

Medical Treatment of Parkinson Disease

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KEYWORDS

- Punding • REM-behavior disorder • Post-synaptic
- Hallucination • Dyskinesia • Pre-synaptic

The cardinal characteristics of Parkinson disease (PD) include resting tremor, rigidity, and bradykinesia.¹ Besides these motor symptoms, patients may also develop autonomic dysfunction, cognitive changes, psychiatric symptoms, sensory complaints, and sleep disturbances. More than 1.5 million people in the United States are believed to have PD, and 70,000 new cases are diagnosed each year.² The annual economic burden of PD in the United States alone is estimated to be \$23 billion. Most of this cost is attributed to lost productivity and uncompensated care delivered by family and household members.³

The motor symptoms associated with PD are believed to arise from dopamine deficiency, although the pathophysiology of parkinsonian symptoms and signs is not yet fully understood.⁴ As dopamine replacement therapy, levodopa has become the standard of care for patients with PD.⁵ Although levodopa clearly improves motor symptoms, allowing many patients to better perform activities of daily living and continue working, this agent is also associated with motor fluctuations, for example, “wearing off” and dyskinesias.^{6–11} Because of these complications, many specialists advocate the early use of dopamine agonists in patients with motor disability. These drugs by class are less potent than levodopa, but are not associated with dyskinesias.

This manuscript addresses the treatment of motor and nonmotor symptoms of Parkinson disease.

THE NIGROSTRIATAL SYNAPSE

The medical management of PD is based on compensating for catecholamine depletion due to a loss of dopamine-producing cells in the substantia nigra through delivery of additional dopamine or directly stimulating the postsynaptic striatal neurons.¹² Dopamine (DA) is synthesized from the amino acid levodopa, and exogenous replacement of levodopa is highly effective in treating motor symptoms. Although levodopa initially produces a robust and predictable response, with disease progression and nigrostriatal neuronal death motor fluctuations and dyskinesias may occur. For this

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reason, DA agonists, medications that bypass the presynaptic neuron and directly stimulate striatal DA receptors, are often used (**Table 1**).

MONOAMINE OXIDASE TYPE B INHIBITORS

The monoamine oxidase type B (MAO-B) inhibitors may be used as a first line treatment or as adjunctive therapy to levodopa in patients with PD. Blockade of MAO-B delays dopamine metabolism, thereby increasing neurotransmitter concentration in the striatum.^{13–15} Inhibitors that selectively block MAO-B avoid the potentially dangerous pressor effect associated with inhibition of MAO-A.¹⁴ The MAO-A enzyme is involved in the metabolism of dietary amines such as tyramine, which is found in cheese.¹⁴ Elevated tyramine levels are associated with dangerously high blood pressure. Studies performed with the specific MAO-B inhibitor selegiline and rasagiline found no pressor effect if the drug is given with tyramine and phenylethylamine.^{14,16}

Rasagiline

Rasagiline was approved in 2006 by the US Food and Drug Administration (FDA) as an initial monotherapy and adjunct therapy in patients with PD taking levodopa.^{17,18} The safety and efficacy of this agent was evaluated in early PD in the TEMPO (Rasagiline Mesylate [TVP-1012] in Early Monotherapy for Parkinson's Disease Outpatients) study.¹⁷ This multicenter, 26-week, parallel-group, double-blind, placebo-controlled clinical trial randomized 404 subjects to rasagiline mesylate at dosages of 1 or 2 mg/d or matching placebo. In this monotherapy study, Unified Parkinson's Disease Rating Scale (UPDRS) changes were statistically different between the 1-mg dose of rasagiline versus placebo (−4.20 units [95% confidence interval, −5.66 to −2.73 units; $P < .001$]) and the 2-mg dose and placebo (−3.56 units [95% confidence interval, −5.04 to −2.08 units; $P < .001$]). There were no differences in the frequency of adverse events or premature withdrawals among the treatment groups. In a continued observation phase of this study, in which subjects initially treated with placebo were converted to rasagiline 1 mg daily, it was found that subjects initially started on active therapy continued to demonstrate benefit compared with the group who started on placebo. Because these findings suggested a possible disease modification effect, an additional trial, Attenuation of Disease progression with Azilect Given Once-daily (ADAGIO), of more than 1100 subjects has been initiated. Data from this study are not fully available.¹⁹

Clinical trials demonstrate the safety and efficacy of adjunctive therapy with rasagiline in levodopa-treated patients.^{18,20} The Parkinson Rasagiline: Efficacy and Safety in the Treatment of "Off" (PRESTO) trial found that levodopa-treated patients taking rasagiline 0.5 or 1.0 mg/d showed improvements in motor fluctuations.¹⁸ This multicenter, randomized, placebo-controlled, double-blind study enrolled 472 subjects experiencing motor fluctuations while receiving levodopa. Reduction in mean adjusted total daily off time was 1.85 hours (29%) with rasagiline 1.0 mg/d, 1.41 hours (23%) with rasagiline 0.5 mg/d, and 0.91 hours (15%) with placebo ($P \leq .02$ versus placebo). Analysis of secondary efficacy outcome measures revealed significant improvements in the UPDRS Activities of Daily Living score and Motor score during off periods. Time without troublesome dyskinesias increased from baseline by 0.51 hours ($P = .050$ versus placebo) in the lower-dose rasagiline group and by 0.78 hours ($P = .004$ versus placebo) in the group taking 1 mg/d. Weight loss, vomiting, anorexia, and difficulty balancing were significantly more common with rasagiline than with placebo.²¹

Rasagiline and entacapone were compared with placebo in the Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily (LARGO) study.^{20,21} Patients

were randomized to receive rasagiline 1 mg/d, entacapone 200 mg with each levodopa dose, or placebo as adjunctive therapy with levodopa. Results showed that decreases in daily off time with rasagiline (1.18 hours) and entacapone (1.20 hours) were significantly superior to the decrease with placebo (0.4 hour; $P \leq .0001$). The amount of on time with dyskinesia did not differ between groups. Active treatment allowed significant reductions in levodopa dose, whereas the placebo group required an increase. There were no significant increases in UPDRS Dyskinesia scores in either the rasagiline or the placebo group. The frequency of dopamine-related adverse events was similar with rasagiline and placebo.²⁰

The use of rasagiline at any dose may be associated with hypertensive crisis (“cheese reaction”) if consumed with tyramine-rich foods and beverages, such as sausage, salami, pickled herring, sauerkraut, aged cheeses (cheddar, blue cheese) and nonpasteurized beer.²² In a recent report of tyramine challenges performed in rasagiline-treated patients at the end of 2 double-blind, placebo-controlled trials, 3 of 22 subjects receiving 0.5 mg/d developed self-limiting systolic blood pressure elevation of 30 mmHg or more on 3 measurements. None of the 12 patients receiving the 1-mg dose experienced this degree of blood pressure elevation in this study.¹⁶ Rasagiline is contraindicated for coadministration with meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John’s wort, mirtazapine, cyclobenzaprine, sympathomimetic amines, and other MOA inhibitors. The prescribing information for rasagiline also warns against coadministration with ciprofloxacin, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).²²

Selegiline

Selegiline is also approved as monotherapy or adjunctive therapy in patients with PD. This agent undergoes extensive first-pass metabolism with only 10% bioavailability and significant levels of desmethylselegiline, L-amphetamine, and L-methamphetamine metabolites; it is associated with a variable pharmacokinetic profile.^{14,23}

Long-term treatment with oral selegiline in PD patients is associated with slower motor decline in the initial and extension phases of the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial.^{24,25} DATATOP randomized 800 treatment-naïve patients with early PD to selegiline 10 mg/d, tocopherol 2000 IU/d, both agents, or placebo to assess whether these medications could delay the need for levodopa.²⁴ This was followed by selegiline 10 mg/d for 5 years, after which a group of 368 patients who had progressed to requiring levodopa were randomized again to continue selegiline or switch to placebo for an additional 2 years.²⁵ Patients who remained on selegiline reported more dyskinesias (34% versus 19%; $P = .006$), but were less likely to have on-off motor fluctuations or freezing of gait compared with placebo. The selegiline group also demonstrated a slower reduction in motor performance on UPDRS scores, the number of daily off periods, an increase in on periods, a reduction in the levodopa dosage, and an increase in the mean levodopa interdose interval. Selegiline was associated with orthostatic hypotension in the DATATOP trial and other studies.^{24–28} Withdrawal of selegiline improved blood pressure stability but also led to a decline in motor function.²⁸

Selegiline Orally Disintegrating Tablets

Selegiline orally disintegrating tablets (ODT), approved in 2006 by the FDA as an adjunct therapy in patients with PD taking levodopa, is a rapidly dissolving oral mucosal drug delivery system.^{29,30} This mode of delivery bypasses the gastrointestinal system and first-pass metabolism in the liver.³⁰ The rapid dissolution on the

Table 1

Adjunctive agents used to treat Parkinson disease

Drug	Mechanism of Action	Dose and Frequency	Adverse Effects
MAO-B inhibitors			
Rasagiline	Decrease breakdown of DA by way of MAO-B blockade	1 mg every day	Weight loss, vomiting, anorexia, balance difficulty
Oral selegiline	Decrease breakdown of DA by way of MAO-B blockade	5–10 mg twice a day	Nausea, dizziness, sleep disorder, impaired cognition, orthostatic hypotension
Selegiline ODT	Decrease breakdown of DA by way of MAO-B blockade	1.25–2.5 mg every day	Dizziness, dyskinesias, hallucinations, headache, dyspepsia
Ergoline dopamine agonists			
Bromocriptine	Direct stimulation of DA receptors	15–30 mg 3–4 times a day	Nausea, hypotension, hallucinations, psychosis, peripheral edema, pulmonary fibrosis, sudden onset of sleep
Pergolide	Direct stimulation of DA receptors	1.5–5.0 mg three times a day	Nausea, hypotension, hallucinations, psychosis, peripheral edema, pulmonary fibrosis, sudden onset of sleep, restrictive valvular heart disease
Cabergoline	Direct stimulation of DA receptors	2–6 mg every day	Nausea, hypotension, hallucinations, psychosis, peripheral edema, pulmonary fibrosis, sudden onset of sleep, dyskinesia
Lisuride	Direct stimulation of DA receptors	0.6–2.0 mg 3–4 times a day with levodopa	Nausea, headaches, tiredness, dizziness, drowsiness, sweating, dry mouth, vomiting, sudden decreases in BP, nightmares, hallucinations, paranoid reactions, states of confusion, weight gain, sleep disorders

Nonergoline dopamine agonists			
Pramipexole	Direct stimulation of DA receptors	1.5–6.0 mg three times a day	Nausea, hypotension, hallucinations, psychosis, peripheral edema, sudden onset of sleep
Ropinirole	Direct stimulation of DA receptors	6–24 mg/d	Nausea, hypotension, hallucinations, psychosis, peripheral edema, sudden onset of sleep
COMT inhibitors			
Tolcapone	Increase levodopa half-life by blocking COMT pathway important in the catabolism of levodopa	100–200 mg three times a day	Diarrhea, dyskinesia, liver toxicity (monitoring required)
Entacapone	Increase levodopa half-life by blocking COMT pathway important in the catabolism of levodopa	200 mg with each dose of levodopa to 1600 mg/d	Exacerbation of levodopa side effects, diarrhea, discolored urine
NMDA antagonist			
Amantadine	Promotes DA release through blockade of NMDA and acetylcholine receptors	50–200 mg twice a day, with special considerations for elderly patients or those with renal insufficiency	Cognitive dysfunction, hallucinations, peripheral edema, skin rash, anticholinergic effects

Abbreviations: BP, blood pressure; COMT, catechol-*O*-methyltransferase; DA, dopamine; MAO-B, monoamine oxidase type B; ODT, orally disintegrating tablets.
Data from Jankovic J, Stacy M. Medical management of levodopa-associated motor complications in patients with Parkinson's disease. *CNS Drugs* 2007;21(8):681.

tongue without the need for water may be useful in patients with dysphagia.³¹ The use of selegiline ODT does not require dietary tyramine restriction up to the highest approved dose of 2.5 mg/d.³²

The ODT formulation of selegiline provides high bioavailability of the parent compound. Pharmacokinetic and pharmacodynamic studies performed on 156 healthy volunteers found 5 times higher area-under-the-curve values for selegiline after administration of selegiline ODT compared with an equivalent dose of conventional oral selegiline.³³ In addition, the plasma concentrations of the 3 major selegiline metabolites were significantly lower after selegiline ODT administration.

Selegiline ODT was evaluated as adjunctive therapy in a 3-month, randomized, placebo-controlled study in 140 patients with PD who experienced motor fluctuations while receiving levodopa.¹³ The reduction in daily off time was 2.2 hours in the selegiline ODT group compared with 0.6 hour in the placebo group ($P = .001$). In addition, selegiline ODT was associated with an additional 1.8 dyskinesia-free on hours daily compared with placebo ($P = .006$). Adverse events were generally similar between the selegiline ODT and placebo groups.¹³ The most common drug-related adverse events observed in the selegiline ODT group were dizziness, dyskinesias, hallucinations, headache, and dyspepsia.

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

Catechol-O-methyl transferase (COMT) is a key enzyme in the peripheral catabolism of levodopa. Inhibiting COMT increases levodopa plasma levels by about 26%.³⁴⁻³⁶ Two COMT inhibitors are available: tolcapone and entacapone.

Tolcapone

Tolcapone is a potent and clinically effective agent, but its use has been limited by concerns about potential liver toxicity.³⁷ Tolcapone has a rapid onset of action, showing therapeutic benefit approximately 2 weeks after treatment initiation. If given as adjunctive therapy in patients on levodopa, tolcapone improves wearing off effects, decreases off time, increases on time, decreases levodopa dosage by 30%, and reduces the number of levodopa doses needed during the day.^{38,39} In addition, after 6 weeks of treatment with tolcapone in a randomized, double-blind, placebo-controlled trial, patients exhibited an increase in on time of more than 2 hours.⁴⁰

Potential adverse effects associated with COMT inhibitors are diarrhea, dyskinesia, and liver toxicity. For tolcapone, the unknown potential for fatal hepatotoxicity prompted the FDA to require monitoring of liver function.³⁷ Initial recommendations called for testing of alanine aminotransferase and aspartate aminotransferase at baseline, every 2 weeks during the first year of treatment, every 4 weeks over the ensuing 6 months, and every 8 weeks subsequently. More recently, the FDA has recommended that alanine aminotransferase and aspartate aminotransferase be tested at baseline and then every 2 to 4 weeks for the first 6 months of therapy, then periodically at intervals deemed clinically relevant.⁴¹

Entacapone

The COMT inhibitor entacapone has not been associated with liver toxicity.³⁷ Entacapone also has a shorter half-life and is given with levodopa.⁴² When administered in 200-mg doses with levodopa, entacapone was associated with a decrease in off time of 2.1 hours per day.⁴³ A 6-month, randomized, double-blind, placebo-controlled study revealed that entacapone therapy significantly increased mean on time, reduced off time, and permitted a decrease of an average of 102 mg/d of levodopa.⁴⁴ These

benefits of entacapone therapy persisted through the 3-year open-label extension of the initial 6-month trial. A new formulation containing 200 mg of entacapone plus levodopa and carbidopa (Stalevo) in a single tablet is also available for the treatment of patients with PD and simple motor fluctuations. Whereas the entacapone dosage remains 200 mg per tablet in all formulations, the carbidopa/levodopa doses are calculated at a 1:4 ratio with levodopa dosages of 50, 75, 100, 125, 150 and 200 mg per tablet.

Trials comparing entacapone and tolcapone are insufficient. In a double-blind trial of patients treated with entacapone for at least 15 days, 150 subjects were randomized to continue entacapone or switch to tolcapone. There were no differences in Investigator Global Assessment, UPDRS subscales II and III, off time or on time in the per protocol population. In addition, during this 3-week assessment period, 27 subjects (36%) withdrew from the study.⁴⁵

LEVODOPA

Symptoms of PD result from the loss of dopaminergic neurons in the substantia nigra. These neurons normally synthesize dopamine from the essential amino acid, tyrosine. The conversion of tyrosine to levodopa is facilitated by the rate-limiting enzyme, tyrosine hydroxylase. Levodopa, whether it is derived from cellular metabolism of tyrosine or from oral supplementation, is converted to dopamine by the enzyme dopa-decarboxylase. Levodopa is competitively absorbed by way of a large neutral amino acid (LNAA) transporter protein in the small intestine. A similar saturable carrier is believed to be present at the blood-brain barrier.⁴⁶ Erratic or delayed gastric emptying may cause individual doses of levodopa to fail or to have a slow onset of effect.⁴⁷ In addition, levodopa dosing during a high protein meal, through competition for sites on the duodenal and blood-brain barrier transport molecules, may reduce levodopa transfer to the blood stream and brain.⁴⁶

As a result of peripheral dopa-decarboxylase, less than 1% of the levodopa administered is actually converted into dopamine in the brain, leading to activation of the area postrema, and may cause nausea, vomiting, and, rarely, cardiac arrhythmia. By adding a dopa-decarboxylase inhibitor (DCI) that does not cross the blood-brain barrier, such as carbidopa or benserizide, sufficient concentration of levodopa reaches the central nervous system. In most patients 75 to 100 mg of a DCI are needed per day to effectively block blood stream conversion to DA. However, patients with early nausea from carbidopa/levodopa therapy often benefit from additional carbidopa (Lodosyn).⁴⁸

Levodopa has been used in the treatment of PD for almost 40 years, and remains the subject of much debate. During the late 1980s and 1990s concerns regarding the potential for hastening disease progression were put forward in the setting of increased emphasis on dopamine agonists. However, the “neurotoxic” concerns raised regarding this amino acid remain completely unproven, and every effort should be made to educate patients that the potential for motor complications associated with levodopa does not translate to hastening disease progression.

In a carefully designed trial to assess the disease modifying effects of levodopa, Fahn and colleagues⁴⁹ conducted a randomized, double-blind, placebo-controlled trial in 361 subjects with early PD. Subjects received levodopa doses of 150 mg, 300 mg, and 600 mg daily or a matching placebo for a period of 40 weeks, followed by a 2-week washout period. The severity of parkinsonism increased more in the placebo group than in all groups receiving levodopa: the mean difference between the total score on the UPDRS at baseline and at 42 weeks was 7.8 units in the placebo

group, 1.9 units in the group receiving levodopa at a dose of 150 mg daily, 1.9 in those receiving 300 mg daily, and 1.4 in those receiving 600 mg daily ($P < .001$), suggesting that levodopa may have a disease-modifying effect. Nonetheless, the subjects receiving the highest dose of levodopa had significantly more dyskinesia, hypertonia, infection, headache, and nausea than those receiving placebo.

AMANTADINE

Amantadine is a noncompetitive *N*-methyl-D-aspartic acid (NMDA) receptor antagonist that has shown potential for reducing dyskinesias in patients with PD.⁵⁰ A study of amantadine as an adjunct to levodopa in 11 patients with advanced PD demonstrated a 52% reduction in severity of dyskinesia compared with no change with placebo.⁵⁰ In a larger, placebo-controlled, double-blind study involving 24 PD patients with levodopa-induced dyskinesias, amantadine was associated with a 24% decline in total dyskinesia score without affecting on time.⁵¹ In another study, 18 patients with advanced PD, motor fluctuations, and dyskinesias received amantadine or placebo in addition to levodopa.⁵² Dyskinesia scores were reduced by 60% in the amantadine-treated patients compared with the placebo-treated patients. In addition, motor fluctuations were also reduced in the amantadine-treated patients.⁵³ In a separate report, these same investigators described reductions in dyskinesia scores unrelated to increases in parkinsonian symptoms.⁵³

DOPAMINE AGONISTS

Dopamine agonists may be used as initial and adjunctive therapy in patients with PD, and reduce off time in levodopa-treated patients by 20% to 40% or an average of 2 hours per day.⁵⁴ The mechanism of action of these agents involves direct stimulation of dopamine receptors. Currently available dopamine agonists have an ergoline or a nonergoline structure.

Ergoline Dopamine Agonists

Bromocriptine is the oldest agent in this class approved for therapy in patients with PD.⁵⁵ It is now rarely used in treating symptoms of PD. Pergolide is an ergoline dopamine agonist that is rapidly absorbed, reaching a peak concentration within 2 to 3 hours of administration.⁵⁵ The drug has a long half-life of approximately 21 hours. In a study of 12 advanced PD patients experiencing motor fluctuations while receiving levodopa, pergolide plus levodopa significantly increased the duration of on time compared with either levodopa alone ($P < .001$) or bromocriptine plus levodopa ($P = .05$). The duration of therapeutic benefit was greater with pergolide than with bromocriptine ($P = .02$).⁵⁶ However, the use of pergolide is now highly restricted after reports of restrictive valvular heart disease and pulmonary fibrosis.⁵⁷ Cabergoline is also an ergoline dopamine agonist that has a long elimination half-life of 65 to 110 hours, and is also restricted for valvulopathy concerns. Comparison of cabergoline and pergolide in a single-blind, crossover study of 48 patients with advanced PD found similar improvements in on and off time with either medication.⁵⁶

Lisuride has been evaluated as an adjunct to levodopa in a 1-year double-blind and 4-year open-label study design.⁵⁷ During the first year of the study, patients were randomized to receive levodopa plus lisuride or levodopa alone. At the end of the year, oral selegiline 10 mg/d was added to both regimens. Motor improvements on UPDRS scores were significantly better in the combination therapy group, and motor complications were rare, and equivalent between the groups.

Apomorphine is a soluble dopamine agonist administered subcutaneously by way of a specially designed syringe or catheter system and is an effective rescue treatment for patients with off periods by way of intermittent injections or as a continuous infusion for patients motor complications that are with difficult to manage. This drug is associated with nausea, orthostatic hypotension, yawning, and drowsiness.⁵⁸ In a pivotal trial in the United States, 20 subjects were randomized to receive active drug and 9 to receive placebo. Results showed marked reductions in UPDRS scores ($P < .001$) at dosages ranging from 2.0 to 10.0 mg per injection in the active group, with a mean effective dose of 5.4 mg. Off-state events were arrested in $95\% \pm 2.4\%$ of outpatient injections in the apomorphine group versus $23\% \pm 13.0\%$ in the placebo group ($P < .001$).⁵⁹

Nonergoline Dopamine Agonists

Pramipexole is a second-generation, nonergoline dopamine agonist with a half-life of 8 to 12 hours.⁶⁰ Pramipexole and levodopa have been compared in a double-blind, randomized study ($n = 301$) of initial treatment of early PD in the Comparison of the Agonist pramipexole with Levodopa on Motor complications of Parkinson's Disease (CALM-PD) study.⁶¹ Eligible subjects were randomized to receive pramipexole or levodopa. A 10-week dose-escalation period was followed by a 21-month maintenance phase, during which open-label carbidopa/levodopa was available to all patients to treat emerging disability. The mean improvement in total UPDRS score from baseline to 23.5 months was greater in the levodopa group than in the pramipexole group (9.2 versus 4.5 points; $P < .001$), despite supplementation with open-label levodopa in both groups. However, initial pramipexole treatment resulted in significantly less wearing off, dyskinesia, or "on-off" motor fluctuations (28%) compared with levodopa (51%) (hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.30, 0.66; $P < .001$). Analysis after 4 years also found that the mean improvement in the total UPDRS score from baseline to 48 months remained higher in the levodopa group than in the pramipexole group. A significantly greater proportion of patients in the pramipexole group (72%) required levodopa supplementation compared with those in the levodopa group (59%; HR 1.64; 95% CI 1.22, 2.21; $P = .001$), however, a significantly smaller proportion of patients in the pramipexole group reached the primary end point of developing dyskinesia, wearing off or "on-off" fluctuations than those receiving levodopa (52% and 74%, respectively; HR 0.48; 95% CI 0.35, 0.66; $P < .001$). Most of the dopaminergic complications in the pramipexole group occurred after the initiation of supplementary levodopa, whereas in the levodopa group most complications occurred before the initiation of supplementary levodopa.

This agent is also well studied as adjunctive therapy to levodopa. A randomized, double-blind, placebo-controlled study compared pramipexole and bromocriptine with placebo in 247 patients with advanced PD and levodopa-associated motor fluctuations showed that pramipexole decreased motor disability compared with placebo. Pramipexole was associated with improvements of 26.7% in the UPDRS Activities of Daily Living score versus 4.8% for placebo ($P = .0002$), and of 34.0% in the UPDRS Motor score versus 5.7% for placebo ($P = .0006$). The average percentage of awake hours off time was reduced by 15% in the pramipexole group ($P = .007$ versus placebo) but not to a significant extent in the bromocriptine group ($P = .2$ versus placebo).⁶² In a pivotal trial of pramipexole as adjunctive therapy, the average improvement in percentage of off time was 31% for pramipexole versus 7% for placebo ($P = .0006$).⁶³ In this study, pramipexole use was also accompanied by an average 27% decrease in levodopa dosage versus 5% for placebo ($P \leq .0001$).

Ropinirole is a nonergoline dopamine agonist with a half-life of approximately 6 hours.⁶⁴ The drug is rapidly absorbed after oral administration. In a prospective, randomized, double-blind study (the Requip 056 Study), Rascol and colleagues⁶⁵ compared the dopamine D2 receptor agonist ropinirole ($n = 179$) with levodopa ($n = 89$) over a period of 5 years in 268 patients with early PD. Eighty-five subjects in the ropinirole group (47%) and 45 subjects in the levodopa group (51%) completed the study. In the ropinirole group, 29 of the 85 patients (34%) received no levodopa supplementation. Time to dyskinesia showed a significant difference in favor of ropinirole (HR for remaining free of dyskinesia 2.82; 95% CI 1.78, 4.44; $P < .001$) with 20% in the ropinirole group and 45% in the levodopa group; however, motor subscores showed a significantly greater reduction in the ropinirole arm than in the levodopa arm ($P = .008$). The mean daily doses given by the end of the study were 16.5 mg of ropinirole, with an average dose of levodopa supplementation of 427 mg/d. The subjects randomized to levodopa received an average of 753 mg/d. A subset of subjects participated in a parallel neuroimaging arm with [¹⁸F]dopa positron emission tomography as an indirect marker of dopamine neuron loss.⁶⁶ The 2-year study demonstrated that those originally assigned to ropinirole ($n = 68$) had a 14.1% decrease of fluorodopa uptake in the putamen, compared with 22.9% decrease in those originally on levodopa ($n = 59$). The interpretation of these data remains controversial. Most recently, 10-year follow-up data have been published demonstrating continued clinical benefit of ropinirole.⁶⁷

In the pivotal study of adjunctive ropinirole therapy in patients with advanced PD, a greater number of patients taking ropinirole had a 20% or greater reduction in levodopa dose and off time compared with placebo (35% versus 13%; $P = .003$).⁶⁸ The reduction in the average percentage of daily off time was 11.7% with ropinirole versus 5.1% for placebo ($P = .039$).

Twenty-four hour ropinirole has been compared with placebo in advanced PD in a 24-week study in subjects with suboptimal control with levodopa.⁶⁸ At week 24, the mean daily dose was 18.8 mg. Mean reduction in off time was 2.1 hours with ropinirole compared with 0.3 with placebo. Quality of life indicators, depression and sleep scales were also improved. A direct comparison with immediate-release ropinirole found the odds of having a 20% reduction in off time were significantly higher for the 24-hour compound compared with the immediate release compound (64% versus 51%). However, subjects in the ropinirole 24-hour arm were titrated to higher total daily doses, 18.6 mg versus 10.4 mg. Levodopa reductions were 162 mg/d versus 113 mg/d. Twenty-four hour ropinirole has a similar adverse event profile as immediate-release ropinirole. As adjunctive therapy, the most common side effects were dyskinesia (13%), nausea (11%), dizziness (8%), and somnolence (7%).^{68,69}

Safety and Tolerability Concerns with Dopamine Agonists

Older ergoline dopamine agonists may cause vasoconstriction, painful reddish discoloration of the skin (erythromelalgia), peptic ulcer disease, and serosal fibrosis.⁴⁸ Of more critical concern is the associated valvulopathy increasingly associated with the use of the ergoline agents, particularly pergolide and cabergoline. Ergoline and nonergoline dopamine agonists have been associated with confusion, hallucination, dyskinesia, sleep disorders, leg edema, and postural hypotension, which may limit the usefulness of these medications.⁴⁸ Recent reports in the literature have linked dopamine agonist therapy with impulsive behaviors, such as pathologic gambling, compulsive eating, and hypersexuality.⁷⁰⁻⁷² The effect seems to be dose dependent and reversible when the dose is reduced or the drug is discontinued. Somnolence

and episodes of irresistible sleepiness seem to be a class effect of dopamine agonists.^{48,73}

MOTOR COMPLICATIONS OF ANTI-PARKINSON THERAPY

Motor fluctuations in PD associated with levodopa are well recognized. Wearing off, defined as a generally predictable recurrence of motor and nonmotor symptoms preceding scheduled doses of antiparkinsonian medication, is related to declining dopamine storage capacity.^{74,75} Wearing off can develop gradually or suddenly and may be predictable or random (“on-off” effect). Factors associated with motor complications include age at disease onset or at initiation of therapy, total daily levodopa dose, duration of treatment, and disease progression. Other off symptoms, believed to be related to low plasma levodopa levels include delayed (“delayed on”) or no response (“no on” or “dose failure”).^{8,9}

In contrast to the re-emergence of off symptoms at low plasma levodopa concentrations, high plasma levels are associated with writhing or twisting involuntary movements, termed “dyskinesias.” Most commonly “peak-dose dyskinesias” are seen, and are classified as an “improvement-dyskinesia-improvement” (IDI) pattern. Another form, the “dyskinesia-improvement-dyskinesia” (DID) pattern, involves involuntary movements such as chorea or dystonia that correspond to rising and declining blood and brain levels of levodopa, and may be related to postsynaptic receptor changes.⁹

In patients with motor fluctuations it is useful to consider treatment of PD in terms of “presynaptic” (levodopa related) and “postsynaptic”(DA agonist) therapies. Given 80% of patients are expected to have motor fluctuations after 5 years of levodopa therapy, using a “balanced” approach may minimize the side effects associated with a monotherapeutic emphasis (**Fig. 1**).⁴⁸

Presynaptic treatment strategies in PD involve theoretical maintenance of physiologic synaptic concentrations of dopamine by keeping plasma levodopa levels within a therapeutic window. Initially, this is accomplished by exogenous replacement with levodopa combined with a DCI. The addition of a COMT inhibitor, such as entacapone or tolcapone, will further increase levodopa delivery. Striatal dopamine concentrations may also be increased by adding rasagiline or selegiline, MAO-B inhibitors that inhibit the metabolism of dopamine.⁴⁸

Postsynaptic strategies act directly on the striatal outflow neuron, and emphasize the use of DA agonists. Because agonists are not dependent on the transport and metabolic pathways of levodopa, they are less dependent on nigrostriatal function. Amantadine may also be considered as a postsynaptic agent.⁴⁸

Wearing Off

The essential concept in treating symptoms of wearing off is to optimize motor function by maintaining steady-state concentrations of medications in what is termed a therapeutic window. This is accomplished easily in early PD, but with disease progression, the therapeutic range narrows, and wearing off is seen at low drug plasma levels. In this event, increasing dosage per dosing interval, changing to a longer-acting formulation, addition of other medications, or decreasing the dosing interval are all reliable strategies.

Dyskinesia

Dyskinesias have not been reported in patients without previous exposure to levodopa. For this reason, treatment of this motor symptom generally requires

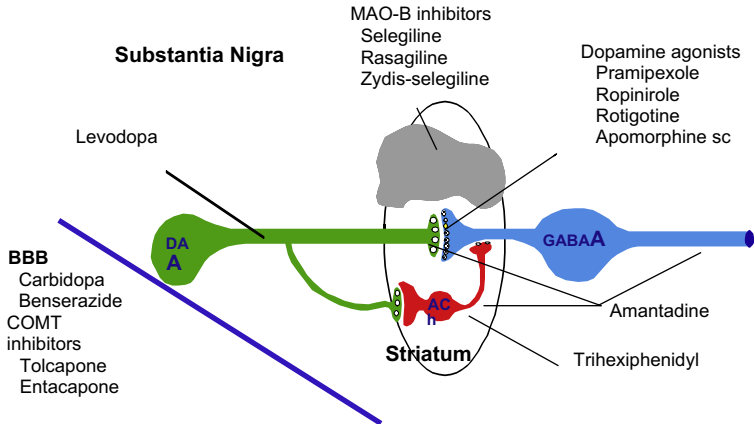


Fig. 1. Presynaptic and postsynaptic therapy in PD. This diagrammatic representation of the substantia nigra and the striatum demonstrates sites of action for medications used in the treatment of PD. Levodopa, metabolized to dopamine, increases the concentration of this neurotransmitter in the brain, and is taken up by the nigrostriatal neuron. Amantadine enhances the release of dopamine in the striatum, and has some anticholinergic effects. MAO-B inhibitors indirectly increase dopamine concentration in the synapse by reducing the rate of dopamine metabolism in glial and neuronal cells. COMT inhibitors and carbidopa cross the blood-brain barrier, but increase the concentration of levodopa in the central nervous system. Dopamine agonists improve dopaminergic tone by acting at the postsynaptic membrane.

postsynaptic therapeutic intervention, initially with DA and presynaptic therapy reduction, and, if still not effective, the addition of amantadine. To manage the symptoms of dyskinesia, the dose of levodopa (with or without the addition of a dopamine agonist) may be reduced, the frequency of levodopa administration increased, or otherwise modulated. Splitting the levodopa dose regimen into more frequent lower doses is sometimes used to manage peak-dose dyskinesia; however, this often provides only modest and temporary relief. A small reduction in levodopa dose may be effective, but as the disease progresses, many patients experience a reduction in the therapeutic window for eliciting a motor response to medication without also causing a dyskinetic response. For most patients this is not acceptable, and they choose to endure the dyskinesia rather than be immobile.

A study by Cristina and colleagues⁷⁶ has shown that partial substitution of levodopa with high doses of dopamine agonists (if tolerability allows) reduces the severity of dyskinesia without the unacceptable “off” period that accompanies the isolated reduction in levodopa dose. In this study, the ropinirole dose was increased stepwise from 18.4 ± 3.5 mg to 34.7 ± 5.5 mg, and the daily levodopa dose was decreased from 734.1 ± 254.8 mg to 502.8 ± 228.4 mg. After 12 months 25/36 patients were still on high doses of ropinirole. Daily doses of levodopa and ropinirole were 489 ± 243 mg and 34.6 ± 4.6 mg, respectively. There was a significant reduction in dyskinesia during “on” periods and a reduction in dystonias during “off” periods ($P < .001$), and the intensity and duration of “off” periods were reduced significantly ($P < .001$). The high-dose dopamine agonist strategy was deemed to be safe, and larger studies are needed to assess this strategy further.

For patients with severe or medical-refractory dyskinesias and sudden off periods, continuous subcutaneous infusion of apomorphine has been shown to be beneficial.^{77–80} A small study has shown that replacement of oral levodopa with a continuous

waking-day subcutaneous infusion of apomorphine reduced the severity of dyskinesia by 65%, and its frequency and duration by 85%.⁸¹ However, subcutaneous infusion is impractical for many patients as shown by low compliance rates in reported studies. More than 50% of patients experience side effects in the form of injection-site nodules or paniculitis.⁸² Continuous infusion of carbidopa/levodopa into the duodenum by way of a percutaneous catheter has been shown to be more effective than optimized oral therapy at controlling motor fluctuations in advanced PD.⁸³ A gel formulation of carbidopa/levodopa (Duodopa) has been approved for use in Canada and European Union countries.⁸⁴ Duodopa has gained fast track status from the US Food and Drug Administration (FDA) and may soon provide patients with late-stage PD in the United States with another effective treatment option.⁸⁵

Clozapine, an atypical neuroleptic, has been shown to be effective in the treatment of levodopa-induced dyskinesia in patients with severe PD, in a placebo-controlled study in 50 patients.⁸⁶ A reduction in severity of dyskinesia and in the duration of "on" periods with dyskinesia was seen to favor the clozapine group ($P < .05$ and $P = .003$; respectively). However, 3 patients in the clozapine group (12%) developed eosinophilia, although this resolved rapidly after withdrawal of the drug. Clozapine can induce other serious adverse events such as neutropenia and agranulocytosis in patients with PD, and blood monitoring for the management of these effects is necessary.^{87,88} These associations, together with risks of myocarditis, dilated cardiomyopathy, and malignant neuroleptic syndrome, require careful follow-up.⁸⁹

Finally, patients experiencing severe and disabling dyskinesia as a result of antiparkinsonian therapy may be considered for surgical treatment. Ablation of brain areas that are involved in PD can reduce Parkinsonian symptoms and permit a reduction in the required dose of levodopa, and also directly affect the expression of motor complications. Deep brain stimulation (DBS) is now the favored method of antiparkinsonian surgery as it mimics the effects of ablative procedures but does not create a brain lesion. Thalamic, subthalamic nucleus, and pallidal DBS have been shown to reduce motor complications in PD patients.⁹⁰ Deuschl and colleagues⁹¹ demonstrated a significant improvement in overall quality of life in patients treated with bilateral subthalamic DBS compared with matched controls who received only best medical therapy.⁹¹ This outcome took into account motor efficacy and reduction of dyskinesia. Continuous subthalamic stimulation with DBS at earlier stages of the disease to reduce the required levodopa dose and therefore prolong time to development of dyskinesia has recently shown promise in a randomized trial by Schupbach and colleagues.⁹² The perioperative surgical risks, however, are not trivial and need to be assessed for each individual.⁹³

NONMOTOR SYMPTOMS IN PARKINSON DISEASE

Nonmotor symptoms in PD are increasingly recognized as significant cause of disability, and may involve almost any aspect of the nervous system. Autonomic nervous system dysfunction includes gastrointestinal disturbances, urogenital dysfunction, orthostatic hypotension, and thermoregulatory difficulties. Higher cortical dysfunction results in cognitive changes, whereas basal ganglia disturbances may result in impulsive or compulsive behaviors. Brainstem involvement may result in fatigue, bulbar, respiratory, and sleep dysfunction.

Cognitive Disorders

Dementia is reported in approximately 20% of PD patients, and in more than 35% of patients beyond 70 years of age.^{94–96} A long-term follow-up study of 233 subjects

found features of dementia were present in 60.1% of subjects by 12 years, and others report significant cognitive symptoms in more than 80% of end-stage patients.⁹⁷ Symptoms of dementia may be subdivided into subcortical and cortical presentations.⁹⁸ Subcortical dementia affects information processing (visuospatial, attentional, and executive functions). Cortical dementia is seen in Alzheimer disease (AD) and diffuse Lewy body (DLB) disease, and interferes with storage processing (memory and language).⁹⁹

Cholinesterase inhibitors have been shown to improve cognitive impairment and other behavioral problems associated with PD, but may aggravate parkinsonian symptoms.^{100,101} A double-blind, randomized, placebo-controlled, 10-week study of 14 patients on donepezil (5 or 10 mg/d) was associated with a 2.1 point increase in the mean Mini Mental State Evaluation (MMSE) score compared with 0.3 point increase on placebo, without worsening of parkinsonism.¹⁰² A study of 541 PD patients with symptoms of dementia randomized to rivastigmine or placebo demonstrated significant benefit in the mean Alzheimer Disease Assessment Scale-Cognitive Component (ADAS-cog) score (2.1 points in the active group versus 0.7 in the placebo group [$P < .001$]) and the MMSE (0.8 in the active group versus 0.2 in the placebo group [$P = .03$]).¹⁰³ Nausea, vomiting, dizziness, and tremor were significantly more frequent in the rivastigmine group. It should be noted that 55.5% of the active subjects were receiving 9 to 12 mg, a dose substantially lower than the suggested dose of 24 mg/d. A follow-up report demonstrated sustained benefit in a 48-week extension study.¹⁰⁴ Another rivastigmine report of 487 subjects reports significant improvements in attention.¹⁰⁵ A 12-week study comparing donepezil and rivastigmine found similar improvements in cognition, but that donepezil was better tolerated.¹⁰⁶

Memantine is reported to improve symptoms in moderate cases of AD and PD, but is also known to trigger psychosis in some PD patients. Because the memantine potencies at NMDA receptors and dopamine D2 receptors are of a similar order of magnitude, it is likely that the clinical features of memantine can be attributed to its action at both types of receptors.¹⁰⁷

Psychiatric Disorders

Psychosis in PD is linked to cognitive decline and mortality, and the criteria for psychosis in PD were recently reviewed by a National Institutes of Health working group.¹⁰⁸ A review of PD patients with psychosis found that after 2 years, hallucinations were linked to dementia (68%), nursing home placement (42%), or death (25%).^{109,110} Psychosis in PD typically begins 10 years after diagnosis, and early onset psychosis suggests the diagnoses of DLB disease, AD, or a pre-existing psychiatric diagnosis. Autopsy series report high concentrations of Lewy bodies in the parahippocampus, amygdala, and frontal, temporal, and parietal lobes.

Symptoms of psychosis include hallucinations and delusional thought. Presence or passing (vague images in the peripheral vision) hallucinations and visual illusions are early symptoms. Persistent images are superimposed on the normal environment.¹⁰⁸ Visual hallucinations are by far the most common type of hallucinations, and are usually well-formed people or animals, or inanimate objects.¹⁰⁸ Caregivers report that alerting stimuli will usually improve symptoms. Delusions are paranoid, usually spousal infidelity or abandonment. Grandiose, somatic and religious delusions are infrequent.¹¹¹

Delirium is common in PD patients due to their comorbid medical problems and multiple medications. Distinguishing delirium from drug-induced psychosis may be difficult, especially in a patient with dementia.¹¹² Fluctuating levels of consciousness, marked declines in cognitive performance, increased confusion, and disorientation

from baseline are the hallmark signs. In psychotic patients, baseline memory, orientation, and cognition are unimpaired.

Two trials compared low-dose clozapine versus placebo with a significantly better outcome for clozapine regarding efficacy and motor functioning.^{113,114} More recently, 27 subjects with PD and recent-onset psychosis were randomly allocated to 2 arms of 22 weeks treatment with quetiapine or clozapine. Both drugs were equally effective. Clozapine had an advantage over quetiapine in controlling the frequency of hallucinations ($P = .097$) and had a significant advantage in reducing delusions ($P = .011$).^{115,116} In 2 further placebo controlled trials, olanzapine did not improve psychotic symptoms and significantly caused more extrapyramidal side effects.^{117,118} Fourteen patients meeting entry criteria were started on aripiprazole 1 mg/d and titrated up to a maximum dose of 5 mg as needed. Although some patients had a favorable response, aripiprazole was associated with an exacerbation of motor symptoms.¹¹⁹

Depression

Depression is reported in 30% to 90% of patients with PD.^{120,121} A recent metaanalysis suggests that the average prevalence of major depressive disorder is 17%, with dysthymia occurring in 13% and minor depression in 22% of PD patients.¹²² If depression is suspected, inquiry concerning early morning awakening, low mood with diurnal variation, apathy, crying, withdrawal, and suicidal tendencies are helpful. Unique features attributed to depression in the Parkinson population include increased dysphoria, irritability, sadness, anxiety, brooding, cognitive deficits, pessimism, and suicidal ideation without action.¹²³ In addition, PD patients seem to have less guilt and self-blame than other populations.¹¹²

Two large surveys have found that 16 to 20% of patients with PD were taking antidepressant medications.^{124,125} The tricyclic antidepressants, such as amitriptyline or nortriptyline, may be helpful in the treatment of depression, and in addition may improve sialorrhea because of their anticholinergic side effects. These drugs must be used cautiously in patients with cognitive compromise. SSRIs are also helpful in the treatment of depression in patients with PD and seem to be well tolerated.¹²⁶ Of the SSRIs, sertraline has low selectivity for serotonin relative to dopamine reuptake and has been suggested to have the most favorable profile; compared with tricyclics it improves quality of life, particularly in activities of daily living, mobility, and stigma, and may even improve motor symptoms.¹²⁷

Anxiety Syndromes and Panic Attacks

Up to 40% of patients experience clinically significant anxiety, including panic disorder, generalized anxiety, and phobic disorders.¹²⁸ Symptoms difficult to differentiate from PD include tremor, numbness, tingling sensations; somatic symptoms include breathlessness, sweating, chest discomfort, gastralgia, restlessness, and dizziness.¹²⁹ A more unique, yet rare, group of symptoms attributed to this population are a fear of institutionalization, of going insane, or of dying. Treatment of off-period symptoms should be addressed by adjusting dopaminergic therapy; generalized anxiety may require anxiolytic or antidepressant therapies.¹¹²

Impulse Control Disorders

Behavioral disturbances in PD associated with dopaminergic therapy have been recognized for more than 30 years. Hyperlibidinous behavior is emphasized in the early literature on levodopa, but more recently pathologic gambling, compulsive shopping, and binge eating have been recognized.¹³⁰ In addition, some PD patients will

develop compulsive motor behaviors, termed punding, such as endless fumbling through a bag, rearranging collectable objects, or journaling.¹³¹ Dopamine dysregulation syndrome describes patients taking high, and often inappropriate, doses of dopamine replacement therapy, who exhibit severe dyskinesias, cyclical mood disorder with hypomania or manic psychosis, and impairment of social and occupational functioning.¹³² Impulse control disorder (ICD) syndrome comprises several maladaptive behaviors that emerge with PD progression and increasing antiparkinson medications. These include disruptive behaviors or punding, destructive behaviors (compulsive spending or gambling, binge eating, or hypersexuality), and addictive behaviors regarding antiparkinson medications.¹³³

Symptoms of ICD most often respond to reduction or withdrawal of dopaminergic therapy, particularly dopamine agonists. Others reports include SSRIs, quetiapine, valproic acid, naltrexone, topiramate, donepezil, and clozapine.¹³⁴ Acamprosate was approved for the treatment of alcohol dependence in 2004. Because acamprosate is a mGluR5 antagonist and seems to modify D2 receptor density in the nucleus accumbens, it may modify impulsive behavior without significant adverse motor effects.^{135,136} There are also reports of improvement after deep brain stimulation surgery, in the context of dopaminergic therapy reduction. However, some also report worsening or emergence of ICD behaviors after surgery.¹³⁴

Sleep Disorders

Sleep difficulties are estimated to occur in 60% to 98% of patients, and nighttime awakenings are 3 times more frequent in PD patients than in healthy age-matched controls (38.9% versus 12%).¹³⁷ Polysomnography found that PD patients not taking medication had less total sleep time, less sleep efficiency, more frequent awakenings, and greater overall waking time compared with controls.¹³⁸ Excessive daytime sleepiness (EDS) is associated with advancing disease, increasing dopaminergic therapy, longer duration of disease and male gender.^{139,140} Contributing factors include intrinsic abnormalities in PD, concurrent medical illness, sedating medication, and the effects of nocturnal sleep disturbance. With the exception of selegiline, all anti-PD medications have some potential to induce excessive daytime sleepiness. Circadian rhythm disruption is common in advancing PD, and patients often nap frequently during the day with resulting nighttime wakefulness. The advanced sleep phase syndrome in which the patient retires early in the evening is also common in PD. Environmental factors such as noise, frequent awakenings by a bed partner, and nocturia are common causes of insomnia in the normal and PD population.¹³⁷

In rapid eye movement (REM) sleep behavior disorder there is failure of the normal suppression of EMG activity during REM sleep and an absence of atonia. Affected individuals physically act out their dreams, sometimes causing injury to themselves, their bed partners, or caregivers. One study showed that 50% of PD patients undergoing screening polysomnography as part of a research protocol were found to have REM sleep behavior disorder, suggesting a 38% increase in risk of developing PD in patients diagnosed with REM sleep behavior disorder followed for a mean of 13 years.^{141,142}

Sleep attack is a clinical phenomenon of an unavoidable and abrupt transition from wakefulness to sleep. Similar case histories for apomorphine, bromocriptine, cabergoline, pergolide, and lisuride are reported.¹⁴³ Hauser and colleagues¹⁴⁴ retrospectively reviewed reports of daytime somnolence in 22 of 45 subjects participating in 3 double-blind, randomized, placebo-controlled pramipexole clinical trials. Although no differences between active and placebo groups were seen in the double-blind

phase, 21 of 37 subjects reported somnolence in the open-label extension studies, and 14 subjects had moderate to severe difficulties with EDS.

REM behavior disorder, often the initial manifestation of parkinsonism, may respond to nighttime clonazepam or melatonin (**Table 1**). Modafinil 200 to 400 mg/d is effective in reversing EDS and the sedative effects of anti-PD medications.¹⁴⁵ Despite the subjective improvement in daytime drowsiness reported by a substantial percentage of PD patients, no objective benefit on Multiple Sleep Latency Test, Epworth Sleepiness Scale (ESS), Fatigue Severity Scale, or Hamilton Depression Scale could be demonstrated in a double-blind placebo-controlled study.¹⁴⁶ Nocturnal administration of sodium oxybate has been found in an open-label polysomnographic study involving 38 subjects to improve excessive daytime sleepiness and fatigue in patients with PD.¹⁴⁷

Constipation

Prolonged gastrointestinal transit time is seen in more than 80% of PD patients, and constipation is described in 60% of patients.¹⁴⁸ Mean colonic transit time is more than double the normal population. Paralytic ileus affects 7.1% of PD patients; symptoms often include abdominal bloating, pain, nausea, vomiting, and abdominal distension.¹⁴⁹ Anismus, or an inability to relax the external anal sphincter for defecation, is seen in off periods.¹⁵⁰

Effective treatments for constipation include increasing fluid intake, psyllium, polyethylene glycol, bisacodyl, and magnesium sulfate.¹⁵¹ Lubiprostone activates intestinal ClC-2 chloride channels and increases intestinal fluid secretion without altering serum electrolyte levels.¹⁵² Tegaserod maleate, a novel selective serotonin receptor type 4 (5-HT₄), is a partial agonist that stimulates upper gastrointestinal motility.¹⁵³ Another agent, macrogol, an isosmotic electrolyte, has been found to significantly increase the frequency of bowel movements and improve stool consistency.¹⁵⁴ Prucalopride at 4 mg/d, a selective, high-affinity 5-hydroxytryptamine receptor agonist, increased bowel frequency in about 50% of patients with severe chronic constipation, but this agent has not been specifically tested in patients with PD.¹⁵⁵ Other strategies include neostigmine, symbiotic yogurt containing components such as *Bifidobacterium* and fructooligosaccharide, sphincteric botulinum toxin injections, and sacral nerve stimulation.¹⁵⁶

Urological Dysfunction

Lower urinary tract symptoms occur in 38% to 71% of patients with PD, and are attributed to loss of the dopaminergic inhibitory effect on micturation.¹⁵⁷ Detrusor overactivity (DO) causes urgency, frequency, and incontinence. Bladder contraction is mediated through the cholinergic, parasympathetic (muscarinic) pelvic nerve, whereas relaxation results from noradrenergic sympathetic receptors at the hypogastric nerve.¹⁵⁸ Urethral contraction is linked to noradrenergic, sympathetic hypogastric nerve and cholinergic (nicotinic), somatic pudendal nerve activity.

Sexual dysfunction occurs in 12% to 60% of men with PD.¹⁵⁹ A review of sexual functioning of 32 women found difficulties with arousal (87.5%), reaching orgasm (75.0%), and sexual dissatisfaction (37.5%). In the same survey, 43 men reported erectile dysfunction (68.4%), sexual dissatisfaction (65.1%), premature ejaculation (40.6%), and difficulties reaching orgasm (39.5%). Associated illnesses, use of medications, motor difficulties, depression, anxiety, and advanced stage of PD contributed to sexual dysfunction.¹⁶⁰

Increased urinary frequency due to overactive bladder often improves not only with levodopa treatment¹⁶¹ but also with antimuscarinic oxybutynin (5 mg 3–4 times daily),

oxybutynin transdermal patch (1 patch twice a week), tolterodine (2 mg 3 times daily), solifenacin (5–10 mg/d), or darifenacin (7.5–15 mg/d).¹⁶² More recently, botulinum toxin injections into the bladder wall have been reported to be beneficial.^{163,164} Sildenafil citrate has been found to be safe and effective in the treatment of erectile dysfunction associated with PD, but may unmask orthostatic hypotension.¹⁶⁵

Orthostatic Hypotension

Orthostatic hypotension is reported in 10% to 20% of patients, and increases with age and severity of PD; if unrecognized, it may lead to unnecessary evaluations for dizziness and syncope. Symptoms include light-headedness, initial dizziness on standing, fatigue, and pain across the back of the shoulders and neck. Frequent monitoring of standing and sitting blood pressure are helpful in following this problem, and may often be done by caregivers.^{112,166}

Orthostatic hypotension can be treated with salt, fludrocortisone, and midodrine.^{167,168} In 2007, the FDA approved DOPS (Droxidopa, Chelsea Therapeutics) for the treatment of orthostatic hypotension.¹⁶⁹ Droxidopa (*L-threo*-3,4-dihydroxyphenylserine or L-DOPS) is a synthetic amino acid precursor of norepinephrine that has been marketed in Japan since 1989 for the treatment of orthostatic hypotension.

Salivary Disturbances

Sialorrhea has been reported in as many as 78% of patients with PD.¹⁷⁰ Although the exact mechanism of sialorrhea remains poorly understood, it is usually a function of excessive saliva production or difficulties in clearing saliva from the mouth. In the PD population, this symptom is most likely from the combination of infrequent and impaired swallowing. Three major pairs of salivary glands (parotid, submandibular, and sublingual) produce more than 90% of saliva. Drooling is a highly embarrassing PD symptom, and is often easily treated with botulinum toxin injections.^{171,172}

SUMMARY

Treatment of symptoms of PD should be subclassified into motor and nonmotor categories. In the patient at the early stages of PD, motor symptoms should always be emphasized, but with time and disease progression nonmotor problems are increasingly important. At the early stages of PD, decisions to initiate therapy are based on the patient's perceptions of disability, and appropriate therapies may include MAO-B inhibition, dopamine agonists, and levodopa. In the event of motor complications, a balanced approach with dopamine agonists and levodopa is recommended. Severe dyskinesias and unpredictable wearing off periods often require deep brain stimulation, but in the future less cumbersome and less costly continuous infusion therapies may be available. Eventually, nonmotor symptoms will become the primary focus of care, and a careful review of the array of these symptoms may lead to interventions that greatly improve the patient's quality of life.

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