Review

Pharmacological Treatment of Parkinson Disease
A Review

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IMPORTANCE Parkinson disease is the second most common neurodegenerative disease worldwide. Although no available therapies alter the underlying neurodegenerative process, symptomatic therapies can improve patient quality of life.

OBJECTIVE To provide an evidence-based review of the initial pharmacological management of the classic motor symptoms of Parkinson disease; describe management of medication-related motor complications (such as motor fluctuations and dyskinesia), and other medication adverse effects (nausea, psychosis, and impulse control disorders and related behaviors); and discuss the management of selected nonmotor symptoms of Parkinson disease, including rapid eye movement sleep behavior disorder, cognitive impairment, depression, orthostatic hypotension, and sialorrhea.

EVIDENCE REVIEW References were identified using searches of PubMed between January 1985 and February 2014 for English-language human studies and the full database of the Cochrane Library. The classification of studies by quality (classes I-IV) was assessed using the levels of evidence guidelines from the American Academy of Neurology and the highest-quality data for each topic.

RESULTS Although levodopa is the most effective medication available for treating the motor symptoms of Parkinson disease, in certain instances (eg, mild symptoms, tremor as the only or most prominent symptom, aged <60 years) other medications (eg, monoamine oxidase type B inhibitors [MAOBIs], amantadine, anticholinergics, β-blockers, or dopamine agonists) may be initiated first to avoid levodopa-related motor complications. Motor fluctuations may be managed by modifying the levodopa dosing regimen or by adding several other medications, such as MAOBIs, catechol-O-methyltransferase inhibitors, or dopamine agonists. Impulse control disorders are typically managed by reducing or withdrawing dopaminergic medication, particularly dopamine agonists. Evidence-based management of some nonmotor symptoms is limited by a paucity of high-quality positive studies.

CONCLUSIONS AND RELEVANCE Strong evidence supports using levodopa and dopamine agonists for motor symptoms at all stages of Parkinson disease. Dopamine agonists and drugs that block dopamine metabolism are effective for motor fluctuations and clozapine is effective for hallucinations. Cholinesterase inhibitors may improve symptoms of dementia and antidepressants and pramipexole may improve depression. Evidence supporting other therapies for motor and nonmotor features is less well established.

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Parkinson disease is a chronic, progressive disease affecting 1% of the population older than 60 years[1] (**Table 1**). The disease course varies considerably, with those diagnosed early in adulthood living longer with the disease than those diagnosed later in life.[3]

Loss of dopamine-secreting neurons within the substantia nigra and presence of Lewy bodies are the major pathological findings in Parkinson disease. Early in the disease course, dopamine deficiency is the predominant neurochemical abnormality. As the disease progresses, involvement of nondopaminergic brain regions results in levodopa-resistant motor and nonmotor symptoms.

COMTI *catechol-O-methyltransferase inhibitor*

DDS *dopamine dysregulation syndrome*

ICD *impulse control disorders*

LCIG *levodopa-carbidopa intestinal gel*

MAOBI *monoamine oxidase type B inhibitors*

PDD *Parkinson disease dementia*

Although Parkinson disease is incurable, therapies can improve quality of life for many years. We discuss the pharmacological management of important motor and nonmotor features of Parkinson disease (**Table 2**) and adverse effects of therapy (**Table 3**). The **Box** provides definitions for commonly used terms.

Methods

Search

References were identified using searches of PubMed between January 1985 and February 2014 for English-language human studies and the full database of the Cochrane Library. The search strategy and search results are provided in the eAppendix in the Supplement.

Study Classification

Studies were classified using the American Academy of Neurology (AAN) Classification Scheme Requirements for Therapeutic Questions and rated on quality of evidence: class I (CI) and class II (CII) relate to randomized clinical trials (RCTs), class III (CIII) indicates other controlled trials, and class IV (CIV) indicates other[7] (eTable 1 in the Supplement). The AAN Classification of Recommendations guidelines[8] (eTable 2 in the Supplement) were used to provide a level of recommendation (A = established effective; B = probably effective; C = possibly effective; U = data inadequate or conflicting) for each therapy. Randomized clinical trials were arbitrarily classified by size: those with 50 or fewer participants were considered small, those with 51 to 200 were intermediate, and those with more than 200 participants were designated as large.

Study Inclusion

Meta-analyses and individual RCTs fulfilling criteria for the highest quality of evidence (CI and CII) were primarily included, but if few or none were identified for a topic, then lower-quality evidence was reviewed. Published guidelines for management of Parkinson disease were also included. All nonpharmacological studies and studies on ergot dopamine agonists (bromocriptine, cabergoline, lisuride, and dihydroergocryptine) and piribedil (unavailable in North America) were excluded.

Table 1. Epidemiology of Parkinson Disease

Epidemiological Features	Details
Mean age of onset, y[124]	65
Men:women[125]	1.5:1
Incidence, per 1000 person-years[125]	
Patients aged 55-65 y	0.3
Patients ≥85 y	4.4
Prevalence, %[123]	
Total population	0.3
Patients >60 y	1
Idiopathic:hereditary, %[126]	90:10
Life expectancy[2]	Varies with age of onset and occurrence of dementia
Clinical subgroups, %[127]	
Tremor-dominant	8
Akinetic-rigid	26
Mixed	66
Parkinson disease protective factors[128]	Cigarette smoking, high coffee consumption
Parkinson disease risk factors[2]	Family history of Parkinson disease, pesticide exposure, head injury, constipation[a]

[a] Constipation may actually be an early symptom rather than a risk factor.

Results

Initiation of Therapy for Motor Symptoms in Early Parkinson Disease

There are no established disease-modifying or neuroprotective therapies.[9] Medication should be initiated when patients experience functional impairment or social embarrassment from their symptoms. **Figure 1** illustrates mechanisms of action of available medications. Initial therapy selection typically depends on a patient's specific symptoms and age (**Table 4**; **Figure 2**, **Figure 3**, **Figure 4**).

If motor symptoms are mild but require therapy, before moving to more potent treatment such as a dopamine agonist or levodopa, a monoamine oxidase type B inhibitor (MAOBI; selegiline or rasagiline) may be tried. A meta-analysis of MAOBIs in early Parkinson disease demonstrated a small symptomatic benefit.[10] A potential disease-modifying effect of rasagiline (1 mg-dose) has been reported[11] (1 large CI study) but not confirmed by additional clinical trial evidence.

A 2003 Cochrane review involving 9 heterogeneous studies determined that anticholinergic medications are more effective than placebo for improving motor function in Parkinson disease, but data on their benefits for tremor (generally considered their main indication) were inconclusive.[12,13] Lower-quality, older studies suggest that β-blockers may improve parkinsonian tremor and motor function. Propranolol is used most often.[12,14-17] Clozapine has been shown to improve Parkinson disease tremor (1 CII, 2 CIII, and 2 CIV studies)[12,18]; this is used exclusively for bothersome or disabling tremor resistant to other therapies.

Evidence supporting amantadine for treatment of Parkinson disease (6 small CIII RCTs) is mixed. A 2009 Cochrane review concluded that there is insufficient evidence for its efficacy due to poor study quality,[19] whereas expert opinion from the International Parkinson and Movement Disorder Society and European Federation of Neurological Societies concluded that amantadine is likely efficacious for symptomatic monotherapy and adjunct therapy.[12,20]

Table 2. Main Motor and Nonmotor Symptoms of Parkinson Disease

Features	Timing	Frequency, %[a]
Primary motor symptoms		
Rest tremor[b]	At diagnosis or later	~ 70 at diagnosis
Bradykinesia	At diagnosis	All[c]
Rigidity	At diagnosis or later	~ 90
Early nonmotor symptoms		
Hyposmia	May precede diagnosis	25-97
Fatigue	May precede diagnosis	~ 60
Depression	May precede diagnosis	~ 25
Rapid eye movement sleep behavior disorder (RBD)	May precede diagnosis by 15 y or more[4]	~ 30
Constipation	May precede diagnosis	~ 30
Late symptoms		
Treatment-resistant axial symptoms	5-10 y after symptom onset	
Freezing/postural instability/falls	.	~ 90 by 15 y
Dysphagia		~ 50 by 15 y
Psychiatric disturbances	5-10 y after symptom onset	
Anxiety		~ 55
Autonomic disturbances	5-10 y after symptom onset	
Postural lightheadedness		~ 15
Sialorrhea		~ 30
Urinary urgency		~ 35
Nocturia		~ 35
Sexual dysfunction		~ 20
Cognitive impairment:	Likelihood increases with time since symptom onset	
Mild cognitive impairment		~ 35 at diagnosis, 50 after 5 y
Dementia		>80 at 20 y after diagnosis

[a] Frequency of symptoms are estimated from a composite of studies.[129-133]

[b] Some patients can present with an isolated parkinsonian rest tremor, but without bradykinesia the diagnosis of Parkinson disease cannot be made clinically.

[c] Based on the UK Parkinson Disease Society Brain Bank Clinical Diagnostic Criteria, bradykinesia is essential for the diagnosis of Parkinson disease.

For those with more severely impaired activities of daily living, levodopa or a dopamine agonist is usually initiated. Multiple large CI trials demonstrate that levodopa provides the greatest symptomatic benefit for Parkinson disease[12] and is associated with less freezing, somnolence, edema, hallucinations, and risk of impulse control disorders (ICDs) than dopamine agonists. However, dopamine agonists are also efficacious in early Parkinson disease[21] and are less likely than levodopa to cause dopaminergic motor complications, particularly dyskinesia.[22,23] Because younger age-of-onset of Parkinson disease is a risk factor for dyskinesia,[24] dopamine agonists are usually introduced as initial treatment for patients younger than 60 years. However, there is increasing evidence in open-label, observational, naturalistic follow-up studies that the early advantage of dopamine agonists over levodopa diminishes over time (approximately 10 years).[25-27]

Our experience supports the approaches outlined above and in Figure 2, Figure 3, and Figure 4. In patients with mild symptoms, we begin with a lower potency medication, such as an MAOBI, which may have a milder adverse effect profile and often a less frequent dosing regimen. Serotonin syndrome is a theoretical risk when using MAOBIs concurrently with another serotonergic medication. As Parkinson disease progresses, medication should be adjusted to obtain optimal symptom control. In addition to the diminishing benefits of initial dopamine agonist therapy in delaying dyskinesia after age 60, greater predisposition to cognitive and psychiatric adverse effects with age also influences treatment choices. Elderly patients, especially those with preexisting cognitive dysfunction, are at greater risk of developing psychiatric adverse effects. Thus, in older patients, the risk to benefit ratio favors levodopa compared with dopamine agonists and alternative therapies.

Managing Motor Fluctuations

Managing Symptom Reemergence Between Medication Doses

Strategies for reducing the time that medication is not optimally effective ("off" time) include increasing the dosage of dopaminergic medication, adding another dopaminergic medication, dividing the levodopa dosage into smaller but more frequent doses (levodopa dose fractionation), or adding a catechol-O-methyltransferase inhibitor (COMTI) or MAOBI to inhibit the breakdown of levodopa and dopamine and prolong their effects.[28] Few trials have compared these therapeutic options. Rasagiline (an MAOBI) and entacapone (a COMTI) were not significantly different in reducing off time in 1 large CI study,[29] and a subsequent substudy provided evidence that

Table 3. Adverse Effects of Dopaminergic Treatment[a]

Symptom	Adverse Effect	Time to Onset After Treatment Initiation	Frequency, %[b]
Motor complications	Motor fluctuations	3-5 y	~ 40 by 4-6 y; ~ 70 by ≥9-15 y
	Dyskinesia	3-5 y	~ 35 by 4-6 y; >85 by ≥9-15 y
Impulsive and compulsive behaviors	Impulse control disorders	Any time	~ 15
	Dopamine dysregulation syndrome	Any time	Up to 4
	Punding	Any time	Up to ~ 15
Nausea		Immediate	~ 15
Hallucinations		Generally later in disease course; earlier in older patients	>70 by 20 y

[a] See Box for definitions of uncommon terms.

[b] Frequency of symptoms estimated from a composite of studies.[133-136]

adjunct rasagiline is more effective than entacapone at reducing the severity of motor symptoms in the off time.[30] A CII, open-label trial showed no significant difference in reduced off time, rate of motor complications, or daily levodopa dose with entacapone compared with levodopa dose fractionation.[31]

In most available CI (2 large) and CII (2 large and 3 intermediate) studies, entacapone and tolcapone (COMTIs) significantly reduced off time compared with placebo and baseline and had similar adverse effects, such as nausea, diarrhea, orthostatic hypotension, and dyskinesia.[28,32,33] These 2 COMTIs have not been directly compared, but a "switching" study[34] (a double-blind study in which patients taking entacapone were randomized to stay on entacapone or switch to tolcapone) and uncontrolled evidence support greater efficacy of tolcapone.[35,36] However, hepatic monitoring is necessary due to rare cases of fatal hepatotoxicity with tolcapone.[37]

There is extensive, conflicting evidence for use of selegiline (a MAOBI) to reduce off time.[21,38] Orally disintegrating selegiline significantly reduced off time compared with placebo in 1 intermediate CII study,[39] but not in an intermediate CI study.[40] Adjunct rasagiline decreased daily off time in 2 large CI studies.[29,41]

Dopamine agonists may be added to levodopa to reduce off time. Adjunctive pramipexole, ropinirole (including their extended- and prolonged-release formulations), and transdermal rotigotine (24-hour continuous delivery) significantly reduced off time compared with placebo (in at least 1 large CI study each and several intermediate CII studies)[20,21,28]. Prolonged-release ropinirole was more efficacious in maintaining a 20% or more reduction in off time compared with immediate-release ropinirole (1 large CI study)[42] and there was no significant difference in benefit between rotigotine and pramipexole for the outcome of wearing-off–type motor fluctuations (1 large CI study).[43] Intermittent, as needed, subcutaneous apomorphine provides rapid delivery to reduce bothersome off periods (1 small CII study), but may increase dyskinesia.[28] A retrospective review of patients receiving continuous subcutaneous apomorphine infusion also demonstrated a significant reduction in off time compared with the patients' baseline.[44]

Controlled-release levodopa-carbidopa does not reduce off time more than immediate-release levodopa-carbidopa (4 small CIII trials).[28] However, a new extended-release, levodopa-carbidopa formulation reduced off time compared with the immediate-release formulation in 1 large CI study.[45] An intermediate CI study of levodopa-carbidopa intestinal gel (LCIG), administered directly into the duodenum by pump through a gastrostomy catheter, confirmed early, small, open-label studies showing a marked reduction in off time.[21,46,47]

Management of Dyskinesia

It is unnecessary to treat mild nontroublesome dyskinesia. Dopaminergic medication reduction strategies will reduce dyskinesia but typically worsen parkinsonism.[48] Amantadine is frequently used for reducing dyskinesia severity and duration (1 small CI, 1 small CII, and several lower-quality studies),[28,49-51] and is usually well tolerated. Clozapine has been shown to improve dyskinesia (1 small CIII study).[21] Levodopa-carbidopa intestinal gel may be useful in the future, and exploratory trials of other agents are ongoing.

In our experience, levodopa-related wearing-off–type motor fluctuations respond, to a variable extent, to all of the reviewed therapeutic options, and, when 1 is suboptimally effective, 1 or more alternatives may be combined with greater success. Some patients require a combination of 3 or 4 different types of medications. Amantadine can be extremely effective in managing dyskinesia and efficacy is generally retained in the long-term despite common concerns about tachyphylaxis.[52] It is important to regularly reevaluate the ongoing efficacy and need for various drugs, although levodopa remains the mainstay of treatment for all patients. We do not routinely use controlled-release levodopa-carbidopa and usually discontinue this in patients with motor complications given its unreliable pharmacokinetics, although when administered at bedtime it may provide better overnight Parkinson disease symptom control when nighttime symptoms are problematic. Levodopa-carbidopa intestinal gel appears promising in the management of carefully selected patients with disabling motor fluctuations.

Box. Definitions of Common Parkinson Disease–Related Terms

"On" period: Periods when the patient experiences a good response to medication

"Off" period: Periods when benefit from Parkinson disease medications wears off and symptoms reemerge (wearing-off–type motor fluctuations)

Motor fluctuations: Alterations between on and off periods

Dyskinesia: Involuntary, nonrhythmic choreic or choreo-dystonic movements most often related to peak dopamine levels; they can lead to social embarrassment, impaired motor function, injury, and weight loss

Rapid eye movement (REM) sleep behavior disorder: Characterized by the loss of muscle atonia during REM sleep resulting in acting out of dreams, often with aggressive or violent behavior, sometimes resulting in injury to the patient or his/her bed partner

Impulse control disorders: Include pathological gambling, hypersexuality, binge eating, and compulsive shopping

Dopamine dysregulation syndrome: A form of addictive behavior with the compulsive overuse of dopaminergic medications (typically shorter-acting medications, such as levodopa and apomorphine) impairing physical, social, and occupational functioning[5]

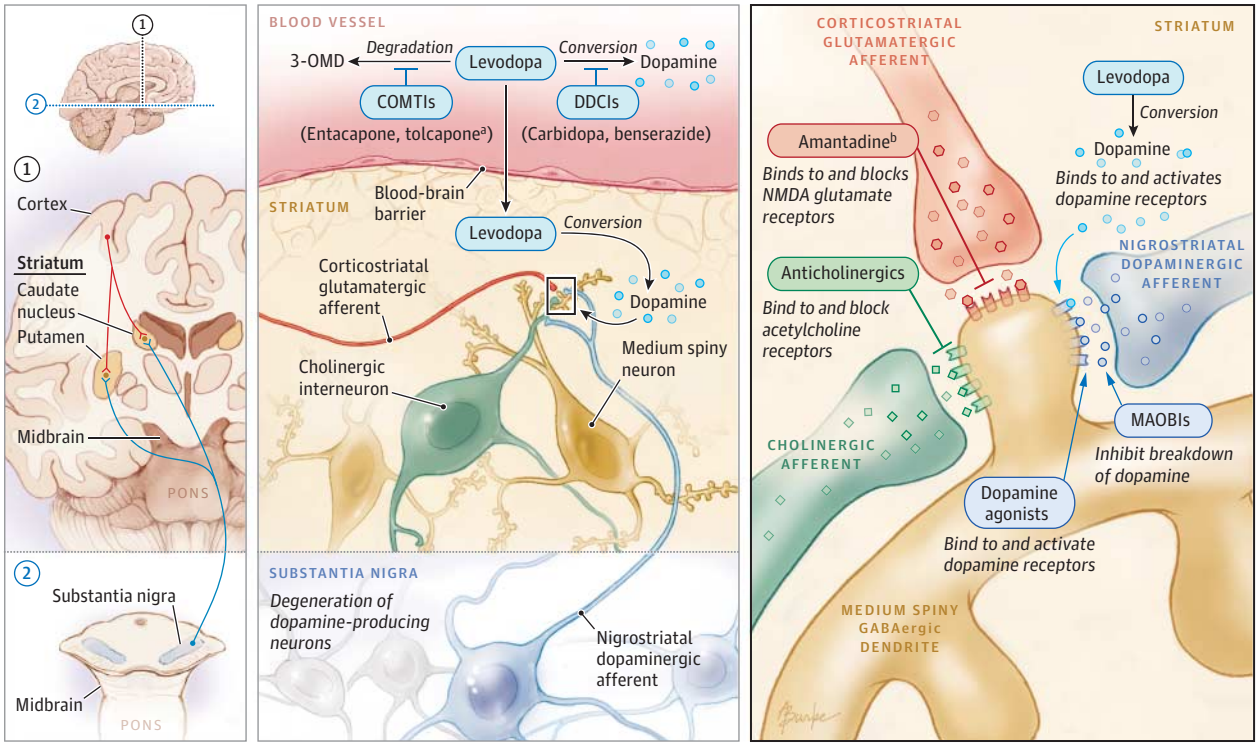
Punding: Repetitive, often purposeless, stereotyped behaviors, such as sorting or disassembling[6]

Management of Other Medication Adverse Effects

Nausea

Nausea is a frequent, generally transient adverse effect of dopaminergic therapy. Slow titration of dopaminergic therapy and medication administration with food can reduce nausea. However, in the long-term, food may delay gastric emptying, and dietary protein may interfere with levodopa absorption.[53] The dopa decarboxylase inhibitors carbidopa and benserazide prevent peripheral conversion of levodopa to dopamine. An additional dose of carbidopa 30 minutes before the regular levodopa preparation may abolish levodopa-induced (but not dopamine agonist–induced) nausea.[54] Domperidone, a peripheral dopamine D_2-receptor antagonist (unavailable in the United States), reduced nausea from dopaminergic medications in several small CIII and CIV studies.[55,56] Trimethobenzamide has also been used for the same purpose.[57] Metoclopramide, prochlorperazine, and promethazine can worsen parkinsonian symptoms and should be avoided.

Figure 1. Schematic Illustration of Neurologic Pathways Affected in Parkinson Disease and Sites of Action of Medications for the Treatment of Motor Symptoms



Available medications to treat the motor symptoms of Parkinson disease act on complex neurologic interactions in the striatum that affect motor activity. Dopaminergic afferents from the substantia nigra, glutamatergic afferents from the cerebral cortex and thalamus, and cholinergic striatal interneurons all converge to influence the activity of the main efferent neurons of the striatum, the medium spiny GABAergic neurons. Levodopa is transported from the peripheral circulation across the blood-brain barrier and is converted centrally to dopamine, replacing the neurotransmitter deficient in Parkinson disease. Outside the blood-brain barrier, in the peripheral circulation, dopamine decarboxylase inhibitors (DDCIs) block the conversion of levodopa to dopamine, and catechol-O-methyltransferase inhibitors (COMTIs) block its degradation to 3-O-methyldopa (3-OMD). In the striatum, levodopa, dopamine agonists, and monoamine oxidase type B inhibitors (MAOBIs) all have dopaminergic effects. Anticholinergic drugs and amantadine act on postsynaptic receptors for other neurotransmitters in the striatum. These neurotransmitters bind to and activate multiple different subtypes of receptors present on the various presynaptic afferents in the striatum, as well as on postsynaptic efferent medium spiny neurons. NMDA indicates *N*-methyl-D-aspartate.

[a] Tolcapone, unlike entacapone, is able to cross the blood-brain barrier and block degradation of levodopa and dopamine.

[b] Amantadine has dopamine releasing effects in addition to affecting NMDA glutamate receptors.

Impulsive and Compulsive Behaviors Including ICDs, Dopamine Dysregulation Syndrome, and Punding

Impulse control disorders are typically, but not exclusively, associated with dopamine agonist use.[58] A history of obsessive-compulsive disorder, impulsive personality, or addictive behaviors increases the likelihood of ICDs.[59] Given the effect of ICDs, these need to be discussed on initiation of a dopamine agonist and monitored regularly. Dopamine agonist dose reduction or discontinuation, potentially offset by increasing levodopa, is a generally effective treatment of ICDs.[60-62] Withdrawal symptoms including anxiety, depression, fatigue, pain, orthostatic hypotension, and drug cravings (the dopamine agonist withdrawal syndrome) unresponsive to increasing levodopa may occur in 15% to 20% of patients.[63]

Zonisamide markedly reduced the severity of impulsive behaviors and global impulsiveness refractory to dopaminergic medication dose reduction in a small CIII study.[64] Amantadine improved pathological gambling resistant to dopamine agonist dose reduction or withdrawal or behavioral strategies in 1 small CII study.[65] In small case series (1 CIV study each), topiramate[66] and valproate[67] were effective.

Management of dopamine dysregulation syndrome (DDS) typically involves a gradual reduction of levodopa and immediate discontinuation of "booster" doses of medications (such as subcutaneous apomorphine boluses and rapid-acting levodopa formulations).[5] No studies have formally examined management of DDS, but in a small case series of 4 patients (1 CIV study), all 4 responded to valproate.[68]

Improvement of punding may follow reduction or cessation of dopaminergic medication; amantadine and quetiapine may also be beneficial (1 small open-label, prospective, CIII study).[69]

Psychosis

Hallucinations are both a feature of later-stage Parkinson disease and a consequence of Parkinson disease medication, whereas additional psychotic symptoms are generally drug-related. Clozapine and quetiapine have been most extensively studied for the treatment of psychosis in Parkinson disease given the propensity of other neuroleptics to worsen parkinsonism. Clozapine is consistently efficacious (1 intermediate CI study and 1 intermediate CII study [both with open-label extensions of the study treatment use] and 2 comparative studies

Table 4. Treatment of Motor Symptoms of Parkinson Disease

Medication Class	Efficacy[a]	Dosage	Level of Recommendation[b]		Indication	Adverse Effects
			Monotherapy[c]	Adjunct Therapy		
Levodopa-PDDI						
Levodopa-carbidopa	1	Titrate to initial dose of 100/25 mg thrice daily; max, 1500/375 mg/d or more based on symptoms	A	A	All motor symptoms	Nausea, orthostatic hypotension, dyskinesia, and hallucinations
Levodopa-benserazide	1	Titrate to initial dose of 100/25 mg thrice daily; max, 1500/375 mg/d or more based on symptoms	A	A	All motor symptoms	Same as levodopa-carbidopa
Dopamine agonists						
Pramipexole	2	Start 0.125 mg thrice daily; max, 4.5 mg/d	A	A	All motor symptoms	Nausea, orthostatic hypotension, hallucinations, ICDs, edema, and increased sleepiness (including sleep attacks)
Pramipexole extended release	2	0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg, or 3.15 mg once daily	A	A	All motor symptoms	Same as pramipexole
Ropinirole	2	Start 0.25 mg thrice daily; max, 24 mg/d	A	A	All motor symptoms	Same as pramipexole
Ropinirole prolonged release	2	6-24 mg once daily	A	A	All motor symptoms	Same as pramipexole
Rotigotine	2	Start 2 mg/24 h; max, 16 mg/24 h	A	A	All motor symptoms	Same as pramipexole
MAOBIs						
Selegiline	3	2.5 mg once daily; max, 5 mg twice daily	A	U	Early, mild symptoms, and MF	Stimulant effect, dizziness, headache, confusion, and exacerbation of levodopa adverse effects
Rasagiline	3	1 mg once daily	A	A	Early, mild symptoms, and MF	Headache, arthralgia, dyspepsia, depression, flulike syndrome, exacerbation of levodopa adverse effects, and constipation
COMTIs						
Entacapone	3	200 mg with each dose of levodopa; max, 8/d		A	MF	Dark-colored urine and exacerbation of levodopa adverse effects
Tolcapone	3	100-200 mg thrice daily		A	MF	Dark-colored urine, exacerbation of levodopa adverse effects, and hepatotoxicity
Unspecified						
Amantadine	4	Start 100 mg once daily; max, 4 times daily (thrice daily is typical)	U	C	Gait dysfunction and dyskinesia	Hallucinations, confusion, blurred vision, ankle edema, livedo reticularis, nausea, dry mouth, and constipation
β-Blocker						
Propranolol	5	Start 40 mg twice daily; max, 320 mg/d	U	U	Tremor	Fatigue and dizziness
Anticholinergic						
Trihexyphenidyl	4	Start 1 mg once daily; typical maintenance dose 2 mg thrice daily	U	U	Tremor	Hallucinations, CI, nausea, dry mouth, blurred vision, urinary retention, and constipation
Benztropine	4	Start 0.5-1 mg once daily; usual dose 1-2 mg thrice daily	U	U	Tremor	Same as trihexyphenidyl
Neuroleptic						
Clozapine	Undetermined[d]	Start 6.25-12.5 mg at bedtime; max, 150 mg/d		C for tremor; U for dyskinesia	Tremor and dyskinesia	Agranulocytosis, myocarditis, seizures, sedation, and orthostatic hypotension

Abbreviations: CI, cognitive impairment; COMTIs, catechol-O-methyltransferase inhibitors; ICDs, impulse control disorders; MAOBIs, monoamine oxidase type B inhibitors; MF, motor fluctuations; PDDI, peripheral dopa decarboxylase inhibitor.

[a] Efficacy scored from 1 (most effective) to 5 (least effective).

[b] Level of recommendation is based on the number and strength of studies (as defined by American Academy of Neurology classes I-IV as outlined in eTable 1 in the Supplement) available: A = established effective; B = probably effective; C = possibly effective; U = data inadequate or conflicting.[137]

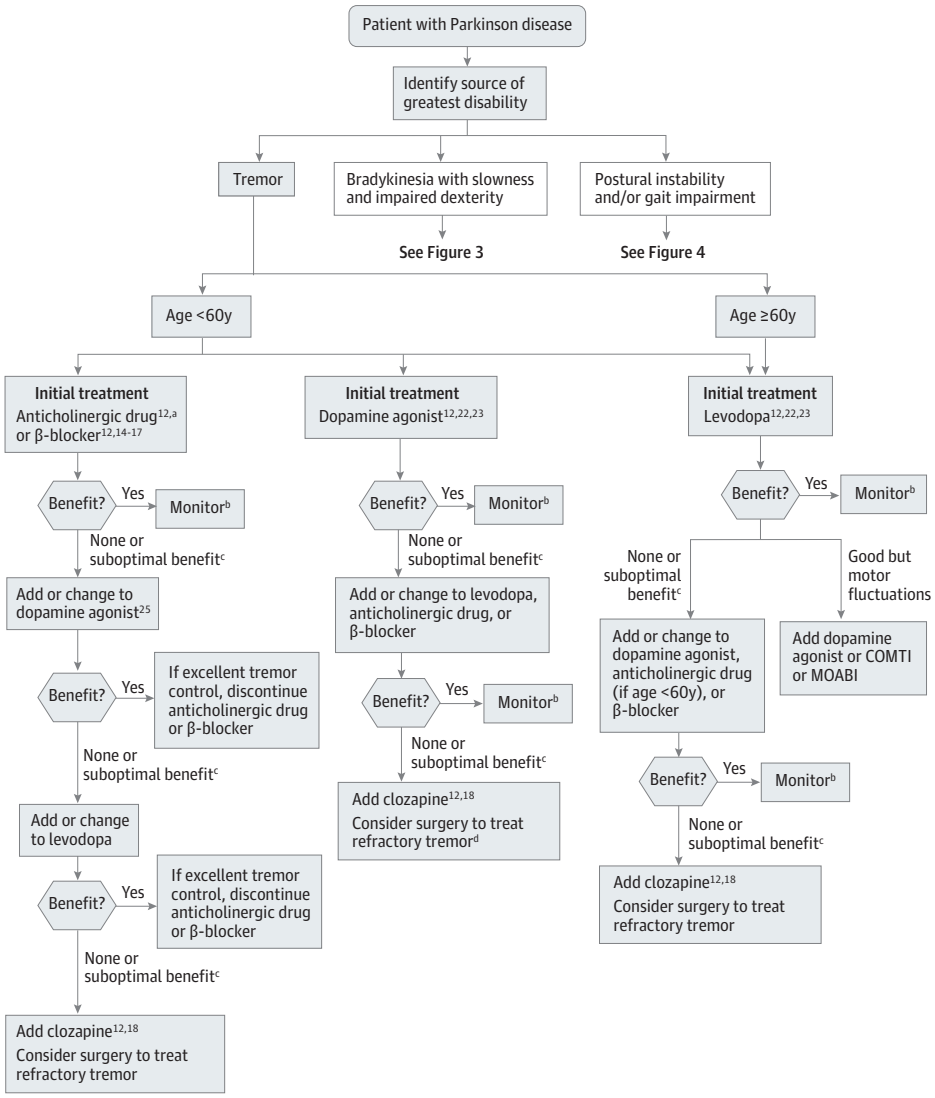
[c] Cells are left empty when medication is not used as monotherapy.

[d] Refers only to the indeterminate efficacy of clozapine for tremor (not hallucinations or dyskinesia).

[small CII and CIII]), whereas results for quetiapine are mixed (4 negative blinded RCTs [1 small CI, 2 small CII, and 1 intermediate CII] and 1 positive blinded RCT [small CII], and varied results in comparative studies with clozapine).[12,70-73] However, quetiapine is often prescribed first because of the risk of agranulocytosis and the requirement for frequent blood monitoring with clozapine.

Olanzapine was found in 2 CII studies (1 small and 1 intermediate) to be ineffective for hallucinations and may cause motor deterioration,[72] and another study was stopped early for these reasons[74]; therefore, olanzapine should not be used for Parkinson disease.[72] Similar motor deterioration has been observed with risperidone and aripiprazole.[75]

Figure 2. Algorithm for the Treatment of Parkinson Disease With Tremor-Dominant Motor Symptoms



[a] Anticholinergic use is anecdotal and not supported by randomized clinical trials.

[b] If the patient experiences inadequate symptom control while on current therapy and there was more than 1 treatment option in the previous step, go back to previous step and try an alternate treatment option. If all options in the previous step fail to provide adequate symptom control, move to the next step in the algorithm.

[c] Suboptimal benefit is defined as improvement in parkinsonian symptoms following initiation of therapy, but the patient still experiences a bothersome or disabling degree of symptoms either continuously or intermittently. In these cases, increase the dose of current medication if the patient is not receiving a maximal dose or add another medication. If benefit is absent, stop the current medication and try another.

[d] Surgery for refractory tremor includes deep brain stimulation or neuroablative lesion surgery (eg, thalamotomy).

The cholinesterase inhibitor donepezil reduced hallucinations in patients with Parkinson disease without dementia (1 small CIII study),[76] and rivastigmine reduced hallucinations in those with dementia (1 intermediate CII study).[77] Ziprasidone was effective for psychosis in Parkinson disease in 2 small CIII studies.[78,79]

In our experience, the treatment options outlined above will almost always adequately control gastrointestinal intolerance and it is extremely rare for gastrointestinal symptoms to limit the use of therapeutically effective doses of levodopa. Most problematic ICDs can be successfully managed. Involvement of caregivers, family, and friends to limit the patient's access to money, Internet sites, food, or casinos, is often helpful. In some patients, ICDs are refractory, especially when symptoms of dopamine agonist withdrawal syndrome occur. We do not use amantadine for pathological gambling because ICDs may be more common in patients taking this drug, and we have seen them develop as a consequence of adding amantadine to levodopa. Management of DDS is extremely challenging and an expert in addiction management should assist in the care of these patients. Hospital admission may be required if prominent mood symptoms, hypomania, or psychotic episodes develop. In many patients, punding behavior can be monitored without treatment; however, when symptoms become disruptive and the patient is only taking levodopa in a dose required to maintain motor control, treatment is often unsatisfactory.

Our approach to new-onset or increased hallucinations includes initial exclusion of systemic illness (such as infection) or other medication use.[80] We then reduce or discontinue antiparkinsonian drugs in order from lowest efficacy, starting with anticholinergics, amantadine, and MAOBIs, followed by dopamine agonists and COMTIs.[81] Finally, the levodopa dose is cautiously reduced and the patient is monitored for a disabling increase in parkinsonism, including the rare occurrence of a neuroleptic malignantlike state. Quetiapine and clozapine can help to avoid these outcomes; clozapine clearly has the highest efficacy for hallucinations and psychosis. Cholinesterase inhibitors may reduce halluci-

nations, but generally not other psychotic symptoms. A very recent intermediate CI study showing efficacy for the selective serotonin 5-HT_{2A} inverse agonist pimavanserin for psychotic symptoms[82] provides new promise for future therapies not requiring extensive monitoring.

Management of Selected Nonmotor Symptoms

Rapid Eye Movement Sleep Behavior Disorder

Clonazepam is a first-line therapy for rapid eye movement sleep behavior disorder (RBD),[83] but only case reports and case series are available on its use in Parkinson disease patients.[84] Similarly, there is little evidence for melatonin specifically in patients with Parkinson disease, but 1 small CI RCT showed benefit in patients with RBD who were not diagnosed with Parkinson disease.[84,85] Rivastigmine improved the frequency of RBD episodes in 1 small CI study.[86]

We prescribe melatonin for patients who do not tolerate clonazepam or as a first-line therapy for patients with relative contraindications to clonazepam (such as dementia, obstructive sleep apnea, and extreme frailty with an increased risk of falls).[84]

Depression

The literature on treatment of depression in Parkinson disease is mixed. A 2013 systematic review and meta-analysis assessed 6 RCTs (2 small CI, 1 intermediate CI, 1 intermediate CII, 2 small CIII) of antidepressants for depression in patients with Parkinson disease (involving sertraline, citalopram, paroxetine, venlafaxine, desipramine, and nortriptyline).[87] There was no statistically significant superiority of antidepressants compared with placebo, as a group or by class, but tricyclic antidepressants were superior to selective serotonin receptor inhibitors (SSRIs; 2 studies[88,89]). However, a sensitivity analysis that excluded studies with questionable results, high risk of bias (3 of 6 studies), or both found antidepressants to be efficacious. Two other recent meta-analyses showed no significant pooled effect of antidepressants and insufficient evidence to support use of SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), or pramipexole, but tricyclic antidepressants were found more efficacious than placebo.[90,91] All 3 studies (large CI, intermediate CII, small CIII)[92-94] assessing pramipexole for depression in patients not requiring further treatment of motor symptoms were positive, but only the largest was placebo-controlled.

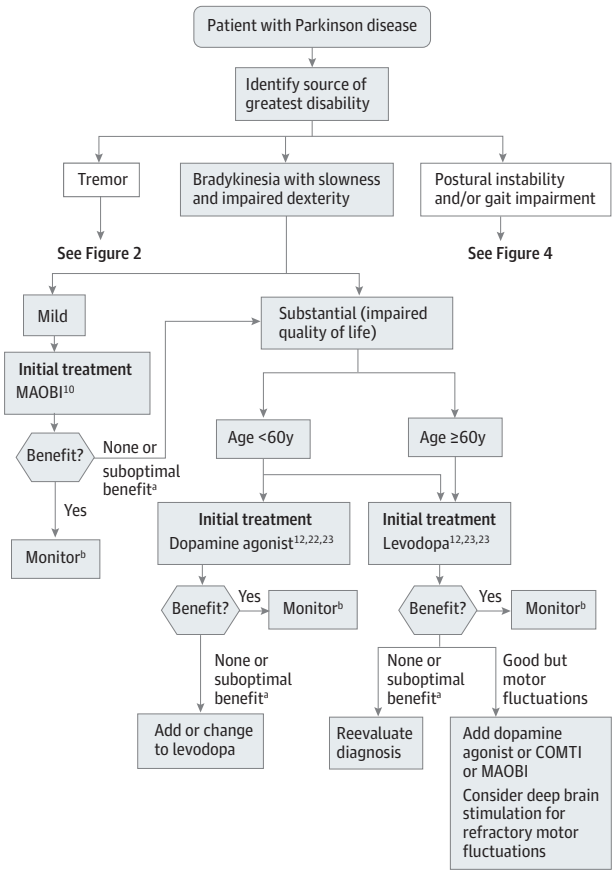
Although evidence is lacking for the use of specific SSRIs and SNRIs to treat patients with Parkinson disease–related depression, in our experience, both can be effective for this indication. Sertraline, escitalopram, citalopram, and extended-release venlafaxine are commonly used due to familiarity and low likelihood of major adverse effects. Although we find tricyclic antidepressants, in particular nortriptyline and desipramine, effective, they are used less frequently due to concerns about adverse effects in older patients who are cognitively impaired. Pramipexole is an option, especially when both motor and mood symptoms are being targeted.

Cognitive Impairment

Patients with Parkinson disease often develop mild cognitive impairment and may progress to Parkinson disease dementia (PDD). Few studies have assessed treatment of mild cognitive impairment in patients with Parkinson disease. A small CIV pilot study of atomoxetine in patients with Parkinson disease and executive dysfunction demonstrated a clinically significant improvement and a small CII study of atomoxetine for treatment of depression in patients with Parkinson disease reported improvements in global cognitive performance.[95,96]

Cholinergic dysfunction may be partially responsible for the cognitive impairment seen in the majority of patients with Parkinson disease over time.[97] There are no published studies of cholinesterase inhibitors for Parkinson disease–related mild cognitive impairment, but a phase 4 RCT of the rivastigmine transdermal patch is currently under way (NCT01519271) and a study of donepezil for patients with Parkinson disease–related mild cognitive impairment and PDD is planned (NCT01014858). Rasagiline improved some measures of attention and verbal fluency in patients with Parkinson disease and mild cognitive impairment (1 intermediate CII study), sug-

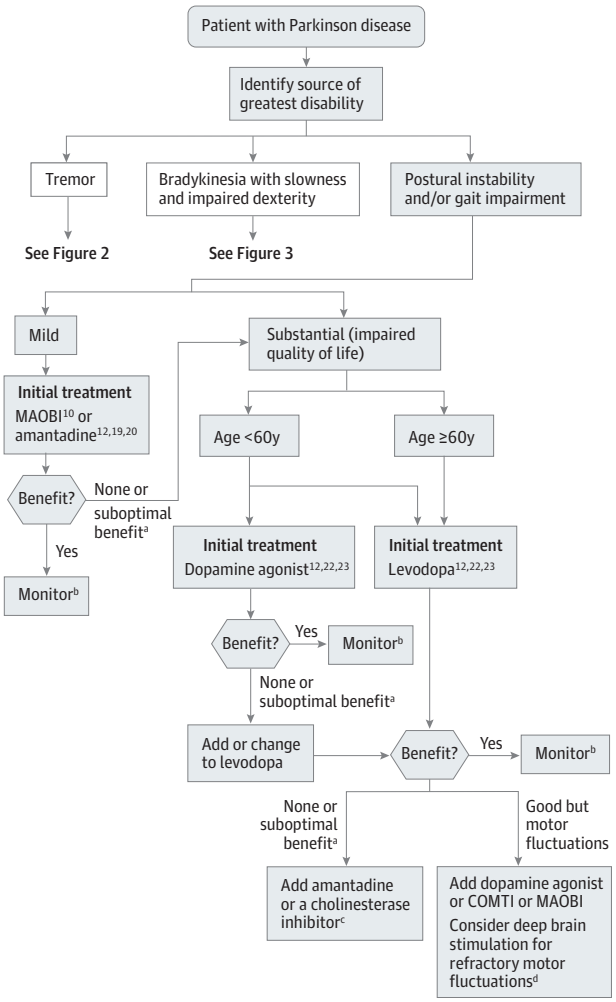
Figure 3. Algorithm for the Treatment of Parkinson Disease With Predominant Bradykinesia and Impaired Dexterity



[a] Suboptimal benefit is defined as improvement in parkinsonian symptoms following initiation of therapy, but the patient still experiences a bothersome or disabling degree of symptoms either continuously or intermittently. In these cases, increase the dose of current medication if the patient is not receiving a maximal dose or add another medication. If benefit is absent, stop the current medication and try another.

[b] If the patient experiences inadequate symptom control while on current therapy and there was more than 1 treatment option in the previous step, go back to previous step and try an alternate treatment option. If all options in the previous step fail to provide adequate symptom control, move to the next step in the algorithm.

Figure 4. Algorithm for the Treatment of Parkinson Disease With Predominant Postural Instability and Gait Impairment



[a] Suboptimal benefit is defined as improvement in parkinsonian symptoms following initiation of therapy, but the patient still experiences a bothersome or disabling degree of symptoms either continuously or intermittently. In these cases, increase the dose of current medication if the patient is not receiving a maximal dose or add another medication. If benefit is absent, stop the current medication and try another.

[b] If the patient experiences inadequate symptom control while on current therapy and there was more than 1 treatment option in the previous step, go back to previous step and try an alternate treatment option. If all options in the previous step fail to provide adequate symptom control, move to the next step in the algorithm.

[c] Persistent ambulatory problems including freezing, postural instability, and falls despite optimal dopaminergic therapy are generally refractory to other treatments. Trials of amantadine or a cholinesterase inhibitor, added to ongoing dopaminergic therapy for other symptoms of Parkinson disease, can be considered.

[d] Consider deep brain stimulation if motor fluctuations are refractory to medical therapy and postural instability and/or gait impairment remains responsive to levodopa.

gesting a favorable benefit on executive function.[98] A longer-term study is ongoing (NCT013823420).

A recent Cochrane review found that cholinesterase inhibitors are associated with improvements in global assessment, cognitive function, behavioral disturbance, and activities of daily living in patients with PDD.[99] Five placebo-controlled trials have assessed cholinesterase inhibitors for PDD.[70,100] Rivastigmine moderately improved measures of dementia, cognition, and behavioral symptoms (1 large CII trial). Three small studies of donepezil (2 CI and 1 CII) showed variable benefit, whereas 1 large CII study did not achieve its predefined primary end points, but secondary outcomes suggested that donepezil may improve cognition, executive function, and global status in PDD.[100] There are no blinded RCTs of galantamine for PDD, but 1 small, open-label CIII study suggested benefit. Conflicting data exist for the use of memantine, a *N*-methyl-D-aspartate receptor antagonist, in PDD.[70]

In our experience, achieving clinically meaningful benefit with cholinesterase inhibitors in PDD is variable and unpredictable. Still, the response in some patients can be striking; therefore, a trial is warranted. However, exacerbation of tremor can limit their use. Gastrointestinal symptoms can also be problematic and the rivastigmine transdermal patch is generally better tolerated than the oral formulation. Response to memantine has been disappointing.

Orthostatic Hypotension

Orthostatic hypotension can be a major problem in Parkinson disease and should be regularly evaluated. Orthostatic hypotension can be an inherent component of Parkinson disease as a manifestation of autonomic dysfunction, but it can also be an adverse effect of dopaminergic medication. One small CII study reported improvement in symptoms of orthostatic hypotension and clinical global impression, focusing on orthostasis with use of fludrocortisone or domperidone compared with nonpharmacological measures; although not all participants had orthostatic hypotension at baseline.[101]

Midodrine was evaluated for treating neurogenic orthostatic hypotension in 3 studies (2 intermediate CI and 1 small CII) that included patients with Parkinson disease,[102-104] and a small CIII trial of pyridostigmine for orthostatic hypotension included 3 patients with Parkinson disease.[105] Results were positive, but patients with Parkinson disease were not analyzed separately. A small crossover trial of yohimbine for orthostatic hypotension in patients with Parkinson disease was negative,[106] whereas a small CII comparison study of yohimbine and pyridostigmine vs placebo involving some patients with Parkinson disease demonstrated a significant improvement only for yohimbine.[107]

In a small CIII study, indomethacin significantly reduced orthostatic symptoms and drop in blood pressure with standing.[108] Droxidopa, a synthetic precursor of norepinephrine, caused an objective improvement in orthostatic hypotension but not of orthostatic hypotension symptoms in a placebo-controlled RCT in Parkinson disease and multiple system atrophy (published in abstract form only).[109]

In our experience, domperidone (not uniformly available in the United States) controls dopamine agonist–induced hypotension, especially when it occurs on the introduction of dopamine agonist treatment. It can also improve orthostatic hypotension worsened by levodopa. Before or in concert with trials of fludrocortisone and midodrine, we use nonpharmacological techniques for managing orthostatic hypotension, including increasing salt and fluid consumption, elevating the head of the bed, and compression stockings. Quickly drinking 2 8-ounce glasses of cold water can have a rapid ameliorative effect on orthostatic hypotension. Monitoring for supine hypertension is important when using antihypotensive drugs.

Table 5. Treatment of Nonmotor Symptoms of Parkinson Disease

Nonmotor Symptom	Medication	Dosage	Level of Recommendation[a]	Adverse Effects
Nausea	Domperidone[b]	10 mg thrice daily; max, 20 mg 4 times daily	U	Cardiac arrhythmia, sudden cardiac death, breast pain, drowsiness, dry mouth, headache, hot flashes, and nausea
RBD	Clonazepam	0.25-2 mg at bedtime	U	Sedation and confusion
	Melatonin	3-15 mg at bedtime	U	Daytime sleepiness, dizziness, and headache
Depression	Citalopram	10-20 mg once daily	U	Akathisia, anorexia, nausea, drowsiness, and sexual dysfunction
	Fluoxetine	10-50 mg once daily	C	Same as citalopram
	Paroxetine	20-40 mg once daily	U	Same as citalopram
	Sertraline	25-200 mg once daily (rarely >100 mg)	U	Same as citalopram
	Venlafaxine extended release	37.5-225 mg once daily	B	Drowsiness, insomnia, sexual dysfunction, and gastrointestinal symptoms
	Nortriptyline	25-150 mg/d single or divided	C	Anticholinergic effects[d], orthostatic hypotension, ventricular arrhythmias, heart block, drowsiness, sexual dysfunction, and weight gain
	Desipramine	25-150 mg/d single or divided	B	Same as nortriptyline
Hallucinations	Clozapine	6.25-150 mg at bedtime or divided (often effective in very low doses)	B	Agranulocytosis, seizure, myocarditis, cardiomyopathy, and sedation
	Quetiapine	12.5-400 mg at bedtime or divided	C	Extrapyramidal symptoms and sedation
	Rivastigmine[c]	1.5-6 mg twice daily; transdermal patch, 4.5-9.8 mg/24 h	C	Gastrointestinal symptoms, bradycardia, vivid dreams, and exacerbation of rest tremor
PD-MCI	Atomoxetine	Target dose, 80 mg once daily	U	Alopecia, dry mouth, sexual dysfunction, gastrointestinal symptoms, dizziness, and increased heart rate and blood pressure
PDD	Rivastigmine	1.5-6 mg twice daily; transdermal patch, 4.5-9.8 mg/24 h	B	Same as rivastigmine
	Donepezil	5-10 mg once daily	B	Same as rivastigmine
	Galantamine	4-12 mg twice daily	U	Same as rivastigmine
Orthostatic Hypotension	Fludrocortisone	0.05-0.1 mg once or twice daily	C	Hypertension, metabolic abnormalities (including hypokalemia), gastrointestinal symptoms, and myopathy
	Domperidone[b]	10 mg thrice daily; max, 20 mg 4 times daily	C	Same as domperidone
	Midodrine	2.5-10 mg thrice daily	U	Hypertension, nausea, weakness, heartburn, headache, scalp tingling, and chills
	Pyridostigmine	50 mg thrice daily	U	Hypertension, gastrointestinal symptoms, sweating, and increased salivation/bronchial secretions
	Indomethacin	50 mg thrice daily	U	Hypertension, edema, metabolic abnormalities, gastrointestinal symptoms, headache, and renal damage
	Yohimbine	2 mg thrice daily	U	Blood pressure changes, sexual dysfunction, hallucinations, seizure, and renal failure
	Droxidopa	300 mg thrice daily	U	Hypertension, tachycardia, nausea, vomiting, and headache
Sialorrhea	Glycopyrrolate	1 mg thrice daily	B	Anticholinergic effects[d]
	Atropine	1-2 drops of 1% concentration up to 4 times daily	U	Same as glycopyrrolate
	Ipratropium bromide	1-2 sprays (21 μg); max, 4 times daily	U	Same as glycopyrrolate
	BTA	Varies by formulation	B	Dysphagia, dry mouth, and injection-associated discomfort
	BTB	Varies by formulation	B	Same as BTA

Abbreviations: BTA, botulinum toxin type A; BTB, botulinum toxin type B; PDD, Parkinson disease dementia; PD-MCI, Parkinson disease mild cognitive impairment; RBD, rapid eye movement sleep behavior disorder.

[a] Level of recommendation is based on the number and strength (as defined by American Academy of Neurology classes I-IV as outlined in eTable 1 in the Supplement) of studies available: A = established effective; B = probably effective; C = possibly effective; U = data inadequate or conflicting.[137]

[b] Domperidone has a black box warning in the United States.

[c] Rivastigmine for hallucinations in patients with dementia.

[d] Anticholinergic effects include cognitive impairment, hallucinations, blurred vision, dry mouth, urinary retention, and constipation.

Sialorrhea

Atropine drops were effective for sialorrhea in 6 patients with Parkinson disease, but systemic adverse effects, including delirium and hallucinations, occurred (1 small CIII study).[2] Ipratropium bromide spray did not improve objective or subjective measures of drooling following 2 weeks of treatment (1 small CI study),[110] whereas glycopyrrolate significantly improved mean sialorrhea scores (1 small CI study).[111] Although a pilot study (small CI) of intraoral tropicamide film[112] failed to show benefit, a phase 2 study is currently under way (NCT01844648).

Treatment with botulinum toxin type A (BTA) injections significantly improved an objective measure of saliva quantity, measures of social embarrassment, and drooling frequency in a small CII study.[113] Benefits were also reported in 2 small RCTs (1 CI and 1 CIII) of BTA for sialorrhea in mixed populations including patients with Parkinson disease.[4,114] Botulinum toxin type B (BTB) injections reduced drooling, disability, and embarrassment related to sialorrhea (1 intermediate CI, 1 small CII, and 1 small CIV studies).[115-117] Injections of BTA and of BTB had similar effectiveness and safety in a small CII pilot study of patients with amyotrophic lateral sclerosis or Parkinson disease.[118] Dysphagia is a potential adverse effect and may limit use.

In our experience, anticholinergic drugs with relatively low central activity may be useful but are poorly tolerated in older patients with cognitive dysfunction, whereas glycopyrrolate may be very effective and better tolerated due to limited blood-brain barrier penetration. Injections of BTA can be effective and are well tolerated; standard parotid injections can be supplemented with submandibular injections for improved efficacy but have potentially more complications.

Discussion

In this review we have summarized the evidence from the literature addressing initial treatment and management of various disease- and treatment-related symptoms. Our recommendations are in agreement with several recently published guidelines on the management of Parkinson disease (eTable 3 in the Supplement). High-quality evidence is available for some treatment recommendations, for example initial therapy, but for other issues, such as management of dyskinesia, nausea, RBD, and orthostatic hypotension, data are limited. For these problems we have made recommendations based on our review of published evidence and our experience.

Levodopa is the most effective treatment for Parkinson disease. Figure 2, Figure 3, and Figure 4 provide a treatment algorithm for Parkinson disease motor symptoms based on age, symptom characteristics, and responses to treatment. Table 4 summarizes treatment options for motor symptoms including indications, level of recommendation for efficacy, doses, and adverse effects.

Many patients incorrectly believe that levodopa loses efficacy after 5 years or that it is toxic to dopamine neurons. These concerns, and a fear of developing motor complications, especially dyskinesia, often result in a "levodopa phobia." However, dyskinesia is often mild and can usually be successfully treated.[119] Age is especially important because younger patients develop dyskinesia earlier and more frequently following the initiation of levodopa, and older patients are more prone to cognitive and psychiatric adverse effects with all anti-Parkinson medication, requiring careful assessment of risk to benefit ratios. Dyskinesia and motor fluctuations that impair quality of life are indications for deep brain stimulation and this treatment should be considered in younger patients (generally <70 years) who retain a good response to individual doses of levodopa in the absence of cognitive impairment or active psychosis,[120-122] particularly before the development of intractable psychosocial impairment.

As Parkinson disease progresses, both nonmotor and motor symptoms emerge that are unresponsive to dopaminergic medication. Therapies are available for many nonmotor symptoms (**Table 5**), including cholinesterase inhibitors for PDD, antidepressants and pramipexole for depression, botulinum toxin injections for sialorrhea, and clozapine for hallucinations. However, axial motor symptoms, including falls, dysphagia, and postural instability tend to be treatment-resistant.

Conclusions

The quality of evidence for managing Parkinson disease motor and nonmotor symptoms and medication adverse effects is largely moderate. Study methods, inclusion and exclusion criteria, and outcome measures for most nonmotor features have been inconsistent and nonstandardized, and trial durations have been too short to establish extended efficacy and safety outcomes for these chronic problems. Further high-quality RCTs are needed. Finally, given its inexorable progression and complex, multifaceted disability, the greatest unmet therapeutic need is identification of effective neuroprotective and disease-modifying therapy. Multiple therapies are in development based on current hypotheses of disease pathogenesis.[9]

ARTICLE INFORMATION

Author Contributions: Drs Connolly and Lang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Connolly, Lang.
Acquisition, analysis, or interpretation of data: Connolly, Lang.
Drafting of the manuscript: Connolly.
Critical revision of the manuscript for important intellectual content: Connolly, Lang.
Administrative, technical, or material support: Connolly, Lang.
Study supervision: Lang.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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