	Unknown	1p32

Understanding the pathobiology of these genetic PD subtypes has advanced the field's understanding of causative factors leading to the majority of "idiopathic" PD as well. PD is now thought to occur because of the confluence of several interrelated neurobiological risk states that each

grow more problematic in the setting of aging. These include (1) autophagy-lysosomal dysfunction (ALD), (2) oxidative stress and dopamine toxicity, (3) selective neuronal vulnerability, and (4) network frailty and the prion-like spread of toxic alpha-synculein pathology. First, ALD is implicated in PD with GBA1 and LRRK2 mutations and may play a bidirectional causative role in propagating toxic alpha-synuclein aggregation, which in turn may deleteriously affect autophagy-lysosomal function. Second, the generation of toxic oxidative species by neuronal dopamine metabolism may impair mitochondrial function, which may in turn lead to secondary ALD related to the turnover of dysfunctional mitochondria. Third, ALD and oxidative stressors may make certain projection neurons with unusually large axonal arborization characteristics particularly vulnerable to the effects of inefficient cellular metabolism. Certain neuronal groups affected by alpha-synuclein pathology show extensively branched axonal trees, perhaps making them particularly vulnerable. In some cases, this vulnerability can be accelerated by local neuroinflammation at the site of nascent neurodegeneration accelerated by adjacent glial cell populations. Finally, toxic alpha-synuclein appears to spread from one cell to the next in "prion-like" fashion where a misfolded peptide aggregate can seed a connected neuron in its functional network, thereby causing it to develop alpha-synuclein pathology as well. These findings have collectively set the stage for new disease-modifying approaches currently being tested in PD clinical trials.

Atypical parkinsonian conditions including PSP, MSA, and CBS manifest with a prevalence rate that is roughly 5% to 10% of PD prevalence. DLB is more common than the other atypical parkinsonisms, although prevalence estimates of DLB are confounded by its significant clinical and pathologic overlap with other common neurodegenerative conditions including PD and AD. Risks for developing PSP and CBS have been linked to allelic variation in the *MAPT* gene, and mutations in the *GBA* gene are seen with increased frequency in both PD and DLB.

PATHOPHYSIOLOGY

PD is most strongly associated with two specific postmortem hallmarks: (a) the development of cytoplasmic, eosinophilic inclusions of the misfolded synaptic protein α-synuclein called Lewy bodies and (b) the loss of SNpc dopaminergic neurons innervating the striatum.

Nigrostriatal dopaminergic denervation is seen as part of the spectrum of normal aging, albeit to a milder degree than is seen in PD. It is estimated that with every year of life after the third decade, we lose 0.5% to 1% of nigrostriatal nerve terminals, including the dorsal putamen a structure charged with mediating speed and precision of motor movements. By the time motor symptoms of PD are present, however, the posterior putamen has undergone profound denervation equating to the loss of over 60% to 80% of dopaminergic terminals. Although in this way, PD could be conceptualized as an accelerated form of nigrostriatal aging, the nerve terminal loss in PD has a particular predilection for the posterior and dorsal putamen compared to more anterior and ventral striatal regions. In contrast, normal aging is associated with more mild and diffuse striatal losses of nerve terminals.

Within the striatum, dopaminergic innervation is organized into two broad conceptual pathways: the direct pathway and the indirect pathway. Although this model is continually updated, it has formed the scientific basis accounting for a number of advances in neurobiology including the development of DBS. In this conceptual model, the striatum is viewed as a series of interconnected relay nuclei that upregulate or downregulate inputs from both the cortex and deep nuclei of the brain stem and spinal cord, yielding a well-regulated motor output to the cortex, thalamus, and brainstem pedunculopontine nucleus, which is part of the mesencephalic locomotor center.

The “direct pathway” is a monosynaptic, D1 receptor–mediated excitatory connection between the striatum and the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNpr). When stimulated, these latter two nuclei lead to an increase in motor output via thalamocortical afferents. The “indirect pathway” is a polysynaptic pathway that depends on inhibitory D2 receptors affecting the globus pallidus pars externa (GPe) and the subthalamic nucleus (STN), which then innervate the GPi/SNpr. The net effect of the indirect pathway is to suppress motor output via thalamocortical afferents. Like many models of complex biological phenomena, the direct and indirect pathway model is an oversimplification of more nuanced network and has been challenged and revised over time. It nevertheless provides a useful conceptual framework to think about the pathologic changes in PD. Since D1 receptors are excitatory and D2 receptors are inhibitory, loss of dopamine in PD has the net effect of reducing transmission through the direct pathway (less stimulation of voluntary motor activity) and increasing

transmission via the indirect pathway (more inhibition of motor activity) leading to an output that is characterized by a paucity of movement.

Significant advances in neurobiology over the last 20 years have improved our understanding of cellular pathology in PD. Abnormal processing of misfolded α-synuclein is now thought to occupy a central role in PD pathogenesis. α-Synuclein itself is an endogenously produced neuronal protein involved in synaptic vesicle trafficking. The breadth of mendelian genetic mutations linked to inherited forms of PD has given rise to several theories about the pathogenesis of sporadic PD, many of which coexist and contribute in additive fashion toward cell death in at-risk neuronal populations including the SNpc. These possibilities include (1) damage to the protein degradation properties of lysosomes leading to α-synuclein accumulation and aggregation; (2) effects from oxidative stress, such as the reaction of oxyradicals with nitric oxide; (3) impaired mitochondrial function leading to both reduced ATP production and accumulation of electrons that aggravate oxidative stress, with the final outcome being apoptosis and cell death; and (4) inflammatory changes in the nigra producing cytokines that augment apoptosis.

A description of contemporary models of PD pathogenesis would be incomplete without discussing the developing hypothesis that pathogenesis and disease progression of PD may be mediated through a prion-like cell-to-cell spread of misfolded α-synuclein. Prion proteins whose unusual morphology allows the induction of pathologic changes in adjacent cells by promoting misfolding of endogenous proteins, thereby transmitting cell death to adjacent neurons in an infectious-like fashion. In vitro and in vivo experiments in preclinical models of PD have shown the ability of misfolded α-synuclein to induce similar changes in adjacent neurons leading to neurodegeneration.

The “Braak model” of PD pathogenesis is a temporal and topographic schema of Lewy body or Lewy neurite deposition based on findings in a cohort of older individuals with Lewy bodies found on autopsy. In the originally proposed model, Lewy body formation begins in the medulla oblongata and then progresses in a rostral fashion to involve the upper brain stem followed by the diencephalon and cortex. Coincidentally, with the brainstem medulla deposition, this model posits also early deposition in the olfactory tubercle, which then may progress to adjacent regions. Lewy body deposition in the original Braak stage 3 (of total six stages) involves the

nigra and is thought to correspond with the onset of motor features of PD. Braak stages 1 and 2 correspond with premotor features of PD, including olfactory, sleep, and autonomic symptoms that can often predate the diagnosis of PD by several years. Similarly, cortical Lewy body formation seen in Braak stages 5 and 6 correspond with cognitive impairment and dementia seen later in the disease course in PD. More recent revisions of this model suggest even earlier involvement of Lewy body deposition in peripheral autonomic nerve terminals, including the intestines, stomach, and myocardium antedating the motor symptoms of PD decades before.

Unlike PD, both PSP and CBS are not thought to be disorders of α-synuclein but instead are attributable to misfolded tau. The parkinsonism seen in these disorders is attributable to tau-based neurodegeneration of the SNpc and basal ganglia. MSA is characterized by the development of argyrophilic cytoplasmic inclusion bodies that are positive for α-synuclein in glial cells rather than typical neuronal Lewy bodies. DLB has neuropathological overlap with PD with dementia (PDD) in that both disorders are characterized by Lewy body formation in the cortex. PDD is clinically defined by the so-called 1-year rule where motor symptoms antedate cognitive symptoms for over 1 year, whereas motor and cognitive symptoms coincide within a year in DLB. Although different in the temporal profile of the emergence of cognitive and neurobehavioral symptoms, typical features of DLB and/or PDD include hallucinations, especially visual, fluctuations in cognition and dream enactment behavior. DLB, however, also features significant cerebral amyloidopathy more characteristic of AD. Although DLB is often characterized as representing an overlap between PD and AD neuropathology, neurofibrillary tangles are less common in DLB compared to prototypical AD.

PRESENTATION AND EVALUATION

The diagnosis of PD is of prognostic importance, as well as of therapeutic significance, because PD almost always responds somewhat to dopaminergic medications whereas the atypical parkinsonian conditions often do not. In general, the features of PD that tend to improve the most with levodopa or dopamine agonists include bradykinesia, especially fine motor distal motor dexterity, and rigidity in the arms and legs. In some individuals, features of rest tremor can improve significantly with levodopa, especially in the presence of more prominent bradykinesia. Axial motor features including

hypophonia, dysphagia, and postural instability are often medication refractory and signify the influence of nondopaminergic changes superimposed on top of nigrostriatal dopaminergic denervation.

While it may be difficult to distinguish between PD and Parkinson-plus syndromes in the early stages of the illness, with disease progression over time, the clinical distinctions of the Parkinson-plus disorders become more apparent with the development of other neurologic findings, such as loss of downward ocular movements in PSP or cerebellar ataxia and autonomic dysfunction (eg, postural hypotension, loss of bladder control, and impotence), which can be seen to a mild-moderate degree in PD but are often very prominent in MSA.

PD begins insidiously and gradually progresses. Three of the most helpful clues that one is likely dealing with an alternative cause of parkinsonism other than idiopathic PD are (1) a symmetrical onset of symptoms (PD often begins asymmetrically on one side of the body), (2) a lack of a substantial clinical response to adequate levodopa therapy, and (3) the absence of rest tremor—though this latter feature is less specific and is present to variable degrees in PD. There are three commonly cited clinical criteria for diagnosing PD: the UK Brain Bank Clinical Diagnostic criteria, the Gelb criteria, and the 2015 Movement Disorders Society (MDS) Criteria. Each criterion emphasizes that bradykinesia, the most prevalent motor feature of PD, must be present and that other causes of parkinsonism should preferably be excluded. The UK Brain Bank criteria use the presence of postural instability as an inclusion criterion for PD, whereas the Gelb criteria deemphasize this feature—given that it can also be seen in atypical parkinsonian conditions—and suggest that asymmetry of motor presentation should be the key inclusion criteria for PD. The MDS criteria for "clinically established" PD require, the absence of exclusionary criteria, the presence of bradykinesia, and at least 2 of 4 supportive criteria: (1) a levodopa treatment response, (2) levodopa-induced dyskinesias, (3) rest tremor, and (4) either olfactory loss and/or cardiac sympathetic denervation. Clinical features suggesting an alternative parkinsonian diagnosis, so-called "red flags," are listed in **Table 61-3** and a comparison of diagnostic features for PD and atypical parkinsonian conditions is presented in **Table 61-4**. One common misdiagnosis is tremor due to essential tremor, which can even be unilateral, although it more commonly is bilateral. Helpful in the diagnosis is that the tremor caused by PD is a predominant rest tremor, whereas essential tremor

is not typically present at rest, but appears with holding the arms in front of the body (postural tremor) and increases in amplitude with activity of the arm (kinetic or action tremor), such as with handwriting or performing the finger-to-nose maneuver. The presence of mixed and asymmetric tremor syndromes can be particularly challenging as sometimes PD and essential tremor may coexist in the same patients.

TABLE 61-3 ■ CRITERIA TO EXCLUDE THE DIAGNOSIS OF PARKINSON DISEASE IN FAVOR OF ANOTHER CAUSE OF PARKINSONISM

	LIKELY DIAGNOSIS
History of:	
Encephalitis	Postencephalitic
Exposure to carbon monoxide, manganese, or other toxins	Toxin induced
Recent exposure to neuroleptic medications or metoclopramide	Drug induced
Onset of parkinsonian symptoms following:	
Head trauma	Posttraumatic
Stroke	Vascular
Presence on examination of:	
Cerebellar ataxia	MSA, primary ataxic disorders
Loss of downward ocular movements	PSP
Pronounced postural hypotension not because of concurrent medication	MSA
Pronounced unilateral rigidity with or without dystonia, apraxia, cortical sensory loss, alien limb	CBS
Myoclonus	CBS, MSA
Falling or freezing of gait early in the course of the disease	PSP
Autonomic dysfunction not because of medications	MSA
Excessive drooling of saliva	MSA
Early dementia or hallucinations from medications	DLB
Dystonia induced with low-dose levodopa	MSA
Neuroimaging (MRI or CT scan) revealing:	
Lacunar infarcts	Vascular parkinsonism
Capacious cerebral ventricles	Normal pressure hydrocephalus
Cerebellar atrophy	MSA, primary ataxic disorders
Atrophy of the midbrain or other parts of the brain stem	PSP, MSA
Effect of medication:	
Poor response to levodopa	PSP, MSA, CBS, vascular, NPH
No dyskinesias despite high-dose levodopa	Same as above

CBS, corticobasal syndrome; CT, computed tomography; DLB, dementia with Lewy bodies; MRI, magnetic resonance imaging; MSA, multiple system atrophy; NPH, normal pressure hydrocephalus; PSP, progressive supranuclear palsy.

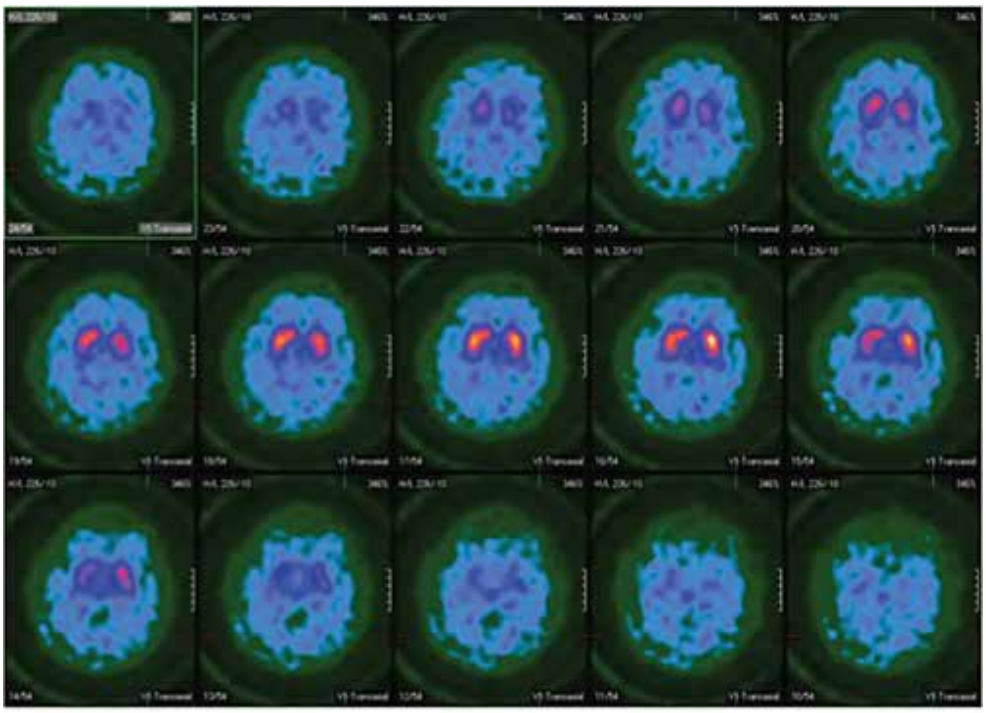
TABLE 61-4 ■ COMPARISON OF DIAGNOSTIC FEATURES FOR PD AND OTHER ATYPICAL PARKINSONIAN CONDITIONS

DISEASE	RELATIVE INCLUSION CRITERIA	CRITERIA SUPPORTIVE OF THE DIAGNOSIS	RELATIVE EXCLUSION CRITERIA
PD	• Bradykinesia • Rigidity • Rest tremor • Asymmetric onset (++)	• Gradually progressive course • Good response to dopaminergic therapies (++) • Motor fluctuations (+++) • Dyskinesias (+++) • Motor symptom duration > 5 y • Olfactory impairment • Rapid eye movement (REM) sleep behavior disorder • Cardiac sympathetic denervation	• Focal brain lesions within the basal ganglia • Recent history of neuroleptic medication use • Severe dysautonomia unrelated to medications • Supranuclear gaze palsy • Prominent postural instability at initial presentation (–) • Prominent cerebellar atrophy on MRI (–) • Freezing of gait developing within 3 y of motor symptom onset (–)
PSP	• Supranuclear gaze palsy (+++) • Slowing of vertical eye movements/saccades (+++) • Tendency to fall in the first year following the onset of motor symptoms (++)	• Gradually progressive course • Symmetric parkinsonism • Increased neck tone and axial rigidity (++) • Early dysphagia • Early cognitive features including apathy, decreased verbal fluency, and pseudobulbar effect • Early frontal release signs on neurologic examination • "Hummingbird sign" on sagittal brain MRI (++)	• Alien limb syndrome • Hallucinations • Early cerebellar signs • Early dysautonomia
CBS	• Asymmetric motor findings at presentation (+) • Limb dystonia at presentation (+) • Limb myoclonus (++) • Alien-limb phenomenon (+++)	• Cortical sensory deficit (++) • Frontal lobe cognitive symptoms including executive dysfunction, behavioral/personality changes, aphasia (++) • Focal cortical parietofrontal atrophy on brain MRI	• Rest tremor • Good response to dopaminergic medications • Hallucinations • Cerebellar signs • Prominent dysautonomia
MSA	• Cerebellar features on examination (++) • Prominent dysautonomia (+++) • Hyperreflexia and other pyramidal tract findings (+)	• Relatively few cognitive features • Respiratory stridor (++) • Orofacial dyskinesias • "Hot cross bun" sign on axial brainstem MRI	• Dysautonomia only in relation to medications • Hallucinations
DLB	• Hallucinations (+++) • Fluctuations in level of alertness (++) • Dementia within 1 y of the onset of motor features of parkinsonism	• REM sleep behavior disorder (+) • Sensitivity to medications, especially neuroleptics (++)	• Active delirium explained by concurrent medications or an alternative process • Supranuclear gaze palsy

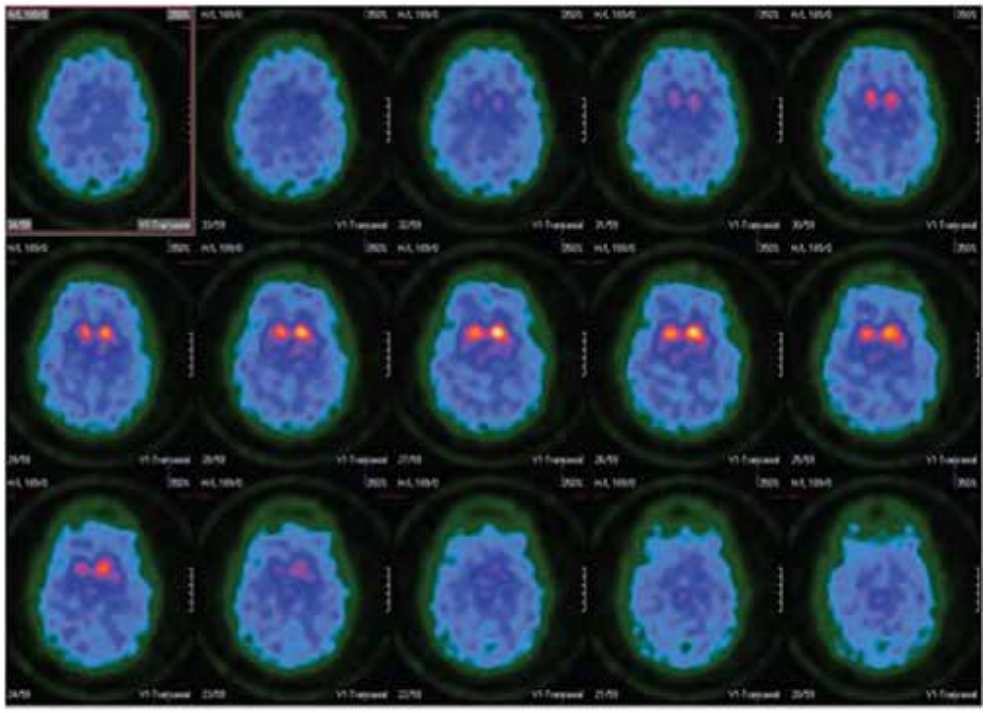
+/– denotes strength of association between a particular feature and a specific disorder. CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PD, Parkinson disease; PSP, progressive supranuclear palsy; REM, rapid eye movement.
The above table presents a summary of published diagnostic criteria. The lists of inclusion and exclusion criteria for any given disorders are not exclusive/exhaustive of all possibilities. For any given disease, not all inclusion criteria are required to make an affirmative diagnosis. Similarly, the presence of a single exclusion criterion does not represent an absolute contraindication to diagnosing a specific disorder.

Although the diagnosis of PD rests largely on the clinical history and examination, there are adjunctive diagnostic measures that can be useful in making the proper diagnosis. A history of a positive response to levodopa or other dopaminergic medications, for example, is seen in almost all patients with PD. That having been said, many patients with atypical parkinsonian conditions—in particular MSA and DLB—will also describe a generally

milder improvement in certain motor features from dopaminergic medications. Dopamine transporter imaging through SPECT (I-123 ioflupane SPECT or DaTscan) scan provides molecular imaging evidence to confirm the loss of nigrostriatal dopaminergic nerve terminals, consistent with parkinsonism (**Figure 61-1**). It cannot, however, differentiate between PD and other causes of neurodegenerative parkinsonism, such as DLB, PSP, or MSA; all of these conditions will have evidence of nigrostriatal losses on dopamine transporter imaging. Dopamine transporter SPECT imaging has been approved to distinguish essential tremor from PD in patients with atypical tremor manifestation. This imaging modality can also be helpful to distinguish PD from drug-induced parkinsonism. Impaired performance on olfactory identification testing has also shown good correlation with postmortem findings of PD in patients presenting for suspected parkinsonism but can also be seen in other neurodegenerative conditions, such as AD or DLB. Scratch-and-sniff tests for odor identification are available commercially and can be completed and scored in the clinic relatively quickly.



A Normal DaTscan: Essential tremor



B Abnormal DaTscan: Primary parkinsonism

FIGURE 61-1. **A.** Normal dopamine transporter imaging through single-photon emission computed tomography (DaT SPECT scan) in a patient with essential tremor. **B.** Asymmetric loss of putaminal dopaminergic nerve terminals affecting the right striatum more than the left consistent with a primary neurodegenerative parkinsonian condition.