

## Parkinson's Disease: Focus on Management Alternatives

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### AUDIENCE

This activity is designed for physicians, pharmacists, nurses, health planners, directors of managed care organizations, and payers of health services.

### GOAL

To understand the impact that Parkinson's disease has on patients and to identify areas of drug therapy that can be optimized to improve a patient's quality of life.

### OBJECTIVES

1. Discuss the epidemiology and pathophysiology of idiopathic Parkinson's disease (IPD).
2. Identify causes of secondary parkinsonism and medications associated with drug-induced parkinsonism.
3. Discuss the cardinal and secondary manifestations of IPD.
4. Outline the 6 stages of IPD.
5. Identify therapeutic alternatives for various levodopa treatment failures.
6. Identify the 3 newer antiparkinson agents and state their mechanisms of action, common adverse effects, drug interactions, and appropriate use.
7. Identify the appropriate use, common adverse effects, and drug interactions of dopamine agonists, anticholinergic agents, monoamine oxidase inhibitors, and catechol-*O*-methyltransferase inhibitors in Parkinson's disease therapy.



### **CONTINUING EDUCATION CREDIT**

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-00-201-HO1. This course expires on January 31, 2003.

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Parkinsonism is a neurologic syndrome characterized by the cardinal manifestations of resting tremor, rigidity, postural instability, and bradykinesia. Dr. James Parkinson first described the condition that now bears his name as the "shaking palsy" in 1817.<sup>1-3</sup> In recent years, there have been a number of advancements in the understanding of parkinsonism, and many new drugs have been developed that aim at symptomatic treatment of the disease.

### **Epidemiology**

Idiopathic Parkinson's disease (IPD) is a neurodegenerative disorder that afflicts approximately 1% of adults over age 65 years in the United States.<sup>2</sup> An estimated 20 new cases per 100,000 people are diagnosed annually.<sup>2,4-6</sup> Prevalence and incidence of this disorder increase with age. The average age of onset has been reported as 55 years,<sup>7</sup> and at least 66% of patients suffering from the disease experience onset of signs and symptoms between the ages of 50 and 69.<sup>4</sup> Idiopathic Parkinson's disease is more commonly seen in men than women, with a male to female ratio of 3:2.<sup>5,8</sup>

### **Etiology**

Evidence increasingly suggests that an active process of neuronal toxicity occurs in patients suffering from IPD. Various mechanisms of cellular degeneration have been theorized. Genetic predisposition,<sup>5,9</sup> environmental toxins,<sup>5,9</sup> mitochondrial enzyme activity abnormalities, and free radical production leading to a state of oxidative stress have been postulated as having roles in neuronal deterioration.<sup>1,9</sup>

### **Pathophysiology**

Idiopathic Parkinson's disease is a disorder of the extrapyramidal system of the brain, which is involved in regulating voluntary smooth muscle activity and sustaining posture and muscle tone.<sup>2</sup> The principal deficit that occurs is a loss of pigmented, dopaminergic neurons in the pars compacta of the substantia nigra, which normally provide

innervation to the caudate and putamen (striatum).<sup>1,10</sup> Although progressive loss of inhibitory dopaminergic neurons is associated with the normal aging process, an 80% to 90% loss of striatal dopamine content is required to cause symptomatic IPD.<sup>10</sup> The occurrence of parkinsonian symptoms is associated with an approximate 60% loss of dopaminergic neurons.<sup>8</sup> In addition to the progressive loss of dopamine in the nigrostriatal tracts, a relative increase in the excitatory neurotransmitter acetylcholine occurs.<sup>2</sup> The pathologic hallmark of the disease is the presence of eosinophilic intraneuronal inclusion bodies within the dopaminergic cells called Lewy bodies.<sup>2,7,11</sup> Small numbers of Lewy bodies are seen in most patients with IPD, and an increasing number may be the rudimentary pathology in late-stage patients who develop dementia.<sup>12</sup>

A number of neurotransmitters are involved in the synaptic organization of the basal ganglia, and thus in motor activity, including acetylcholine, dopamine,  $\beta$ -aminobutyric acid, serotonin, substance P, and glutamate.<sup>1</sup> The symptomatic manifestations of IPD are primarily the result of the disproportion of dopamine and acetylcholine; drug treatment is aimed at correcting the imbalance.<sup>2</sup> However, the other neurotransmitters involved are also conceivable targets for intervention.<sup>1</sup>

### ... DIAGNOSIS ...

Although there is no definitive diagnostic test for Parkinson's disease to date, criteria for IPD have been developed. Many experts in the field consider the presence of 2 of the 3 cardinal motor signs (limb muscle rigidity, resting tremor, postural instability), along with bradykinesia<sup>1,3</sup> and a strong response to an adequate dose of levodopa, essential to diagnose IPD. However, response to levodopa does not confirm a diagnosis of IPD because some secondary forms of parkinsonism also may respond.<sup>8</sup>

Although IPD accounts for approximately 75% to 80% of cases of parkinsonism, the signs and symptoms associated with secondary parkinsonism have a variety of causes that should be acknowledged. The differential diagnosis includes neurodegenerative and metabolic disorders, toxin exposures, hydrocephalus, infection, trauma, and vascular diseases.<sup>6</sup> A brief discussion of causes of secondary parkinsonism, which must be distinguished from the idiopathic form, follows. Treatment of secondary forms should focus on the primary cause

and, thus, will not be further reviewed in this article.

Drugs are often a cause of secondary parkinsonism. In that case, the condition may be reversible by withdrawal of the offending agent. It is imperative to obtain an accurate list of medications when a patient presents with signs of parkinsonism. Drugs commonly associated with secondary parkinsonism block striatal dopamine receptors or deplete striatal dopamine.<sup>8</sup> These agents include antipsychotics (phenothiazines, butyrophenones, thioxanthenes), antiemetics (metoclopramide, prochlorperazine), and the antihypertensive agents methyldopa and reserpine. Other medications implicated in case reports to cause or unmask tremor or parkinsonism include amitriptyline, calcium channel antagonists (verapamil, diltiazem), captopril, amiodarone, cytosine arabinoside, lithium, lovastatin, and various anticonvulsants.<sup>1,4,6,13,14</sup> Several weeks may be required after discontinuation of the suspected agent for symptoms to subside. However, parkinsonism lasting longer than 6 months after discontinuation of a drug may be attributed to IPD unmasked with exposure to antidopaminergic agents.<sup>8</sup>

Toxic agents that have been associated with decreases in striatal dopamine and the development of secondary parkinsonism include carbon monoxide poisoning, the designer drug of abuse methylphenyl-tetrahydropyridine (MPTP, a by-product of meperidine synthesis), cyanide, manganese, herbicides, and petrochemicals.<sup>1,6</sup>

Vascular events resulting from lacunar disease, including stroke, can cause gait disorders that are often confused with parkinsonism. Vascular causes may often be associated with a previous medical history of hypertension or diabetes, clinical signs such as aphasia and hemiparesis, a stepwise or lack of progression of the disease, and a poor response to levodopa.<sup>6</sup> Vascular parkinsonism may be diagnosed by neuroimaging, with magnetic resonance imaging evidence consistent with small infarcts.<sup>8</sup>

Structural lesions that may cause secondary parkinsonism include brain tumors occurring in the basal ganglia or infectious masses that compress the basal ganglia and brain stem. Parkinsonism due to this type of disorder is often acute or subacute in onset and includes neurologic signs and symptoms such as hemiparesis, hyperreflexia, aphasia, sensory deficit, and seizures.<sup>6</sup>

Infectious causes also have been implicated in some forms of secondary parkinsonism. Post-

encephalitic parkinsonism is rarely seen today, but was prominent in the first half of the 20th century. It presented with features similar to those of IPD, with the addition of oculogyric crises. Creutzfeldt-Jakob disease and acquired immune deficiency syndrome (AIDS) also have been linked to rare cases of secondary parkinsonism.<sup>6,9</sup>

Metabolic disorders associated with signs and symptoms of secondary parkinsonism include hypothyroidism or hypoparathyroidism.<sup>6</sup>

Neurodegenerative disorders associated with parkinsonian features include progressive supranuclear palsy, multiple system atrophy, Alzheimer's disease, corticobasal degeneration, Shy-Drager syndrome, striatonigral syndrome, and hemiatrophy-parkinsonism.<sup>6-8</sup>

Hereditary disorders associated with secondary forms of parkinsonism include Wilson's disease, Huntington's disease, and autosomal dominant Lewy body disease.<sup>6,8</sup>

To rule out secondary causes when evaluating a patient with parkinsonism, it is essential to obtain a good medical history of symptom assessment, family illness, and drug use, in addition to neurologic examination.<sup>6</sup>

... CLINICAL FEATURES ...

The 4 primary manifestations of IPD include resting tremor, bradykinesia, rigidity, and postural instability.<sup>3</sup> Resting tremor (4-6 Hz) is often the sole presenting feature of IPD and is present in approximately 75% of patients at some point in the course of the disease.<sup>1,3</sup> Tremor typically involves the hands, often described as "pill-rolling" involving the thumb and index finger, but can involve the jaw or legs.<sup>1,2</sup> Some patients may feel an internal tremor (shaking) that is not visible externally. Emotional or physical stress may worsen tremor. Although tremor is often the most noticeable sign of IPD, it is usually the least disabling, as it is abated by purposeful movement and is absent during sleep. Resting tremor is rarely seen in secondary parkinsonism, with the exception of drug- or toxin-induced syndromes.<sup>8</sup>

Bradykinesia is a diminished ability to initiate movement, a greatly disabling symptom of IPD. Characteristic features of bradykinesia include diminutive slow handwriting (micrographia), facial masking, decreased blinking frequency, gradual decline in clarity and volume of speech, drooling caused by a decreased rate of voluntary

swallowing, and diminished ability to perform motor tasks such as cutting food or combing hair.<sup>1,3,8</sup>

Rigidity, often described as "ratcheting" of the arms or "cogwheel" in quality, involves an increased muscular resistance to passive range of motion that

**Table 1.** Common Secondary Clinical Features of Idiopathic Parkinson's Disease

| Sign/Symptom                 | Comments   |
|------------------------------|--|
| Autonomic dysfunction        | Includes abnormal thermoregulation, increased perspiration, orthostatic hypotension, urinary bladder dysfunction (urgency, frequency, loss of control, nocturia), sexual dysfunction                   |
| Cognitive dysfunction        | Includes dementia (short-term and remote memory affected, usually a late manifestation), bradyphrenia  |
| Craniofacial manifestations  | Includes masked facies, decreased eye blinking, dysarthria, sialorrhea   |
| Dermatologic findings        | Seborrhea affecting face and scalp   |
| Gastrointestinal dysfunction | Includes constipation (affects 50% of patients), impaired gastrointestinal motility, dysphagia, sensation of fullness  |
| Musculoskeletal disorder     | Includes scoliosis, wrist and foot dystonia, peripheral edema  |
| Psychiatric disturbance      | Affects up to 40% of patients; depression, anxiety (panic attacks, social phobia), psychosis (visual hallucinations)   |
| Sensory disturbance          | Includes pain (occurs as aching, tingling, numbness, coldness, burning), paresthesias, cramping, olfactory dysfunction, visual disturbance (occurs as blurring, double vision, impaired accommodation) |
| Sleep disturbance            | Affects 74% to 98% of patients; sleep initiation and maintenance may be affected; worsens with disease progression   |

Source: Adapted from reference 3.

occurs in both flexor and extensor muscles. Rigidity is usually present from the onset of the disease in varying degrees and may contribute to bradykinesia, as well as loss of postural control and associated movements.<sup>1,3,9</sup>

Postural instability usually occurs in later stages of IPD, but is often considered the most disabling manifestation of the disease. Patients may have difficulty initiating and terminating steps as the disease progresses, resulting in a hurried or propulsive gait (festination).<sup>1-3</sup> As postural instability progresses, patients are at a greater risk for falls and often require assistive devices to aid with balance or become wheelchair bound.<sup>3,9</sup>

Criteria for clinical staging of IPD was first developed in 1879 and most recently refined in 1967 by Hoehn and Yahr.<sup>15</sup> This 6-tiered staging for Parkinson's disease is as follows:

- Stage 0: No clinical signs evident.
- Stage I: Unilateral involvement only. Functional impairment usually minimal or absent.
- Stage II: Bilateral or midline involvement. No impairment of balance.
- Stage III: Bilateral involvement. First sign of impaired righting reflexes.
- Stage IV: Fully developed, severely disabling disease. Unassisted standing and walking but markedly incapacitated.
- Stage V: Confined to bed or chair unless aided.

A variety of secondary clinical features of IPD may influence the course of the disease, as well as a patient's quality of life (Table 1). Awareness of associated symptoms in addition to the cardinal features of the disease allows healthcare practitioners to treat specific symptoms and improve the care of patients suffering from this disorder.<sup>3</sup>

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... TREATMENT PRINCIPLES ...

Parkinsonism is a chronic, debilitating disease with no known cure. Current drug therapies are strictly palliative.<sup>2,4</sup> The goals of treatment are to relieve the symptoms of the disease and maintain the patient's quality of life by maximizing independence and mobility.<sup>16</sup> Management of parkinsonism should include programs to optimize the patient's general health and nutritional, emotional, and neuromuscular status.<sup>11</sup> By adopting a holistic approach, the healthcare practitioner can treat the disease symptoms and consider emotional support

for both the patient and caregiver.<sup>17</sup> Support groups, home health services, and healthcare professionals such as pharmacists and social workers are important components of a parkinsonism treatment team. New surgical options are available, primarily for the IPD patient who has been treated with multiple medications or for the patient with levodopa-induced dyskinesias. Surgical neuroablation irreversibly disrupts an abnormal nucleus, whereas deep brain stimulation creates a reversible, functional lesion with adjustable stimulation parameters.<sup>18</sup> These surgeries may be therapeutic options for appropriate patients, but they are beyond the scope of this article.

Drug treatment of Parkinson's disease has centered on increasing dopamine's availability in the central nervous system (CNS), inhibiting the effects of acetylcholine, and preventing further cell membrane damage. Increasing levodopa precursors and synthesis cofactors has not been found to be effective.<sup>1</sup> Agents providing these effects will be discussed individually in the sections that follow.

### Individual Antiparkinson Agents

Brief summaries of information about individual agents are provided in the following section of this article. This information is not intended to be a substitute for the package insert. Full prescribing information should be consulted for complete contraindications, warnings, and precautions before prescribing any of these drugs. Table 2 compares the initial dosing, dosage adjustment, and withdrawal recommendations for individual antiparkinson agents. Table 3 compares the more frequent adverse reactions to antiparkinson agents.

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... DOPAMINE PRECURSOR ...

### Levodopa

Levodopa, the precursor to dopamine, has been the single-most important drug in the antiparkinson armamentarium. Levodopa was investigated for treating parkinsonism as early as 1967, after trials of small doses of dopa were not successful. The levo isomer proved more effective when the dose was increased.<sup>4</sup> Naturally occurring dopamine is formed by the conversion of tyrosine to L-dopa by tyrosine hydroxylase and the subsequent conversion to dopamine by L-amino acid decarboxylase. Exogenous dopamine is unable to cross the blood-brain barrier. Levodopa administered orally enters the blood after it is absorbed from the gastrointestinal (GI) tract, crosses the

**Table 2.** Initial Dosing of Antiparkinson Drugs

| Drug               | Initial Oral Daily Dose   | Adjustment  | MDD   | Discontinuing Therapy   |
|--------------------|---|---|---|---|
| Levodopa           | 0.5-1 g daily divided in two or more doses with food  | Gradually increase dose by 0.75 g every 3-7 days as tolerated   | 8 g   | Gradual to avoid NMS  |
| Carbidopa          | 70-100 mg required to saturate peripheral decarboxylase and avoid nausea  | Increase by 12.5-25 mg as needed to avoid nausea  | 200 mg  | Gradual   |
| Carbidopa/Levodopa | Individualize and titrate; start with one tablet of 10:100 carbidopa/levodopa three or four times daily or one tablet of 25:100 three times daily; see Table 4 for dose when converting from levodopa   | Increase every 1-2 days as needed and as tolerated  |   | Stop levodopa 8 h before starting combination therapy   |
| Anticholinergics:  |   |   |   |   |
| • Benztropine      | • 1-2 mg per day at bedtime   | • Reduce other antiparkinson drugs gradually  | • 6 mg  | Gradual   |
| • Biperiden        | • 2 mg three or four times daily  |   | • 16 mg   | Gradual   |
| • Diphenhydramine  | • 25-50 mg three to four times daily  | • Increase to 5 mg three times daily and before bedtime if required and well tolerated  | • 300 mg  | Gradual   |
| • Procyclidine     | • 2.5 mg three times daily after meals  |   |   | Gradual   |
| • Trihexyphenidyl  | • 1-2 mg in three divided doses with meals; levodopa and trihexyphenidyl dose may need to be decreased<br>• Sustained-release form: substitute milligram for milligram and give at breakfast or in two divided doses every 12 h   | • Increase by 2 mg per day at 3- to 5-day intervals   | • 10 mg   | Gradual   |
| Amantadine         | 100 mg twice daily; decrease to 100 mg daily if taking other antiparkinson drugs or if patient has serious illness<br><br>Adjustment for renal function required<br><i>CrCl (mL/min): Adjusted Dose:</i><br>60 200 mg alternated with 100 mg daily<br>40-50 100 mg daily<br>30 200 mg twice weekly<br>20 100 mg three times weekly<br>10 200-mg load then 100 mg weekly | If efficacy fades, increase to 300 mg daily or discontinue and reintiate  | 400 mg  | Gradual to avoid NMS  |
| Bromocriptine      | 1.25 mg once or twice daily with meals  | If necessary, increase dose by 2.5 mg per day every 2-4 wk  | 40 mg; not studied over 100 mg                              | Gradually, in 2.5-mg/day increments   |
| Pergolide          | 0.5 mg for first 2 days, in divided doses three times daily; cautiously decrease carbidopa/levodopa dose during titration phase.  | Gradually increase dose by 0.1 or 0.15 mg/day every third day over the next 12 days; dosage may then be increased by 0.25 mg/day every third day until optimal therapeutic response is achieved | 5 mg  |   |
| Pramipexole        | Individualize and titrate<br>Normal renal function: 0.375 mg/day given in three divided doses; decrease concomitant levodopa dose about 25%.<br>• CrCl 35-59 mL/min: 0.125 twice daily<br><br>• CrCl 15-34 mL/min: 0.125 every day  | • Every 5-7 days, increase total daily dose by 0.375 mg<br><br>• Every 7 days increase total daily dose by 0.25 mg<br>• Every 7 days increase total daily dose by 0.125 mg                      | • 4.5 mg<br><br>• 1.5 mg twice daily<br>• 1.5 mg once daily | Gradual over 1 wk   |
| Ropinirole         | Individualize and titrate; 0.25 mg three times daily; decrease concomitant levodopa dose about 25% to 30%   | Increase total daily dose by 0.75 mg every week; after week 4, may increase weekly by 1.5 mg/day. If more than 9 mg/day is required, increase by 3 mg/day on weekly basis to maximum dose       | 24 mg   | Gradually over 7 days; reduce from three times to two times daily for 4 days, then once daily |
| Tolcapone          | 100 mg three times daily  | Moderate to severe cirrhosis: do not increase to 200 mg three times daily; not studied in patients with CrCl of <25 mL/min  | 600 mg  |   |
| Entacapone         | 200 mg, up to eight per day<br>Use caution with hepatic-impaired patients   | 59% of patients whose daily levodopa was ≥800 mg required up to a 25% dose reduction  | 1600 mg   | Gradual to avoid IPD and NMS  |
| Selegiline         | 10 mg per day in divided doses (5 mg at breakfast and lunch)  | May be able to reduce levodopa dose by 10% to 30%   |   |   |

MDD = maximum daily dose; NMS = neuroleptic malignant syndrome. CrCl = creatinine clearance; IPD = idiopathic Parkinson's disease.

Source: Adapted from references 19 and 20.

**Table 3.** Adverse Reactions to Antiparkinson Drugs

| Drug                   | Severe Adverse Reactions*  | Common Adverse Reactions   |
|------------------------|--|--|
| Levodopa               | After 1 or more years, patients may experience "on-off" phenomenon or start hesitation; neuroleptic malignant syndrome upon abrupt discontinuation | Difficult urination, dizziness, orthostatic hypotension, irregular heartbeat, depression, mood changes, nausea, vomiting, unusual body movements, anxiety, confusion, nervousness  |
| Anticholinergic agents | Anhidrosis, hyperthermia<br>Withdrawal symptoms: anxiety, extrapyramidal symptoms, tachycardia, orthostatic hypotension                            | Anticholinergic effects (blurred vision; constipation; decreased sweating; difficulty urinating; drowsiness; dry mouth, nose, or throat; nausea; vomiting; light sensitivity)  |
| Pramipexole            | Hallucinations, dizziness, somnolence, extrapyramidal symptoms, headache, confusion, nausea  | Nausea, dizziness, somnolence, insomnia, constipation, asthenia, hallucinations, accidental injury, dyspepsia, general edema   |
| Ropinirole             | Nausea, dizziness, headache, aggravated Parkinson's, hallucinations (dose related), somnolence, vomiting   | Fatigue, syncope, dizziness, dyspepsia, nausea, vomiting, somnolence   |
| Tolcapone              | Diarrhea, hallucinations (> 75 y), dystonia (< 75 y), somnolence (females > males)   | Abdominal pain, anorexia, diarrhea, dizziness, dyskinesia, dystonia, hallucinations, headache, insomnia, nausea, orthostatic complaints, somnolence, syncope, upper respiratory tract infection, vomiting  |
| Selegiline             | With doses greater than 10 mg daily: bruxism, muscle twitches, myoclonic jerks   | Dyskinesias, mood or other CNS changes, abdominal pain, dizziness, dry mouth, insomnia, nausea, vomiting   |
| Amantadine             | Depression, hallucinations, livedo reticularis, peripheral edema, orthostatic hypotension  | Nausea, dizziness, insomnia, impaired concentration  |
| Bromocriptine          | Pulmonary infiltrates on long-term, high-dose therapy (20-100 mg daily); these slowly resolved after therapy was discontinued                      | Hypotension, nausea  |
| Pergolide              | 10% experience orthostatic hypotension, tolerance develops; CNS symptoms, hallucinations, confusion caused discontinuation most frequently         | CNS effects (dyskinesia, hallucinations, insomnia), hypertension, nausea, constipation, diarrhea, dyspepsia, dry mouth, dysphagia, flulike symptoms, rhinitis, weakness, anemia, peripheral edema, twitching, myalgia, sweating, diplopia, urinary frequency |

CNS = central nervous system.

\*Adverse reactions that led to discontinuation of treatment during clinical trials or occurred in more than 2% of patients.

Source: Adapted from references 19 and 20.

blood-brain barrier, and is converted to dopamine in the basal ganglia, where it acts as naturally occurring dopamine. Ninety-five percent of levodopa is converted to dopamine by L-amino acid decarboxylase. The action of this enzyme can be blocked in the periphery by the antagonist carbidopa, which does not cross the blood-brain barrier. Therefore, levodopa enters the CNS and follows the synthetic path to dopamine formation and storage. Combining carbidopa with levodopa results in increased concentrations of levodopa in the CNS and decreased conversion of L-dopa to dopamine in the periphery, where it causes adverse effects.<sup>1</sup>

### Carbidopa

Carbidopa allows higher CNS concentrations of levodopa by inhibiting the peripheral decarboxylation of levodopa. Carbidopa also allows for smoother, more rapid titration of levodopa, reduces nausea and vomiting, and allows concurrent administration of pyridoxine when needed (see Interactions in Table 5).<sup>19</sup> Carbidopa is only indicated for use with levodopa in patients who require individual dose titration of carbidopa and levodopa. It has no effect when used alone and no ability to produce adverse drug reactions by itself. It may precipitate CNS adverse reactions due to

the increased levodopa concentrations available to the CNS.<sup>19</sup> The DuPont Merck Patient Assistance Program (1-800-474-2762) will provide 25-mg tablets of carbidopa free of charge to patients on carbidopa/levodopa therapy who require additional doses of carbidopa to block the adverse effects of levodopa. A dose of 70-100 mg is required to saturate peripheral decarboxylase and avoid nausea. Levodopa should be discontinued at least 8 hours before beginning concomitant therapy with carbidopa/levodopa.<sup>19</sup> Dyskinesias may occur at lower doses with coadministration of carbidopa/levodopa because more levodopa is available to the CNS. If dyskinesias occur, a dose reduction may be required. Elderly patients have an age-related decrease in dopa-decarboxylase; therefore, they may require a lower dose.

**Carbidopa/Levodopa**

Carbidopa/levodopa as immediate- and sustained-release formulations is used in the management of IPD. The sustained-release carbidopa/levodopa formulation may provide a more physiologic replacement of dopamine than other regimens (eg, alternate-day, pulse, or as-needed dosing) that attempt to reduce total levodopa exposure. A 5-year, multicenter study of immediate-release versus controlled-release carbidopa/levodopa found no difference between the 2 groups in the development of dyskinesias or motor fluctuations. However, patients receiving the sustained-release products showed a significant improvement in quality of life, especially social isolation, emotional reactivity, and activities of daily living.<sup>21,22</sup>

Tablets are available with a ratio of 1:4 (25 mg of carbidopa to 100 mg of levodopa, or 50 mg/200 mg) and 1:10 (10 mg/100 mg). Tablets of the 2 ratios may be combined or supplemented with regular-release carbidopa/levodopa to achieve the optimum daily dose. Patients currently receiving carbidopa/levodopa should have the extended-release product substituted at a dosage that will provide approximately 10% higher levodopa doses than those with their previous combination product. These doses may need to be increased to provide up to 30% more levodopa per day.<sup>19,23</sup> Guidelines for conversion from carbidopa/levodopa to extended-release carbidopa/levodopa appear in Table 4.

Drug holidays involve the complete withdrawal of levodopa and are utilized in patients experiencing severe levodopa adverse effects or who are refractory to levodopa therapy. Drug holidays

require inpatient hospital supervision due to the possibility of severe symptoms developing (eg, acute, painful dystonias; thrombophlebitis; pulmonary embolus) Doses may be reduced up to 50% when levodopa is reinitiated. Improvement is only temporary, lasting several months to a year. Drug holidays are no longer recommended because of the serious risks compared with minimal benefits to the patient.<sup>2,4</sup>

*Dietary Note:* Levodopa competes directly with amino acids for absorption across the GI membrane and with amino acid transport mechanisms into the CNS.<sup>1</sup> Patients should take levodopa initially with food to avoid GI adverse effects.<sup>19</sup> Tolerance usually develops to these effects. Patients may eat 15 minutes after taking levodopa if they tolerate the GI effects. Patients experiencing a suboptimal response to levodopa should limit their protein intake at their morning and noon meals to increase absorption and bioavailability of the drug.<sup>16</sup>

... DOPAMINE AGONISTS ...

Dopamine agonists also are used in the treatment of IPD to increase the availability of dopamine in the CNS. Dopamine agonists act directly on the post-synaptic dopamine receptors so dopamine conversion, storage, and release are not necessary.<sup>24</sup> They are being utilized more frequently in early parkin-

**Table 4.** Guidelines for Converting From Regular-Release to Extended-Release Carbidopa/Levodopa

| Total Daily Levodopa Dose (mg) | Carbidopa/Levodopa Extended Release   |
|--------------------------------|---|
| 300-400                        | 200 mg twice daily  |
| 500-600                        | 300 mg twice daily or 200 mg three times daily  |
| 700-800                        | 800 mg in three or more divided doses (300 mg in the morning and early evening, 200 mg later in the evening)  |
| 900-1000                       | 1000 mg in three or more divided doses (400 mg in the morning and early evening, 200 mg later in the evening) |

Source: Adapted from reference 19.

**Table 5.** Management of Interactions With Antiparkinson Drugs

| Drug  | Drug Affected  | Effect   | Management  |
|---|--|--|---|
| Bromocriptine                                       | Alcohol  | Disulfiram reaction  | Avoid combination   |
| Thioridazine  | Amantadine   | Worsening tremor in elderly patients   | Avoid combination   |
| Triamterene/hydrochlorothiazide                     | Amantadine   | Elevated amantadine concentrations   |   |
| Amantadine, other anticholinergics, MAO inhibitors  | Anticholinergics   | Increased anticholinergic adverse effects  | Adjust dose; disappears when dose is decreased                        |
| Antidiarrheals, adsorbent                           | Anticholinergics   | Decreased effects due to drug adsorption   | Separate administration by 1-2 h                                      |
| Cannabinoids, opiates, barbiturates, alcohol        | Anticholinergics or amantadine                                 | Additive effects; abuse potential exists; severe constipation  | Avoid combinations  |
| Ritonavir   | Bromocriptine  | Increased serum concentrations   | Decrease bromocriptine dose by 50%                                    |
| Macrolide antibiotics                               | Bromocriptine  | 268% increase in AUC; 4.7-fold increase in C <sub>max</sub>  | Monitor for bromocriptine toxicity                                    |
| Dopamine antagonists (neuroleptics, metoclopramide) | Bromocriptine or pergolide                                     | Diminished effectiveness   | Avoid combination   |
| Highly protein-bound drugs                          | Bromocriptine or pergolide                                     |  | Use with caution  |
| Tricyclic antidepressants                           | Carbidopa  | Hypertension, dyskinesia   |   |
| Anesthetics   | Carbidopa/levodopa   | Increases endogenous dopamine  | Discontinue carbidopa/levodopa 6-8 h before administration            |
| Pramipexole   | Carbidopa/levodopa   | Increased effect   | Decrease levodopa dose  |
| Tolcapone   | Carbidopa/levodopa   | Decreased clearance, increased half-life from 2 to 3.5 h; twofold increase in relative bioavailability   | Adjust levodopa dosage  |
| Tolcapone   | COMT-metabolized drugs (methyldopa, dobutamine, isoproterenol) | Increased effect   | Dose reduction  |
| Tolcapone   | CYP 2C9 substrates (tolbutamide, warfarin)                     |  | Monitor INR closely, limited information                              |
| Anticholinergics                                    | Digoxin (slow-dissolution oral tablet)                         | Serum levels increased   | Monitor and adjust dose if needed                                     |
| Bromocriptine                                       | Ergot alkaloids  | Hypertension   | Avoid combination   |
| Anticholinergics                                    | Haloperidol  | Decreased haloperidol concentrations; worsening schizophrenia; tardive dyskinesias                       | Avoid combination   |
| Antacids  | Levodopa   | Increased bioavailability  |   |
| Anticholinergics                                    | Levodopa   | Decreased effectiveness due to decreased gastric motility and increased gastric deactivation of levodopa | Avoid combination   |
| Benzodiazepines                                     | Levodopa   | Decreased effectiveness  | Avoid combination   |
| Bromocriptine                                       | Levodopa   | Increased effect   | Decrease levodopa dose  |
| Hydantoins  | Levodopa   | Decreased effectiveness  | Avoid combination   |
| MAO inhibitors                                      | Levodopa   | Increased effect, hypertensive crisis  | Avoid combination; discontinue 2-4 wk before starting therapy         |
| Methionine  | Levodopa   | Decreased effectiveness  | Avoid combination   |
| Papaverine  | Levodopa   | Decreased effectiveness  | Avoid combination   |
| Pramipexole   | Levodopa   | Increased C <sub>max</sub> 40%; decreased T <sub>max</sub> from 2.5 to 0.5 h                             | Decrease levodopa dose  |
| Pyridoxine  | Levodopa   | Inactivation of levodopa's effect  | Use carbidopa (inhibits B <sub>6</sub> action)                        |
| Ropinirole  | Levodopa   | Increased serum concentrations 20%, increased adverse reactions  | Decrease levodopa dose  |
| Selegiline  | Levodopa   | Increased adverse reactions  | Decrease levodopa dose within first 2-3 days of selegiline initiation |

(Table continues on next page)

sonism to avoid using high doses of levodopa and in late stages of the disease to aid in management of levodopa dose-response fluctuations.<sup>7</sup> At least 5 dopamine receptors have been described; they are generally classified into the dopamine type 1 (D1) family or the dopamine type 2 (D2) family.<sup>25</sup> The D1 subfamily consists of the D1 and D5 receptors; the D2 subfamily consists of the D2, D3, and D4 receptors.<sup>25</sup> For the purposes of discussion, D1 and D2 refer to the subfamilies of receptors. Dopamine agonists directly stimulate the D2 receptors, which

are responsible for clinical improvement and adverse reactions such as dystonias and hallucinations.<sup>25</sup> The role of D1 receptors in IPD is still unclear. Therapeutic benefit seems to require stimulation of both D1 and D2 receptors; however, D1 receptors may contribute to dyskinesias and other adverse symptoms.<sup>25,26</sup> Currently available dopamine agonists have varying effects on these 2 receptors. Bromocriptine acts on the D2 receptor and has some antagonist action on D1 receptors; pergolide is an agonist more at the D2 receptor than

**Table 5.** Management of Interactions With Antiparkinson Drugs (*continued*)

| Drug   | Drug Affected   | Effect   | Management   |
|--|---|--|--|
| Tricyclic antidepressants  | Levodopa  | Decreased effectiveness  | Avoid combination  |
| Tolcapone  | MAO inhibitor, nonselective (phenelzine, tranylcypromine) | Inhibition of the majority of pathways responsible for normal catecholamine metabolism     | Avoid combination  |
| Selegiline   | Opioids   | Increased effect of opiate   | Avoid combination  |
| Dopamine antagonists (neuroleptics, metoclopramide)  | Pergolide   | Diminished effectiveness   | Avoid combination  |
| Anticholinergics   | Phenothiazines  | Pharmacologic and therapeutic actions reduced; increased anticholinergic adverse reactions | Avoid combination  |
| Cimetidine   | Pramipexole   | 50% increase in AUC; 40% increase in half-life   | Adjust dose  |
| Cationic drugs (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, quinine) | Pramipexole   | 20% decrease in oral clearance   | Dose adjustment may be needed  |
| Dopamine antagonists, neuroleptics   | Pramipexole   | Decreased effectiveness  | Avoid combination  |
| Ciprofloxacin (CYP 1A2 inhibitor)  | Ropinirole  | 84% increase in AUC; 60% increase in C <sub>max</sub>                                      | Adjust ropinirole dosage   |
| CYP 1A2 inhibitors or substrates   | Ropinirole  | Altered metabolic clearance  | Adjust ropinirole dosage   |
| Estrogens  | Ropinirole  | 36% decrease in oral clearance   | Titrate ropinirole to tolerance or adequate effect; adjust ropinirole dose if estrogen is stopped or started |
| Selegiline   | SSRIs   | Increased effect; serotonin syndrome   | Discontinue fluoxetine 5 wk before starting selegiline   |
| Selegiline   | Tricyclic antidepressants                                 | Increased cardiac effects  | Avoid combination; wait 2 wk before initiating tricyclic antidepressant                                      |
| Selegiline (>20 mg/day)  | Tyramine  | Hypertensive crisis  | Avoid combination  |

MAO = monoamine oxidase; AUC = area under the concentration-time-curve; C<sub>max</sub> = maximum concentration; COMT = catechol O-methyltransferase; CYP = cytochrome P-450; INR = international normalized ratio; SSRI = selective serotonin reuptake inhibitor; T<sub>max</sub> = time needed to achieve maximum concentration.  
 Source: Adapted from references 19 and 20.

at the D1 receptor; ropinirole's and pramipexole's action comes from stimulating the D2 receptor.<sup>27</sup> Both ropinirole and pramipexole bind with higher affinity to D3 than to D2 or D4 receptor subtypes; however, the relevance of D3 receptor binding in Parkinson's disease is unknown.<sup>28,29</sup> Bromocriptine and pergolide also have affinity for other receptors such as serotonin and  $\alpha$ -adrenergic receptors.<sup>26</sup> This makes patients vulnerable to adverse reactions due to action of these drugs at these other receptors.

### **Pramipexole**

Pramipexole (Mirapex®, Pharmacia & Upjohn, Kalamazoo, MI) was approved by the Food and Drug Administration for the treatment of the signs and symptoms of idiopathic Parkinson's disease.<sup>28</sup> In well-controlled clinical trials pramipexole has been effective in both early Parkinson's patients without concomitant levodopa<sup>30,31</sup> and in patients with advanced disease receiving concomitant levodopa.<sup>32-34</sup> Early Parkinson's patients receiving pramipexole experienced 22% to 29% improvements in assisted daily living scores compared with patients receiving placebo.<sup>31</sup> Advanced IPD patients receiving pramipexole showed significant improvement in assisted daily living scores (21%<sup>34</sup> to 26%<sup>32</sup>) and 37% improvement in their total Unified Parkinson Disease Rating Score (UPDRS) compared with patients receiving placebo.<sup>33</sup> The UPDRS is discussed in the Monitoring section later in this article.

Pramipexole is renally eliminated and is secreted by renal tubules by the organic cation transport system. Therefore, dose adjustment is required in patients with renal insufficiency (see Table 2 for dosing information).<sup>28</sup>

There is an age-related risk of hallucinations attributed to pramipexole in both early and advanced stages of parkinsonism.<sup>28,30,31,33,34</sup> The risk ranges from 1.9 to 6.8 times greater than the risk in the placebo groups.<sup>28</sup> Pramipexole may cause or exacerbate dyskinesias when used in conjunction with levodopa. Decreasing the levodopa dose may ameliorate this side effect.<sup>28</sup> Falling asleep during activities of daily living is a newly reported adverse effect of pramipexole and ropinirole.<sup>35</sup> Eight men with no previous history of sleep disturbances have reported these attacks of sudden, irresistible sleep while driving; all these attacks resulted in automobile accidents.<sup>35</sup> Pharmacia & Upjohn issued a Dear Health Care Professional letter in August 1999 to warn of this new adverse reaction.<sup>36</sup>

### **Ropinirole Hydrochloride**

Ropinirole hydrochloride (Requip®, SmithKline Beecham Pharmaceuticals, Philadelphia, PA) is approved for treatment of the signs and symptoms of idiopathic Parkinson's disease.<sup>29</sup> Ropinirole has been effective in both early Parkinson's disease without concomitant levodopa<sup>37,38</sup> and in patients with advanced disease receiving concomitant levodopa.<sup>39</sup> The 6-month extension of the Adler trial by Sethi et al resulted in fewer ropinirole-treated patients having an insufficient therapeutic response compared with patients receiving placebo (48% vs 20%) and fewer ropinirole-treated patients requiring levodopa rescue compared with patients receiving placebo (46% vs 19%).<sup>38</sup> In the initial 6 months of this trial, 47% of ropinirole-treated patients were considered responders (more than a 30% decrease in UPDRS motor scores) compared with 20% of the placebo-treated patients being classified as responders.<sup>37</sup> The use of ropinirole allowed 35% of advanced Parkinson's disease patients on stable levodopa doses to reduce their levodopa doses by 20%.<sup>39</sup> When ropinirole was compared with bromocriptine in early Parkinson's disease patients, ropinirole-treated patients had significant improvements on their assisted daily living scores. This difference was seen within the first 6 months and was maintained throughout the 3-year study.<sup>40</sup>

Ropinirole has a 55% absolute bioavailability, indicating a first-pass effect.<sup>29</sup> Food does not affect the extent of absorption; however, the time to achieve the maximum serum concentration is increased by 2.5 hours when the drug is taken with a meal. No dosage adjustment is necessary based on gender, weight, age, or moderate renal impairment (creatinine clearance of 30-50 mL/min). Ropinirole has not been studied in patients with severe renal impairment.<sup>29</sup>

Syncope, sometimes associated with bradycardia, was observed in association with ropinirole therapy in both early Parkinson's disease patients not receiving concomitant levodopa and in advanced Parkinson's disease patients receiving concomitant levodopa.<sup>29</sup> Patients starting ropinirole therapy or undergoing a dose escalation should be carefully monitored for signs and symptoms of orthostatic hypotension. Hallucinations occurred in 5.2% of Parkinson's patients not receiving concomitant levodopa compared with 1.4% of placebo-treated patients. Ten percent of advanced Parkinson's patients receiving both ropinirole and levodopa experienced hallucinations compared with 4.2% in the placebo group. Ropinirole may potentiate the dopaminergic side effects of levodopa and may cause

or exacerbate dyskinesias.<sup>29</sup> Decreasing the dose of levodopa may ameliorate this side effect. As mentioned in the Pramipexole section, ropinirole also was implicated in the occurrence of extreme sleepiness in one patient.<sup>35</sup> This patient had taken both pramipexole and ropinirole at different times and experienced falling asleep while driving with both drugs. Although Pharmacia & Upjohn issued a Dear Health Care Professional letter for pramipexole, SmithKline Beecham has not issued such a warning for ropinirole. Healthcare professionals would be wise to warn patients taking dopamine agonists of the possibility of this adverse effect.

As with all antiparkinson drugs, the ropinirole dosage should be titrated gradually in all patients (Table 2). The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of nausea, dizziness, somnolence, and dyskinesia.

### **Amantadine**

Amantadine (Symmetrel®, Endo Pharmaceuticals, Inc., Chadds Ford, PA) is an antiviral agent that was serendipitously discovered also to have antiparkinson activity when a patient with Parkinson's disease reported improved symptoms during treatment with amantadine for flu prevention.<sup>41</sup> This effect was then born out in a 6-month trial in IPD patients. Fifty-eight percent of the patients experienced a sustained benefit for up to 8 months; however, 33% of these responders had a steadily diminishing effect, with the decreased effect leveling off after 4-8 weeks of amantadine treatment.<sup>41</sup> Amantadine is used in patients with mild to moderate akinesia and rigidity and in patients not experiencing tremor. It is seen as short-term monotherapy and is not used in advanced disease.<sup>1,42</sup> Its exact mechanism in IPD is unknown, but amantadine is thought to increase dopamine release, block dopamine reuptake, and stimulate dopamine receptors. Amantadine also has some anticholinergic activity. It is considered to be slightly less effective than levodopa but may be more effective than anticholinergic agents, especially for treating patients with akinesia and rigidity.<sup>16</sup> Amantadine added to anticholinergic antiparkinson drugs may allow the patient to receive additional benefit if their response to these agents alone has been marginal.<sup>16</sup> Rapid therapeutic benefit can be attained when amantadine is started with levodopa.<sup>19</sup> The amantadine dose should be held steady at 100-200 mg daily while the levodopa dose is increased (Table 2).

In a recent clinical trial comparing amantadine with placebo added to optimal levodopa therapy in advanced IPD patients, the addition of amantadine yielded 60% lower dyskinesia scores compared with 6% lower scores in placebo-treated patients.<sup>43</sup> Amantadine produced fewer motor fluctuations and reduced the severity and duration of "off" periods.<sup>43</sup> Patients who require a reduction in levodopa dose because of adverse effects may regain some benefit by adding amantadine to their regimen. Because amantadine is renally eliminated, dosage adjustment is required, and renally impaired patients should be closely monitored for increased adverse effects.<sup>16</sup>

### **Bromocriptine Mesylate**

Bromocriptine mesylate (Parlodel®, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is considered adjunctive therapy to carbidopa/levodopa therapy in IPD patients. As an agonist at pre- and postsynaptic D2 receptors, it may inhibit dopamine turnover. Bromocriptine is a tetracyclic ergot alkaloid and was the first dopamine agonist approved for use in Parkinson's disease in the United States.<sup>25</sup> Because of a high incidence of adverse effects and treatment failures, bromocriptine is not as effective in monotherapy as levodopa.<sup>1</sup> Bromocriptine's adverse-effect profile includes dyskinesias, orthostatic hypotension (often dose related), confusion, and hallucinations.<sup>10</sup> Bromocriptine may provide additional benefit to IPD patients receiving levodopa who are experiencing the "wearing-off" phenomenon.<sup>1,19</sup>

### **Pergolide**

Pergolide (Permax®, Athena Neurosciences, Inc., South San Francisco, CA) has been considered an adjunct therapy to carbidopa/levodopa in the treatment of IPD.<sup>23</sup> A potent dopamine receptor agonist at both D1 and D2 receptors, it is 10 to 1000 times more potent than bromocriptine on a milligram-per-milligram basis.<sup>19</sup> Pergolide directly stimulates postsynaptic dopamine receptors in the nigrostriatal system.<sup>19</sup> In a randomized, double-blind, placebo-controlled study, pergolide monotherapy in early IPD patients resulted in a 30% reduction in UPDRS motor scores in 56.6% of pergolide-treated patients compared with 17% of placebo-treated patients.<sup>23</sup> Pergolide also was preferred by patients and physicians over bromocriptine in a crossover study in patients with declining responses to levodopa.<sup>44</sup> Both drugs showed a significant improvement compared with levodopa treatment alone, but pergolide was tolerated better by patients.

... CATECHOL O-METHYLTRANSFERASE INHIBITORS ...

**Tolcapone**

Tolcapone (Tasmar<sup>®</sup>, Roche Laboratories, Inc., Nutley, NJ) is adjunctive therapy to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.<sup>45</sup> It is a selective and reversible inhibitor of catechol O-methyltransferase (COMT). The normal physiologic function of COMT is to eliminate biologically active catechols (dopamine, norepinephrine, epinephrine, and their hydroxylated metabolites). Catechol O-methyltransferase becomes the major enzyme for levodopa metabolism in the brain and periphery when carbidopa is utilized also. Tolcapone's mechanism of action is believed to be related to its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa.<sup>45</sup> Tolcapone studied in conjunction with levodopa and carbidopa produced more sustained plasma levels of levodopa than administration of levodopa and carbidopa alone. These sustained plasma levels may result in increased therapeutic effects on the symptoms of Parkinson's disease, as well as increased adverse effects.<sup>45</sup> In clinical trials tolcapone significantly increased "on" time and decreased "off" time and allowed the use of a lower levodopa dose.<sup>46-49</sup>

After 3 cases of fatal fulminant hepatic failure were reported in postmarketing use, tolcapone now carries a boxed warning and requires an informed consent document be signed by patients before starting therapy.<sup>45,50</sup> Tolcapone should be used only as an adjunct in Parkinson's patients who are experiencing symptom fluctuations while receiving carbidopa/levodopa and who are not responding satisfactorily to, or are not appropriate candidates for, other adjunctive therapies.<sup>50</sup> Liver function tests must be performed at baseline, every 2 weeks for the first year, every 4 weeks for the next 6 months, then every 8 weeks thereafter.<sup>45</sup> This testing regimen also should be followed if the dose is increased to 200 mg 3 times daily. Hepatic enzyme abnormalities occurred in 1% to 3% of patients in clinical trials. Alanine aminotransferase and aspartate aminotransferase levels increased to more than 3 times the upper limit of normal, with these increases occurring in more women than men. Elevations usually occurred within 6 weeks to 6 months of starting treatment.<sup>48</sup> In about one half of patients the enzyme levels returned to normal while continuing tolcapone therapy.<sup>45,48</sup> When treatment was discontinued, enzymes usually

declined within 2-3 weeks but took up to 1-2 months in some cases.<sup>45</sup>

Three to four percent of tolcapone-treated patients in clinical trials experienced severe diarrhea. This was also the adverse reaction that led to the most discontinuations.<sup>45,48</sup> The diarrhea generally resolved on discontinuation of the drug; however, it did lead to hospitalization in some patients. Diarrhea typically presents 6-12 weeks after tolcapone is started, but it may appear as early as 2 weeks and as late as many months after treatment initiation. Diarrhea from tolcapone use may be associated with anorexia. Hallucinations may present shortly after initiation of therapy, typically within the first 2 weeks.<sup>45</sup> The hallucinations may be responsive to a 20% to 25% reduction in the dose of levodopa. Tolcapone may cause or exacerbate pre-existing dyskinesia. Patients in clinical trials continued to experience frequent dyskinesias despite a reduction in their levodopa dose.

**Entacapone**

Entacapone (Comtan<sup>®</sup>, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is another COMT inhibitor that was recently approved by the FDA as adjunctive therapy for patients treated with levodopa and carbidopa.<sup>51</sup> Studies conducted in patients experiencing motor fluctuations associated with the wearing-off phenomenon during treatment with levodopa showed statistically significant increases in the percentages of "on" time per day with entacapone treatment compared with placebo based on patient diaries.<sup>52,53</sup> In one trial, the effect of entacapone was more noticeable in patients with less than 55% "on" time at baseline.<sup>53</sup> In both trials, daily levodopa dosage requirements were lower in the entacapone-treated patients than in the placebo groups. The improvements in percentage of "on" time and the UPDRS scores seen in entacapone-treated patients returned to approximately baseline shortly after withdrawal of the agent.

Adverse effects consistent with enhanced dopaminergic activity, such as dyskinesias and nausea, were common in entacapone-treated patients and often subsided after levodopa dosage adjustments. Other adverse events seen more frequently in entacapone-treated patients included dizziness, diarrhea, and urine discoloration. Elevations in liver enzymes were not reported in premarketing trials; and thus far, the product labeling for this agent does not carry the same warnings and recommendations for monitoring liver function as for tolcapone.<sup>54</sup>

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... ANTICHOLINERGIC AGENTS ...

Anticholinergic agents act as muscarinic receptor antagonists and are used to control tremors caused by excess, unopposed acetylcholine in the neostriatum.<sup>1</sup> Synthetic anticholinergic agents with more selective CNS activity have replaced the use of naturally occurring belladonna alkaloids.<sup>2</sup> Peripheral anticholinergic effects may be the dose-limiting factors. Antihistamines also have central anticholinergic effects and have a lower incidence of peripheral adverse reactions than the natural or synthetic alkaloids. Trihexyphenidyl and benztropine are the 2 agents most frequently used as adjunctive therapy for IPD, but little evidence exists to support the use of one agent over the others.<sup>2,16</sup> If a patient does not respond to one anticholinergic agent, another may be tried.<sup>2,16</sup>

Anticholinergics work by suppressing central cholinergic activity. They also may inhibit the reuptake and storage of dopamine in the CNS, thus prolonging the action of dopamine.<sup>2,16</sup> Anticholinergics are only helpful in patients presenting with tremor; they reduce the incidence and severity of akinesia, rigidity, and tremor by about 20%.<sup>2</sup> They also reduce drooling. Elderly patients may show an increased sensitivity to anticholinergic drugs, thus requiring strict dosage adjustment and monitoring to prevent CNS adverse events from developing in this population.<sup>16,55</sup> Sucking hard candy or a clove may relieve dry mouth; adequate fluid intake and good oral hygiene may relieve these symptoms also.<sup>16,55</sup> Dry mouth may cause difficulty swallowing or speaking and loss of appetite; a reduction in dose or temporary discontinuation may be required. Constipation or difficulty urinating may occur; the constipation may be relieved by stool softeners. Anhidrosis may occur during hot weather; dose reduction may be required so the patient's thermal regulating ability is not impaired.<sup>16</sup>

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... MONOAMINE OXIDASE-B INHIBITOR ...

Selegiline (Eldepryl<sup>®</sup>, Somerset Pharmaceuticals, Inc., Tampa, FL), a monoamine oxidase-B (MAO-B) inhibitor, is utilized early in the management of IPD to prevent further neuronal degeneration. Selegiline's mechanism of action is not fully understood; however, selective type B monoamine oxidase inhibition irreversibly blocks the metabo-

lism of dopamine in the brain, where MAO-B is the major subtype, and extends the duration of action of levodopa.<sup>1</sup> Use of selegiline often permits levodopa dose reductions and increases the duration of effect by 1 or more hours in patients who experience wearing-off effects of levodopa.<sup>2</sup> Selegiline's neuroprotective effect is thought to be a result of shunting dopamine's metabolic path away from free radical production and oxidative stress.<sup>16,56</sup> This beneficial effect lasts about 1 year and only partially protects against the progression of IPD. Selegiline also may interfere with dopamine reuptake at the synapse, thus prolonging its action at the receptor.<sup>1</sup> Some of selegiline's actions may be due to the actions of 2 active metabolites: l-methamphetamine and l-amphetamine.<sup>1</sup> Because selegiline may delay the need for carbidopa/levodopa by 1 year, it may prolong a patient's ability to remain employed full-time.<sup>1,57</sup> Advanced IPD patients may benefit from the relief selegiline provides from wearing-off effects and fluctuations of L-dopa.<sup>2</sup> Patients should be counseled to not exceed the recommended daily dose of 10 mg in order to avoid a hypertensive crisis.<sup>4,16</sup> Healthcare providers should describe the tyramine reaction to both patients and their families and warn patients about avoiding tyramine-containing foods. Patients should be observed for atypical responses, as the MAO system of enzymes is not completely understood and the quality of enzymes may vary from patient to patient.

There is considerable debate in the literature about an increased risk of mortality in patients taking both levodopa and selegiline. The Parkinson's Disease Research Group of the United Kingdom reported an increase in mortality in patients receiving the combination compared with patients taking levodopa alone,<sup>58</sup> and this group confirmed their original report in a second study.<sup>59</sup> The interim analysis at 3 years showed no differences between the levodopa and levodopa/selegiline treatment groups.<sup>60</sup> Both groups showed significant improvement compared with patients receiving bromocriptine. Olanow et al conducted a meta-analysis of selegiline's effect on mortality.<sup>61</sup> They criticized the Parkinson's Disease Research Group of the United Kingdom trial for allowing patients to be rerandomized, with over one half of patients withdrawn from the original treatment group.<sup>61</sup> Their meta-analysis demonstrated no increase in mortality associated with selegiline treatment with or without levodopa.

... TREATMENT INITIATION ...

The timing of treatment initiation in IPD is controversial.<sup>1,16,62</sup> Some clinicians prefer to initiate early treatment to maximize clinical benefits. Others prefer to delay treatment initiation to avoid complications of levodopa metabolism and the risk of accelerating disease progression.<sup>16,24</sup> Functional status impairment is usually a hallmark sign of the need for treatment.<sup>16,27</sup> However, functional status must be evaluated for each individual because of wide variations in disease progression. Factors useful in assessing the need to start treatment include the affected hand (dominant or nondominant), the patient's employment status, specific parkinsonian symptoms (bradykinesia may be more disabling than tremor), and the patient's feelings.<sup>16</sup>

Most experts agree that neuroprotection is the first issue to consider when a patient is newly diag-

nosed with early IPD; many also agree that selegiline is the current agent of choice despite the fact that it does not halt the progression of the disease.<sup>16</sup> There is considerable controversy in the literature as to the timing of the various antiparkinson agents. Further studies are needed to determine the optimal agent with which to initiate therapy. If a patient's employment status is at risk, dopamine agonists could be used first. This is especially true in younger patients, who are at greater risk for developing motor complications from levodopa.<sup>16</sup> Other experts advocate starting with carbidopa/levodopa. When patients treated with single agents (either carbidopa/levodopa or dopamine agonists) require additional treatment, most experts agree that the patient should receive combination therapy rather than pushing the dose of the current drug.<sup>16</sup>

Some practitioners believe levodopa therapy is only useful for approximately 5 years and should be withheld until disabling symptoms appear. Others believe that there is insufficient evidence to support these beliefs and that withholding levodopa therapy deprives patients of the benefits of the drug. Most do agree that levodopa should be added to a patient's treatment when activities of daily living or job performance are affected by the disease.

Many experts favor initiating symptomatic treatment with a dopamine agonist rather than levodopa, taking into consideration factors such as age, cognitive impairment, disease severity, employment status, cost, and combined therapy.<sup>16,23</sup> Patients less than 70 years of age should begin therapy with a dopamine agonist. Older patients should begin therapy with carbidopa/levodopa as they are less likely to develop levodopa-related motor problems. Older patients have an increased risk of

**Table 6.** Annual Cost of Early Parkinson's Disease Therapy

| Drug Class         | Drug                                  | Dose                           | Annual AWP (\$)* |
|--------------------|---------------------------------------|--------------------------------|------------------|
| Anticholinergics   | Benzotropine                          | 1 mg every day                 | 31               |
|                    | Biperiden                             | 2 mg three times a day         | 326              |
|                    | Diphenhydramine                       | 25 mg three times a day        | 70               |
|                    | Procyclidine                          | 5 mg twice a day               | 412              |
|                    | Trihexyphenidyl                       | 2 mg three times a day         | 198              |
| COMT inhibitors    | Tolcapone                             | 100 mg three times a day       | 2002             |
|                    | Entacapone                            | 200 mg up to eight times a day | 168              |
| Dopamine agonists  | Amantadine                            | 100 mg twice a day             | 230              |
|                    | Bromocriptine                         | 2.5 mg every day               | 570              |
|                    | Pergolide                             | 1 mg three times a day         | 4175             |
|                    | Pramipexole                           | 0.25 mg three times a day      | 1044             |
|                    | Ropinirole                            | 1 mg three times a day         | 1019             |
| Dopamine precursor | Levodopa                              | 250 mg twice a day             | 272              |
|                    | Carbidopa/levodopa                    | 25/100 mg three times a day    | 650              |
|                    | Controlled-release carbidopa/levodopa | 25/100 mg three times a day    | 940              |
| MAO inhibitor      | Selegiline                            | 5 mg twice a day               | 1469             |

AWP = average wholesale price; COMT = catechol *O*-methyltransferase; MAO = monoamine oxidase.

\*Source: reference 63.

adverse effects from anticholinergic agents such as cognitive impairment, blurred vision, and dry mouth. Therefore, these agents should be avoided in older patients.

If a patient already has cognitive impairment, treatment should be initiated with carbidopa/levodopa.<sup>16</sup> All unnecessary drugs should be eliminated from the patient's regimen by gradual discontinuation. Sedatives should be discontinued first, followed by anticholinergics, amantadine, selegiline, and dopamine agonists.

When financial realities outweigh the potential for future benefits, treatment should be initiated with the least-expensive medications. Cost of therapy is discussed in a later section of this article and the costs of agents are compared in Table 6.

### Levodopa Management Problems

Approximately 50% to 75% of patients treated with levodopa will experience fluctuations in their response to the drug within 5-6 years.<sup>7,8</sup> These fluctuations include wearing-off (end-of-dose deterioration), "on-off" effects, dyskinesias, and dystonias.<sup>1</sup> Table 7 outlines specific therapeutic alternatives for many Parkinson's disease treatment problems. The reader also is referred to the consensus algorithm developed by a group of movement disorder experts that addresses the many aspects of Parkinson's disease.<sup>16</sup> The algorithm contains an excellent review of Parkinson's disease, in addition to the extensive algorithms for the management of IPD and the problems encountered in later stages (eg, dysautonomias, falls, motor problems, neuropsychiatric problems, sleep disorders). This decision tree is intended to be a guideline for treatment; however, the authors acknowledge the highly individualized nature of the disease and therapy and the need for clinicians to utilize their best judgment for each individual patient.

As IPD progresses, neurons lose their storage capabilities for dopamine, and patients are dependent on the rate of levodopa administration for a therapeutic response. Patients experiencing severe wearing-off of therapeutic effect after 1.5 to 2 hours may require more frequent doses of levodopa or a sustained-release formulation to alleviate this problem.<sup>1,17</sup> Liquid carbidopa/levodopa may be prepared by pulverizing 10 standard carbidopa/levodopa tablets (25/100 mg) and 2 g of ascorbic acid with a mortar and pestle; this mixture then is added to 1 liter of tap water. This solution is stable for 24 hours.<sup>64</sup> Small doses of the liquid are administered at 60- to 90-minute intervals while keeping the

total daily dose the same.<sup>63</sup> Precise titration on a milligram basis can be achieved, and the gastric-emptying problems associated with tablets are bypassed.<sup>63</sup> This may be more effective for the afternoon dose between meals. Dopamine agonists and COMT inhibitors may be beneficial also.

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### ... MONITORING ...

In general no laboratory tests are utilized to monitor the efficacy of antiparkinson drugs. As described earlier, tolcapone does require liver function test monitoring to avoid permanent liver damage. Patients' response to therapy is monitored by assessment of their clinical status, utilizing physical assessment measures of neurologic function. The following should be assessed regularly: facial appearance, salivation, seborrhea, speech, tremor, rigidity/dyskinesia, finger/foot tapping, rapid alternating movement, standing up from chair without assistance of arms and hands, posture, stability, gait, handwriting, and intellectual and psychiatric functioning.<sup>16,55</sup> The Activities of Daily Living subscale of the UPDRS is useful to evaluate a patient's disability and disease progression. Table 8 lists the elements measured in the UPDRS.<sup>65</sup> Copies of this scale may be obtained from the "We Move" Foundation (see address at end of article). Clinicians at Duke University have developed a new clinical rating scale targeted to measure the early to middle stages of Parkinson's disease.<sup>66</sup> This new scale, titled the Duke University Parkinson's Rating Scale (DUPRS), may introduce confusion into the monitoring of Parkinson's disease because of the similarity of its initials to the UPDRS. It is currently undergoing further validity testing.

The most common adverse effects of antiparkinson drugs are nausea, hypotension, and psychiatric problems; these symptoms should be continually monitored. Long-term levodopa treatment is associated with motor fluctuations, dyskinesias, and neuropsychiatric complications. Refer to Table 3 for other frequent adverse effects seen with antiparkinson drugs.

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### ... DRUG INTERACTIONS ...

Table 5 provides information on drug-drug interactions involving antiparkinson agents, the effect certain drugs have on antiparkinson drugs, and how these interactions can be managed.

**Table 7.** Therapeutic Alternatives for Treatment Problems in Parkinson's Disease

| Stage or Problem                              | Therapeutic Alternatives   |
|---|--|
| Mild disease (stages I and II)                | Selegiline for neuroprotection<br>Anticholinergics if tremor predominant<br>Amantadine<br>Group support, exercise, education, nutrition  |
| Functionally impaired (stage III): age ≤ 60 y | Tremor predominant <ul style="list-style-type: none"> <li>• Anticholinergics</li> </ul> Functional disability <ul style="list-style-type: none"> <li>• Sustained-release carbidopa/levodopa (lowest dose possible)</li> <li>• Dopamine agonists</li> </ul>   |
| Age > 60 y                                    | Sustained-release carbidopa/levodopa   |
| Stage IV or V                                 | Immediate-release carbidopa/levodopa<br>Dopamine agonists  |
| Poor symptom control                          | Increase carbidopa/levodopa dose<br>Add or increase dopamine agonist dose<br>Add COMT inhibitor<br>Exclude other causes of parkinsonism  |
| Suboptimal peak response                      | Begin combination dopaminergic therapy <ul style="list-style-type: none"> <li>• Add levodopa to dopamine agonist</li> <li>• Add dopamine agonist to levodopa</li> </ul> Increase dose of carbidopa/levodopa or dopamine agonist<br>Add immediate-release dose to the morning dose<br>Add COMT inhibitor as levodopa adjunct<br>Switch dopamine agonists  |
| Wearing off                                   | Begin combination dopaminergic therapy <ul style="list-style-type: none"> <li>• Add levodopa to dopamine agonist</li> <li>• Add dopamine agonist to levodopa</li> </ul> Increase frequency of levodopa dosing<br>Increase dose of carbidopa/levodopa (sustained or immediate release)<br>Add COMT inhibitor and decrease levodopa dose<br>Change to sustained-release carbidopa/levodopa<br>Add liquid carbidopa/levodopa<br>Add selegiline if not already taking  |
| On-off  | Begin combination dopaminergic therapy <ul style="list-style-type: none"> <li>• Add levodopa to dopamine agonist</li> <li>• Add dopamine agonist to levodopa</li> </ul> Add COMT inhibitor<br>Modify distribution of dietary protein   |
| Freezing                                      | Increase or decrease carbidopa/levodopa dose<br>Add dopamine agonist<br>Increase or decrease dopamine agonist dose<br>Discontinue selegiline<br>Gait modification, assistance device   |
| No "on" time                                  | Manipulate time and dose of levodopa<br>Add COMT inhibitor<br>Avoid dietary protein<br>Increase gastrointestinal transit time  |
| Dystonias                                     | Early morning foot dystonias <ul style="list-style-type: none"> <li>• Nocturnal sustained-release carbidopa/levodopa</li> <li>• Nocturnal dopamine agonist</li> <li>• Early morning carbidopa/levodopa</li> </ul> Peak dose dystonias <ul style="list-style-type: none"> <li>• Lower dose of carbidopa/levodopa</li> <li>• Add or increase dopamine agonist dose</li> <li>• Consider <i>Botulinum</i> toxin injections if other treatments fail</li> </ul> End of the dosing cycle dystonias <ul style="list-style-type: none"> <li>• More frequent doses of carbidopa/levodopa</li> <li>• Add or increase dose of dopamine agonist</li> <li>• Restrict carbidopa/levodopa to several early to midday doses</li> </ul> |
| Peak-dose dyskinesias                         | Substitute immediate- for sustained-release product.<br>Discontinue selegiline<br>Lower individual doses of carbidopa/levodopa<br>Add dopamine agonist as carbidopa/levodopa doses are decreased   |
| Delayed onset                                 | Give levodopa on an empty stomach before meals<br>Crush or chew tablets and take with a full glass of water<br>See dietary note listed below   |

COMT = catechol *O*-methyltransferase.  
Source: Adapted from references 1, 7, and 16.

... COST OF PARKINSON'S DISEASE ...

Table 6 outlines the annual cost of treating early Parkinson's disease based on the average wholesale prices of the drugs; these prices may differ significantly from the actual cost to the patient. The table was developed for doses that would be seen during the early stages of disease. Dosage of all Parkinson's disease drugs is based on response, so this cost is a low estimate at best. It is readily apparent that the anticholinergics are the least-expensive drugs used to treat Parkinson's disease; however, they cause numerous adverse effects and have limited appropriate uses in Parkinson's patients. Controlled-release carbidopa/levodopa is more expensive than the regular-release product. This cost must be weighed against its benefit in smoothing out plasma levodopa concentrations and decreasing levodopa adverse reactions. In a pharmacoeconomic analysis of standard versus controlled-release carbidopa/levodopa, patients switched from the standard to the controlled-release form experienced significantly more "on" hours without chorea (2.2 hours) and decreased "off" hours per day.<sup>67</sup> Total daily levodopa doses increased, but the dosing frequency decreased. Medication costs increased 21%, and patients also taking selegiline decreased their expenses for selegiline by 20%.<sup>67</sup> Costs for bromocriptine and pergolide did not increase, the cost for anticholinergics decreased slightly, and the cost for amantadine increased. The total drug cost

per hour "on" without chorea decreased by \$2.85, but this decrease was not statistically significant.<sup>67</sup>

Selegiline is expensive but may be a good investment for its neuroprotective effect if the patient can afford it. Although Bryson et al did not perform a formal cost-utility analysis, they point out characteristics of selegiline that may make the drug cost effective.<sup>56</sup> Selegiline's positive impact on end-of-dose fluctuations and its levodopa-sparing effect reduce the overall disability of patients and improve their quality of life.<sup>56</sup> Selegiline's neuroprotective effect slows the onset and progression of disability.<sup>56</sup> Any treatment that improves disability would result in reduced hospitalization, medical care costs, physician visits, and home-based care.<sup>56</sup>

As can be expected, the recently released dopamine agonists (ropinirole, pramipexole) are considerably more expensive than the older drugs (bromocriptine, amantadine). Pergolide is the most expensive Parkinson's drug. Hoerger et al related UPDRS activities of daily living scores and motor scores to disease progression, costs, and patient utility in a cost-effectiveness model of pramipexole in the United States.<sup>68</sup> Disease progression paths were developed for patients with both early and advanced disease. Cost data were computed on the basis of medical costs (including hospitalization); ancillary and community care costs;

lost productivity for patients who can no longer work; drug costs for pramipexole, levodopa, pergolide, and bromocriptine; and nursing home costs.<sup>68</sup> Early-stage patients had an incremental total cost-effectiveness ratio for pramipexole of \$8857 per quality-adjusted life-year (QALY).

**Table 8.** Unified Parkinson's Disease Rating Scale

| Subscale  | Parameters Measured  |   |
|---|--|---|
| I. Mentation, behavior, and mood                        | Intellectual impairment<br>Thought disorder  | Depression<br>(Motivation/initiative)   |
| II. Activities of daily living                          | Speech<br>Salivation<br>Swallowing<br>Handwriting<br>Cutting food/handling utensils<br>Dressing<br>Hygiene   | Turning in bed/adjusting bedclothes<br>Falling (unrelated to freezing)<br>Freezing when walking<br>Walking<br>Tremor<br>Sensory complaints related to parkinsonism  |
| III. Motor examination                                  | Speech<br>Facial expression<br>Tremor at rest (head, upper and lower extremities)<br>Action or postural tremor of hands<br>Rigidity<br>Finger taps<br>Hand movements | Rapid alternating movements of hands<br>Leg agility<br>Arising from chair<br>Posture<br>Gait<br>Postural stability<br>Body bradykinesia and hypokinesia             |
| IV. Complications of therapy (in the past week)         | Dyskinesias<br>Duration<br>Disability<br>Pain<br>Early morning dystonia<br>Clinical fluctuations<br>"Off" periods<br>Predictability, onset, duration                 | Other complications <ul style="list-style-type: none"> <li>• Anorexia, nausea, vomiting</li> <li>• Sleep disturbances</li> <li>• Symptomatic orthostasis</li> </ul> |
| V. Modified Hoehn and Yahr staging                      | Adds 2 additional stages to scale described in text<br>1.5 = Unilateral plus axial involvement<br>2.5 = Mild bilateral disease, with recovery on pull test           |   |
| VI. Schwab and England Activities of Daily Living Scale | Rates independence as a percentage; 10-point scale, 0% to 100%<br>0% = Bedridden, vegetative<br>100% = Completely independent; unaware of any difficulty             |   |

Source: Adapted from reference 65.

Advanced-stage patients had a ratio of \$12,294 per QALY. These ratios compared favorably to the cost-effectiveness ratios of many commonly prescribed therapies (eg, \$32,678 per QALY for alteplase, \$35,000 per QALY for dialysis, \$113,000 per QALY for coronary artery bypass surgery).<sup>68</sup>

The new COMT inhibitor tolcapone costs approximately twice as much as the new dopamine agonists. Keep in mind that the levodopa dose can be reduced when tolcapone is concomitantly administered with levodopa, which would result in a small savings for levodopa therapy.

The personal cost of Parkinson's disease may be greater than the financial cost. Whetten-Goldstein et al found that society's mean total cost per IPD patient was approximately \$6000 annually (\$9000 for patients under 65 years of age), with lost earnings compensation accounting for the greatest single element.<sup>17</sup> In their sample of IPD patients in North Carolina, physician visits and hospital expenses were the largest healthcare costs.<sup>17</sup> The family burden for these patients was heaviest on the side of providing informal care rather than the financial costs.<sup>17</sup> The caregiver, usually an elderly spouse, provided an average of 22 hours of care per week. Pain, fatigue, and depression were common even in early stages.<sup>17</sup> This study points out the importance of considering all aspects of Parkinson's disease, not just the disease symptoms.

Just as we lack comprehensive clinical trials comparing newer antiparkinson drugs, we also lack pharmacoeconomic data for every drug used to treat Parkinson's disease. The focus of the article by Hoerger et al was pramipexole, not the other drugs, and their sample size was relatively small (193 patients).<sup>68</sup> Considerations when making formulary decisions must include the large patient variability seen in IPD—variability in response to, tolerance of, and adverse effects from different drugs. Certainly any drug that increases a patient's quality of life should be available to that patient.

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... INVESTIGATIONAL DRUGS ...

In the last 2 years several new drugs have been approved after a long period with no new drugs in the antiparkinson class. The good news is that many additional therapies are currently under investigation. Agents in development include glutamate *N*-methyl-D-aspartate ion-channel antagonists (remacemide, budipine) and dopamine uptake inhibitors (brasofensine).<sup>51</sup> A great deal of research

is being conducted in the area of nerve growth promoters (brain-derived and glial-derived neurotrophic factors) and cell- and gene-based therapies.<sup>51,70</sup> Additional selective MAO inhibitors (lazabemide, rasagiline)<sup>51,69</sup> and several dopamine agonists (cabergoline, lisuride, apomorphine)<sup>51</sup> are in clinical trials, including the first full D1 receptor agonist, ABT-431.<sup>70</sup> Currently available products such as riluzole are being investigated for use in IPD.<sup>51</sup> New dosage forms in development for products currently marketed include liquid and transdermal forms of levodopa, a selegiline transdermal patch, and fast-dissolving as well as sustained-release selegiline oral products.<sup>51</sup> In the early stages of development these innovative therapies (eg, the nerve growth factors) are considered symptomatic treatment. However, if they prove to restore full function with no additional treatment required, they would be considered curative.<sup>69</sup> Research in disease prevention is aimed at identifying the causes and subsequently the risk factors of developing IPD; interventions would then be aimed at avoidance of those risk factors.<sup>69</sup>

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... PATIENT EDUCATION AND SUPPORT ...

Empowering patients through education is an important aspect of care for Parkinson's disease patients. Patients are probably aware that IPD is a chronic disease with no known cure. This knowledge can cause anxiety and frustration. Early education should focus on health maintenance, and problem-oriented education can be accomplished as particular symptoms arise.<sup>16</sup> One study that used a disease-assessment questionnaire with individualized recommendations to patients and physicians resulted in patients exercising more, visiting their physicians less frequently, and using less levodopa.<sup>71</sup> This study of patients' self-reporting was only for a 6-month period, so the results may not carry forward in time. However, it shows that education and increased exercise may pay off for the patient.

The primary purpose of treatment is to make the patient symptom-free and functional for as long as possible with as few adverse reactions as possible. Support of emotional needs for both patients and caregivers is essential. Patients, families, and significant others should be educated about realistic expectations for various treatments. Patients and their families should be encouraged to adhere to their treatment regimens and keep a diary of their symptoms and daily medication administration

The American Parkinson's Disease Association, Inc.  
1250 Hylan Blvd, Suite 4B  
Staten Island, NY 10305-1946  
800-223-2732

National Parkinson's Foundation, Inc.  
1501 NW 9th Avenue  
Miami, FL 33136-1407  
800-433-7022  
www.parkinson.org

Parkinson's Disease Foundation  
710 W. 168th St, 3rd Floor  
New York, NY 10032  
800-457-6676

The Parkinson Action Network  
818 College Ave, Suite C  
Santa Rosa, CA 95404  
707-544-1994  
www.pdaction.org

"We Move" Foundation  
Department of Neurology  
Mount Sinai Medical Center  
1 Gustave L. Levy Place  
New York, NY 10029  
www.wemove.org

times. Information about support groups for Parkinson's patients and their families can be obtained from the following organizations:

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**CONTINUING PHARMACY EDUCATION**



This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-00-201-H-01. This course expires January 31, 2003.

**Instructions**

After reading the article "Parkinson's Disease: Focus on Management Alternatives," select the best answer to each of the following questions.

1. In the United States, what approximate percentage of adults over age 65 years suffer from idiopathic Parkinson's disease (IPD)?

- a) 1%
- b) 5%
- c) 10%
- d) 15%

2. What is the principal deficit that occurs in patients suffering from IPD?

- a) loss of the excitatory neurotransmitter acetylcholine
- b) loss of striatal glutamate
- c) loss of the substantia nigra
- d) loss of inhibitory dopaminergic neurons

3. Which of the following agents has NOT been reported as a cause of drug-induced parkinsonism?

- a) metoclopramide
- b) prochlorperazine
- c) methyl dopa
- d) benztropine

4. Which of the cardinal manifestations of IPD is often the sole presenting feature?

- a) resting tremor
- b) bradykinesia
- c) rigidity
- d) postural instability

5. A 60-year-old man presents to the pharmacy with fully developed IPD. He has the ability to stand and walk without assistance, but is markedly incapacitated. What stage of IPD does this patient represent?

- a) stage I
- b) stage II
- c) stage III
- d) stage IV

6. Which of the following is a secondary clinical feature of IPD?

- a) diarrhea
- b) dementia
- c) dry mouth
- d) hypertension

(CPE QUESTIONS CONTINUED ON FOLLOWING PAGE)

**Parkinson's Disease: Focus on Management Alternatives**

ACPE Program Number: 064-000-00-201-H-01

(PLEASE PRINT CLEARLY)

Name \_\_\_\_\_

Home Address \_\_\_\_\_

City \_\_\_\_\_

State/ZIP \_\_\_\_\_

Daytime Phone # \_\_\_\_\_

States in which CE credit is desired: \_\_\_\_\_

Social Security # \_\_\_\_\_

Please circle your answers:

- |            |             |             |             |
|------------|-------------|-------------|-------------|
| 1. a b c d | 6. a b c d  | 11. a b c d | 16. a b c d |
| 2. a b c d | 7. a b c d  | 12. a b c d | 17. a b c d |
| 3. a b c d | 8. a b c d  | 13. a b c d | 18. a b c d |
| 4. a b c d | 9. a b c d  | 14. a b c d | 19. a b c d |
| 5. a b c d | 10. a b c d | 15. a b c d | 20. a b c d |

Please complete the Program Evaluation on following page, and send with \$15 fee, payable to University of Tennessee, to:

Glen E. Farr, PharmD  
University of Tennessee College of Pharmacy  
600 Henley Street, Suite 213  
Knoxville, TN 37902

## ...CPE QUIZ...

7. Which of the following treatments has not been successful in treating Parkinson's disease?

- a) increasing dopamine's availability in the central nervous system
- b) inhibiting the effects of acetylcholine
- c) preventing further cell membrane damage
- d) increasing levodopa precursors

8. Which of the following drugs is considered the single most important drug in the Parkinson's armamentarium?

- a) selegiline
- b) benzotropine
- c) levodopa
- d) amantadine

9. Levodopa's site of therapeutic action in Parkinson's disease is in which organ?

- a) gastrointestinal tract
- b) heart
- c) kidney
- d) basal ganglia

10. Selegiline's mechanism of action involves the inhibition of which of the following enzymes?

- a) L-amino acid dehydroxylase
- b) Catechol O-methyltransferase
- c) monoamine oxidase A
- d) monoamine oxidase B

11. Anticholinergic agents control \_\_\_\_ in the treatment of Parkinson's disease.

- a) tremors
- b) hallucinations
- c) festinating gait
- d) paresthesias

12. Which of the following antiparkinson drugs can cause serotonin syndrome if used concomitantly with selective serotonin reuptake inhibitors?

- a) levodopa
- b) carbidopa
- c) tolcapone
- d) selegiline

13. Approximately how many patients experience fluctuations in their response to levodopa within 5 to 6 years?

- a) 1-5%
- b) 25%
- c) 50-75%
- d) 100%

14. Ensuring adequate support for patients and caregivers is important in which stage of Parkinson's?

- a) stage III
- b) stage IV
- c) stage V
- d) all stages

(CPE QUESTIONS CONTINUED ON FOLLOWING PAGE)

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### CPE PROGRAM EVALUATION

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

*Please circle your answers:*

|  |                |              |                 |                   |
|--|----------------|--------------|-----------------|-------------------|
| My pharmacy practice setting is:                               | Independent    | Chain        | Hospital        | Consultant        |
| The objectives of the lesson were achieved.                    | Yes            | No           |                 |                   |
| The quality of presentation of the material was:               | Excellent      | Good         | Fair            | Poor              |
| The information presented will be useful to me in my practice. | Strongly agree | Mildly agree | Mildly disagree | Strongly disagree |

How long did it take you to read the material and respond to the Continuing Education questions? (Please specify the number of hours.)

\_\_\_\_\_

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Knoxville, TN 37902

*(CPE questions continued from previous page)*

**15. How much carbidopa is required on a daily basis to avoid the nausea caused by inadequate peripheral decarboxylase inhibition?**

- a) 5-10 mg
- b) 20-30 mg
- c) 70-100 mg
- d) over 200 mg

**16. Dose reduction should be gradual when discontinuing several Parkinson's drugs to avoid which life-threatening reaction?**

- a) hallucinations
- b) neuroleptic malignant syndrome
- c) orthostatic hypotension
- d) diarrhea

**17. Therapeutic options for a patient who is experiencing "wearing-off" do not include \_\_\_\_\_.**

- a) add catechol O-methyltransferase inhibitor and decrease levodopa dose
- b) change to sustained-release carbidopa/levodopa
- c) add liquid carbidopa/levodopa
- d) drug holiday

**18. Levodopa competes with which dietary ingredient, causing decreased bioavailability and decreased effectiveness?**

- a) dietary protein
- b) divalent cations
- c) highly lipophilic foods
- d) dark green vegetables

**19. Which newer antiparkinson agent now carries a black box warning?**

- a) levodopa
- b) tolcapone
- c) ropinirole
- d) pramipexole

**20. Which of the following drugs may require dose adjustment when administered concomitantly with levodopa?**

- a) ropinirole
- b) pramipexole
- c) tolcapone
- d) all of the above