Parkinson’s disease (PD) is a chronic neurodegenerative condition associated with a significant burden on patients, their caregivers, and society. Direct and indirect costs related to PD are estimated to exceed $20 billion annually already, a figure projected to double in the future because of the rising number of affected individuals. Part 1 discussed the burden of PD, as well as its etiology, pathophysiology, diagnostic considerations, and methods of patient assessment, with implications for managed care. Part 2 discusses the therapeutic options available to treat motor symptoms of PD, costs of these options, and their cost-effectiveness in relation to improving outcomes. Nonmotor neuropsychiatric comorbidities will be addressed in Part 3.

Pharmacologic Therapy of Motor Symptoms

Table 1 presents the most commonly used agents to treat motor symptoms in PD and their cost for 1 month of therapy. Primary adverse effects of these drugs are listed in Table 2.

Goals of Therapy. There currently is no cure for PD, and no existing therapy has been shown clearly to slow or reverse progression of the disease. The most important goals of management are thus to preserve functional independence and health-related quality of life (HRQOL). Achievement of these goals can reduce the need for healthcare resource utilization and reduce total costs. Toward this end, treatment is directed at providing symptomatic relief, for both motor and nonmotor symptoms, while minimizing undue adverse effects.

However, this has proven problematic in practice. The most effective therapy for treating motor symptoms, levodopa, has been associated with an increased risk of motor fluctuations. This risk is greatest in younger-onset patients, with escalating dosages of medication and longer duration of treatment. These motor fluctuations can impair HRQOL and cause significant functional and social disability, directly contrary to management goals. Levodopa-induced motor fluctuations and dyskinesias are difficult to treat. This has led to a treatment paradigm in PD of maximizing therapy with other agents—levodopa-sparing therapies—for as long as possible before using levodopa. However, this paradigm is not adhered to by all clinicians.

Abstract

In the absence of a cure, the primary goals in managing Parkinson’s disease (PD) are to preserve functionality and health-related quality of life. Meeting these goals can minimize healthcare-resource utilization and long-term healthcare costs. Although effective treatment of motor symptoms of the disease is a central consideration to facilitate improved outcomes, management of nonmotor symptoms is now recognized as an equally important target of intervention, since nonmotor symptoms can contribute greatly to disability. The article addresses the current treatment options of choice for reducing motor symptoms of PD and their most rational use. Cost-effectiveness is a major consideration for managed care and is also analyzed for many available treatment options.
### Table 1. Dose and Cost of Medications for Parkinson’s Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Usual Dose</th>
<th>Cost ($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbidopa/levodopa immediate-release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>10/100-mg tabs</td>
<td>300-1500 mg levodopa/day in divided doses</td>
<td>63.90-319.50</td>
</tr>
<tr>
<td></td>
<td>25/100-mg tabs</td>
<td>300-1500 mg levodopa/day in divided doses</td>
<td>78.30-391.50</td>
</tr>
<tr>
<td></td>
<td>25/250-mg tabs</td>
<td>300-1500 mg levodopa/day in divided doses</td>
<td>33.30-198.80</td>
</tr>
<tr>
<td>Sinemet</td>
<td>10/100-mg tabs</td>
<td>300-1500 mg levodopa/day in divided doses</td>
<td>82.80-414.00</td>
</tr>
<tr>
<td></td>
<td>25/100-mg tabs</td>
<td>300-1500 mg levodopa/day in divided doses</td>
<td>92.70-463.50</td>
</tr>
<tr>
<td></td>
<td>25/250-mg tabs</td>
<td>300-1500 mg levodopa/day in divided doses</td>
<td>39.60-237.60</td>
</tr>
<tr>
<td>Carbidopa/levodopa controlled-release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>25/100-mg tabs</td>
<td>400-2200 mg levodopa/day in divided doses</td>
<td>97.20-534.60</td>
</tr>
<tr>
<td></td>
<td>50/200-mg tabs</td>
<td>400-2200 mg levodopa/day in divided doses</td>
<td>100.80-554.40</td>
</tr>
<tr>
<td>Sinemet</td>
<td>25/100-mg tabs</td>
<td>400-2200 mg levodopa/day in divided doses</td>
<td>139.20-765.60</td>
</tr>
<tr>
<td></td>
<td>50/200-mg tabs</td>
<td>400-2200 mg levodopa/day in divided doses</td>
<td>133.80-735.90</td>
</tr>
<tr>
<td>Carbidopa/levodopa/entacapone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stalevo 50</td>
<td>12.5/50/200-mg tabs</td>
<td>Maximum of 8 tabs/day</td>
<td>652.80 (based on 8 tabs/day)</td>
</tr>
<tr>
<td>Stalevo 100</td>
<td>25/100/200-mg tabs</td>
<td>Maximum of 8 tabs/day</td>
<td>652.80 (based on 8 tabs/day)</td>
</tr>
<tr>
<td>Stalevo 150</td>
<td>37.5/150/200-mg tabs</td>
<td>Maximum of 8 tabs/day</td>
<td>652.80 (based on 8 tabs/day)</td>
</tr>
<tr>
<td>Stalevo 200</td>
<td>50/200/200-mg tabs</td>
<td>Maximum of 6 tabs/day</td>
<td>489.60 (based on 6 tabs/day)</td>
</tr>
<tr>
<td><strong>Dopamine Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>2.5-mg tabs</td>
<td>75-45 mg/day in divided doses</td>
<td>197.10 (75 mg/day)</td>
</tr>
<tr>
<td>Parlodol</td>
<td>2.5-, 5-mg caps</td>
<td>75-45 mg/day in divided doses</td>
<td>389.89 (75 mg/day)</td>
</tr>
<tr>
<td>Pramipexole (Mirapex®)</td>
<td>0.125, 0.25 mg</td>
<td>0.25 mg tid</td>
<td>193.65</td>
</tr>
<tr>
<td>Pramipexole (Mirapex®)</td>
<td>0.5-, 0.75-, 1-, 1.5-mg tabs</td>
<td>1 mg tid</td>
<td>232.44</td>
</tr>
<tr>
<td>Ropinirole (ReQuip®)</td>
<td>0.25-, 0.5-, 1-, 2-, 3-, 4-, 5-mg tabs</td>
<td>2 mg tid</td>
<td>231.02</td>
</tr>
<tr>
<td>Rotigotine (Neupro®)</td>
<td>2 mg/24-hr patches</td>
<td>2 mg/24 hr</td>
<td>84.38</td>
</tr>
<tr>
<td>Rotigotine (Neupro®)</td>
<td>4, 6 mg/24-hr patches</td>
<td>4-6 mg/24 hr</td>
<td>288.75</td>
</tr>
<tr>
<td>Apomorphine (Apokyn®)</td>
<td>30 mg/3-mL cartridge</td>
<td>2-6 mg SC 3-5x/day prn</td>
<td>737.64</td>
</tr>
<tr>
<td><strong>COMT Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone (Comtan®)</td>
<td>200-mg tabs</td>
<td>200 mg tid or qid</td>
<td>250.47-333.96</td>
</tr>
<tr>
<td>Tolcapone (Tasmar®)</td>
<td>100-, 200-mg tabs</td>
<td>100 mg tid</td>
<td>362.03</td>
</tr>
<tr>
<td><strong>MAO Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline (Azilect®)</td>
<td>0.5-, 1-mg tabs</td>
<td>1 mg qd</td>
<td>268.54</td>
</tr>
<tr>
<td><strong>Selegiline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>5-mg tabs, caps</td>
<td>5 mg bid</td>
<td>99.00</td>
</tr>
<tr>
<td>Elderyl®</td>
<td>5-mg caps</td>
<td>5 mg bid</td>
<td>170.00</td>
</tr>
<tr>
<td>Zelapar®</td>
<td>1.25-mg orally disintegrating tabs</td>
<td>1.25-2.5 mg q AM</td>
<td>144.85-289.69</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>100-mg tabs, caps</td>
<td>100 mg bid</td>
<td>37.31</td>
</tr>
<tr>
<td>Symmetrel</td>
<td>100 mg</td>
<td>100 mg bid</td>
<td>68.90</td>
</tr>
<tr>
<td>Carbidopa (Lodosyn®)</td>
<td>25-mg tabs</td>
<td>25 mg tid or qid</td>
<td>68.10-91.20</td>
</tr>
</tbody>
</table>

*Based on McKesson’s average wholesale price as of February 15, 2008, 30-day supply. COMT indicates catechol-O-methyltransferase; MAO, monoamine oxidase.
Part 2: Treatment of Motor Symptoms

When to Start Therapy. Timing the onset of therapy remains controversial. Prior to initiating symptomatic therapy for the mildly afflicted patient who is not functionally impaired, enrolling the patient in a neuroprotection trial should be considered. Some clinicians and specialists initiate treatment for very mild symptoms in view of studies that suggest early treatment may offer an advantage. If early therapy is considered, patient age should be a factor in regard to treatment selection. Younger patients with early PD (young-onset) are more prone to motor fluctuations with chronic levodopa treatment. In these patients, dopamine agonists are considered the first line by many clinicians (discussed below).

Although there was concern that levodopa itself enhanced progression of PD, current clinical evidence does not support this idea. There is no evidence that shows worsening of PD with levodopa. To the contrary, recent studies suggest that levodopa may actually slow progression of disease symptoms. Thus, early therapy with levodopa should not be withheld based on this concern.

In contrast to very early treatment of symptoms, other clinicians prefer to delay dopaminergic therapy for PD until clinically significant disability or

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### Table 2. Adverse Effects of Primary Drugs Used in Parkinson's Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main Adverse Effects and Complications</th>
</tr>
</thead>
</table>
| Carbidopa/levodopa          | Initiation of therapy: nausea, sedation, vomiting, orthostatic hypotension  
Chronic therapy: delusions, hallucinations, vivid dreams, sleep disturbances  
Impulse control disorder (pathologic gambling, compulsive shopping, binge eating)—more commonly seen with dopamine agonists  
Motor fluctuations and dyskinesias are complications with prolonged therapy  
Abrupt discontinuation: return of parkinsonian symptoms and potential for neuroleptic malignant syndrome (fever, rigidity) |
| Dopamine agonists (pramipexole, ropinirole) | Nausea, somnolence, postural hypotension, edema, and hallucinations may limit therapy  
During initial therapy, somnolence, edema, and hallucinations were more common than with levodopa in one study  
Sudden sleep attacks may occur—treatment with modafinil may reduce daytime sleepiness  
Impulse control disorder (more often than with levodopa)  
Nausea and other peripheral dopaminergic effects can be treated with domperidone or ondansetron  
Less likely than levodopa to cause motor fluctuations or dyskinesias  
Rotigotine patch: application-site reactions may occur  
Apomorphine: vomiting (emetic properties); avoid ondansetron to prevent emesis, as it may result in hypotension and loss of consciousness |
| COMT inhibitors             | Only used in combination with levodopa  
Diarrhea is most common in first month  
Nausea, dyskinesias (may require dose reduction of levodopa)  
Urine discoloration—the patient should be informed of this before treatment  
Daytime sleep attacks have occurred with entacapone  
Serious hepatotoxicity with tolcapone but not entacapone; informed consent and twice-monthly hepatic function tests for 6 months required with use of tolcapone; no liver-function monitoring required for entacapone |
| MAO-B inhibitors           | Nausea and orthostatic hypotension  
Possible interactions with tricyclic antidepressants, SSRIs, meperidine (see package insert)  
Increased levodopa adverse effects, especially in elderly (eg, dyskinesias)  
No significant adverse interaction with tyramine-rich foods (unlike MAO-A inhibitors used to treat depression) |
| Amantadine                  | Nausea, confusion, dizziness, insomnia, hallucinations, and edema are main adverse effects  
Livedo reticularis has been reported  
Dose reduction required in renal insufficiency  
Severe psychosis has been reported in elderly in presence of high plasma levels  
Abrupt discontinuation: worsening of parkinsonian symptoms and potential for neuroleptic malignant syndrome and delirium |

COMT indicates, catechol-O-methyltransferase; MAO-B indicates monoamine oxidase type B; SSRIs, selective serotonin reuptake inhibitors.
functional impairment occurs. In these mildly affected patients, nondopaminergic therapy, such as amantadine or monoamine oxidase type B (MAO-B) inhibitors, is an option. The reluctance to start dopaminergic therapy early in the disease reflects concerns about the adverse effects of these agents and the long-term consequences of treatment. Side effects, including sedation, nausea, and orthostatic hypotension, may be more disabling than the motor impairment.

Whether an early or later treatment approach is adopted, maintaining functionality for as long as possible is the goal of clinical management. This not only improves HRQOL of the patient but also reduces direct costs associated with the need for office visits and lessens indirect costs by mitigating dependence on caregivers and allowing less time off from work.

**Levodopa: Cornerstone of Therapy.** Levodopa remains the most effective agent for treatment of motor symptoms in PD. As a prodrug of dopamine, levodopa crosses the blood-brain barrier (BBB) and is decarboxylated to dopamine in the nigrostriatal pathways. Levodopa is always given with carbidopa, a peripheral dopa-decarboxylase inhibitor, which prevents peripheral metabolism of levodopa and allows a higher percentage of a dose to cross the BBB. Combined use with carbidopa also minimizes the adverse effects of peripheral dopamine, such as nausea and hypotension.

Initially, patients will have a good and sustained response to levodopa with small amounts of levodopa given 3 times a day. This “honeymoon” period may last for up to 5 years. However, as treatment continues and PD progresses, motor complications occur in virtually all patients. These motor complications include a shortened duration of drug benefit termed “wearing off” and drug-induced dyskinesias. The half-life of levodopa is approximately 90 minutes. With progressive disease, the benefits of each dose become shorter, with a wearing off of benefit before the next dose. Additionally, patients may experience loss of benefit from a usually effective dose, or unpredictable “on-off” in which there is a sudden loss of drug effect and recurrence of severe PD symptoms termed **on-off motor fluctuations.**

The motor complications occur in up to 70% of patients after 9 years of treatment.

With disease progression, the nonmotor features of PD, including depression, anxiety, autonomic dysfunction, cognitive impairment, and sleep disturbance, become increasingly important. These nonmotor features often do not respond to dopaminergic therapy and must be identified and treated. Postural instability is a motor symptom that may become resistant to therapy, resulting in falls and injury despite good overall control of motor symptoms. HRQOL declines further as these symptoms worsen. Anxiety, depression, and/or panic attacks can be seen during off periods, and can be very distressing to the patient.

**Optimizing Levodopa Therapy.** Optimizing treatment in PD is of extreme importance to care management, because this assures the best possible chance to minimize long-term disability. The currently available drugs provide an array of choices for optimizing benefit. Furthermore, patient education, encouragement of physical activity and exercise, and monitoring drug compliance play a major role in maximizing function and achieving treatment goals.

Levodopa treatment is an important part of long-term treatment. Applying methods to maximize the duration of effect of levodopa and minimize the side effects is paramount. For example, nausea and vomiting are prominent adverse effects during the initiation of levodopa therapy. This side effect may reduce the compliance of the PD patient. By adding additional carbidopa, this side effect can be greatly minimized. Some patients may require higher doses of carbidopa, up to 200 mg/day, to adequately control nausea; this is possible by adding carbidopa alone to the levodopa/carbidopa regimen.

Controlled-release levodopa/carbidopa formulations may be considered in patients with wearing-off effects. However, erratic absorption of this dosage form may be seen in some patients. The unpredictability of controlled-release formulations may result in a slower and unpredictable onset of action and at times worsening dyskinesias in the afternoon or evening. Switching from standard levodopa/carbidopa to the controlled-release formulation may also be somewhat troublesome, requiring dose titration. Initiating therapy with the controlled-release formulation may be advantageous, although studies have not been convincing. In patients with gastric slowing and/or advanced motor fluctu-
tions, the use of liquid levodopa/carbidopa may allow more precise titration over the course of the day, but is cumbersome because of the need to drink appropriate amounts every hour. Liquid levodopa or the orally dissolving formulation of levodopa may also be useful in patients who are unable to swallow and may be useful during off periods.\(^{11}\)

Suggestions for managing dyskinesias and motor fluctuations during levodopa therapy are shown in Table 3.\(^{7,8,11,12}\)

Dopamine Agonists. Dopamine agonists have been used as monotherapy in early PD or in combination with levodopa in more advanced disease. Adverse effects of dopamine agonists are more common than with levodopa, and slow dose titration over time is indicated. There is increasing use of these agents as initial therapy in PD, to help delay the need for levodopa and reduce overall levodopa dosage. Controlled comparisons of dopamine agonists, including ropinirole and pramipexole with levodopa as initial therapy, have demonstrated a reduction in the wearing-off phenomenon and dyskinesias in the dopamine agonist–treated groups. These reductions were seen even when levodopa was added to the dopamine agonist group to control parkinsonian symptoms.\(^{5,11,13,15-17}\) In these trials, subjects treated with dopamine agonists did not have as much improvement in their motor scores as the levodopa group; however, patients in both groups reported good subjective control of symptoms. Some patients have achieved good motor control with dopamine agonist monotherapy for up to 5 years.

However, because of the less robust effect of dopamine agonists, virtually all patients will eventually require the use of levodopa.

Many specialists start therapy with dopamine agonists in younger patients with PD (<50 years of age), because these patients are much more prone to developing severe motor complications.\(^{10,18,19}\) In contrast, levodopa/carbidopa monotherapy is advocated by most specialists over dopamine agonists for initial therapy in older patients and those with cognitive dysfunction. Dopamine agonists are more likely than levodopa to cause cognitive side effects including confusion and hallucinations, particularly in the elderly.\(^{8,10,18,19}\)

When given as adjunctive therapy to levodopa in more advanced disease, dopamine agonists have improved Unified Parkinson's Disease Rating Scale (UPDRS) scores, increased on time during wakeful hours, and enabled lower doses of levodopa to be given.

Ropinirole is a unique dopamine agonist with a transdermal patch delivery system. It may offer more stable plasma levels, is given only once daily, and is effective in both early and advanced disease.\(^{11,20}\) This agent may help to optimize compliance with therapy. However, only the lower-dose patches are currently available in the United States, limiting its usefulness to early treatment.

Apomorphine is a dopamine agonist given subcutaneously for more advanced disease and resistant motor fluctuations. Apomorphine has a rapid onset of action and a duration of benefit of approximately 90 minutes. It can be a very effective treatment for patients with unpredictable off times, dosage failures, and early-morning off times. Apomorphine is a potent emetic, and trimethobenzamide should be given before initiating therapy.\(^{11}\)

Rotigotine, apomorphine, pramipexole, and ropinirole are nonergot dopamine agonists. They have not been associated with vasoconstriction-related events, valvular heart abnormalities, or retroperitoneal fibrosis, which have been associated with ergot dopamine agonists.\(^{12}\) There appears to be no significant difference in clinical efficacy between the

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**Table 3. Treatment Options for Management of Levodopa-related Motor Fluctuations and Dyskinesias\(^{2,8,11,12}\)**

<table>
<thead>
<tr>
<th>Motor Fluctuations (particularly “wearing-off” effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce each individual dose of levodopa and increase frequency of administration</td>
</tr>
<tr>
<td>Addition of a dopamine agonist, MAO-B inhibitor, or COMT inhibitor to prolong levodopa response</td>
</tr>
<tr>
<td>Switch to controlled-release levodopa/carbidopa</td>
</tr>
<tr>
<td>Consider use of carbidopa, levodopa, plus entacapone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dyskinesias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce each dose of levodopa</td>
</tr>
<tr>
<td>Addition of agents known to treat dyskinesias, such as amantadine</td>
</tr>
<tr>
<td>Reduce or stop anticholinergic therapy</td>
</tr>
</tbody>
</table>

MAO-B indicates monoamine oxidase type B; COMT, catechol-O-methyltransferase.
different dopamine agonists, although comparative studies are limited. An evidence-based comparison reported similar effectiveness for pramipexole and ropinirole in delaying dyskinesia when given as early treatment. The ergot derivative bromocriptine is rarely used in PD because of its adverse effects, high cost, and complex titration schedule. Another ergot-derivative dopamine agonist, pergolide, was withdrawn from the market because of its propensity to cause cardiac-valve regurgitation.

**Other Pharmacologic Agents.** Although some of these medications for PD may be used for symptom treatment in early patients, most are designed to maximize the derived benefit of levodopa by augmenting its efficacy, reducing its adverse effects, or treating symptoms not adequately managed by levodopa alone. All of these measures essentially help to optimize levodopa therapy.

**MAO-B Inhibitors.** MAO-B inhibitors prevent metabolism of dopamine in the brain, enhancing dopamine availability. Similar to the dopamine agonists, the MAO-B inhibitor selegiline has been shown to delay levodopa therapy in early PD. It was effective for this purpose in the large DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) trial, but most beneficial effects occurred during the first year of the study, without long-term benefit. The efficacy of selegiline for treating motor fluctuations has been modest. Another MAO-B inhibitor available in the United States, rasagiline, is more potent than selegiline. It has also shown clinical efficacy in early PD. In the TEMPO (TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients) study, the efficacy of rasagiline was sustained for up to 6 months when given as monotherapy in early disease. Rasagiline has also demonstrated effectiveness as add-on therapy for controlling motor fluctuations in patients with more advanced disease. In the PRESTO (Parkinson's Rasagiline: Efficacy & Safety in the Treatment of "Off") trial, patients treated with rasagiline showed a reduction in daily off time over placebo. Reduction in off time was 1.85 hours in the 1-mg/day group and 1.41 hours in the 0.5-mg/day group compared with 0.91 hours in the placebo group.

An oral disintegrating-tablet formulation of selegiline, Zydis selegiline, has been approved by the US Food and Drug Administration for add-on therapy in PD. When given as adjunctive therapy with levodopa, off time was reduced by approximately 2 hours compared with placebo. Zydus selegiline has increased plasma levels over oral selegiline because of the reduction in first-pass metabolism by the liver. The reduction in first-pass metabolism has also been associated with a reduction in amphetamine metabolites.

Unlike the MAO-A inhibitors used in the treatment of major depression, MAO-B inhibitors do not cause significant hypertension at recommended doses when given with tyramine-rich foods, or with levodopa. However, there is a small risk for development of serotonin syndrome when MAO-B inhibitors are combined with medications affecting the serotonergic system, including selective serotonin reuptake inhibitors (SSRIs).

**Catechol O-Methyltransferase (COMT) Inhibitors.** These agents are designed to further optimize levodopa therapy by inhibiting the activity of COMT, a peripheral enzyme that metabolizes levodopa. Thus, combined therapy with both carbidopa (to inhibit dopa-decarboxylase) and a COMT inhibitor maximizes levodopa bioavailability for BBB transport. The COMT inhibitors entacapone and tolcapone enhance the bioavailability of levodopa and prolong its plasma half-life, without increasing peak plasma levels.

Both entacapone and tolcapone have been useful in patients with motor fluctuations, especially the wearing-off phenomenon. Entacapone has been shown to reduce off time, increase on time, and improve motor function in levodopa-treated patients with motor fluctuations. Treatment with entacapone often enables a reduction in daily levodopa dosage. Tolcapone has also been shown to significantly reduce off time in patients with motor fluctuations. Its use has been limited by a potential for hepatotoxicity. Treatment with tolcapone requires twice-monthly liver function tests during the initial 6 months of use. Entacapone has not been associated with serious hepatotoxicity and has emerged as the most frequently used COMT inhibitor, with tolcapone being reserved for patients who fail entacapone therapy. The benefit of COMT inhibitors is
Amantadine. Amantadine is an older medication with many different actions in the central nervous system, including inhibition of N-methyl-D-aspartate receptors, enhancement of dopamine release from presynaptic terminals, and modest anticholinergic activity. Amantadine has demonstrated effectiveness for relieving tremor in early PD. In more advanced illness, amantadine has been shown to improve levodopa-induced dyskinesias. Amantadine requires dose reduction in renal impairment and should be used with caution in patients with cognitive impairment. The primary role of amantadine is in reduction of dyskinesia.

Anticholinergic Agents. Anticholinergic agents, such as trihexyphenidyl and benztropine, are the oldest treatments that have been used in PD. They are most effective for treating resting tremor. Anticholinergics are typically reserved for the younger patient (<60 years of age) with predominant tremor illness and preserved cognitive function. These agents should be used with caution in older patients because of their potential for side effects, including constipation, blurry vision, urinary retention, confusion, and hallucinations. One benefit of both trihexyphenidyl and benztropine is their low cost.

Guidelines for Treating Motor Symptoms in PD. The following comments and recommendations are based on guidelines, recommendations in the literature, and opinions of experts in the field:

- Levodopa remains the most effective agent for treatment of motor symptoms in PD and is the mainstay of therapy.
- Levodopa should generally be considered for initial therapy in older patients with more advanced disease.
- The nonergot dopamine agonists, such as pramipexole or ropinirole, are effective agents for initial and advanced treatment of motor symptoms. These agents should be considered in early illness to help delay the need for levodopa therapy. These agents have been shown to reduce motor complications in younger-onset patients when used as initial therapy.
- Although its use can be delayed, levodopa will eventually be required in virtually all patients as the disease progresses.
- For motor fluctuations and dyskinesias in more advanced disease, the recommendations should be considered.
- In patients with a combination of motor wearing off and peak-dose dyskinesias, levodopa dose reduction and use of adjunctive therapies may be useful. In patients with medically resistant motor fluctuations, deep brain stimulation (DBS) surgery should be considered.

Surgery for PD. DBS of the subthalamic nucleus (STN) is an effective surgical procedure in appropriate candidates for treating medically resistant motor symptoms of PD and improving HRQOL. This technique is now considered the surgical method of choice for patients with advanced disease. DBS-STN has been shown to significantly reduce both the primary symptoms of PD and its motor complications, including tremor, bradykinesia, wearing off, dyskinesias, and dystonia. Many patients treated with DBS-STN may reduce their medication burden. A recent meta-analysis showed a 55.9% reduction in daily levodopa equivalent dosage. This meta-analysis also showed a 69.1% reduction in dyskinesias, a 68.25% reduction in off periods, and a 34.5% improvement in quality of life. Optimal patients have medically refractory motor fluctuations or tremor, stable medical problems, and normal cognitive function. Outcomes of surgery are better in younger patients. Side effects of surgery include hemorrhage, stroke, infection or failure of hardware, and memory loss. Pallidotomy or thermocoagulation of the globus pallidus interna can also alleviate major symptoms of PD, but is now used less often than DBS. DBS is more effective than pallidotomy for improving primary motor symptoms.

Treatment Effects on HRQOL in PD

HRQOL is poor in patients with PD, particularly in advanced disease, typically related to growing disability. Nonmotor symptoms, especially depression and cognitive impairment, and motor complications of levodopa contribute greatly to a poor HRQOL. Declining HRQOL is associated with increases in both direct and indirect costs, emphasizing the importance of effective treatment.
strategies to reduce disability, optimize levodopa therapy, and prevent or treat nonmotor symptoms.

The impact of drug therapy or other strategies to improve HRQOL has not been well studied, in part related to lack of a standardized HRQOL assessment instrument. However, in studies that are available (using various measurements for HRQOL), the following have been shown to improve HRQOL to some degree in patients with PD: DBS-STN\textsuperscript{29,36}; unilateral pallidotomy\textsuperscript{36}; rasagiline in early PD\textsuperscript{22,36}; entacapone adjunct to levodopa (conflicting data)\textsuperscript{36}; oral levodopa\textsuperscript{33}; duodenal infusion of levodopa versus oral levodopa\textsuperscript{36}; switching from standard levodopa to controlled-release levodopa\textsuperscript{36}; pramipexole\textsuperscript{33,37}; and patient education regarding aspects of PD.\textsuperscript{29}

In a 4-year study, HRQOL improvement was seen with levodopa and pramipexole, each given as monotherapy, in patients with early PD.\textsuperscript{33} Improvement was mainly seen during the first year, then declined during the next 3 years of follow-up. HRQOL benefits over the 4-year period tended to be greater with pramipexole. Benefits with pramipexole appeared to be mediated by improvement of nonmotor features, in contrast to improved motor function with levodopa.

**Nonpharmacologic Therapy**

Exercise and lifestyle changes can improve the well-being of patients and possibly functionality.\textsuperscript{5,6} Participation in physical training programs that emphasize stretching, exercise, and balance training may improve balance, gait speed, and activities of daily living.\textsuperscript{5} Voice training can improve the speech disorders that often occur in PD.\textsuperscript{5}

The correct diet is of high importance in PD. Levodopa absorption can be impaired by ingestion of amino acids especially in patients with motor fluctuations, potentially reducing its effectiveness. A high-fiber diet or fiber supplements can minimize constipation.\textsuperscript{5,11}

The antioxidant properties of vitamins A, C, and E have not clearly shown benefit in PD. However, vitamins A and C are under investigation for potential neuroprotectant properties.\textsuperscript{3}

**Neuroprotection**

Ropinirole, pramipexole, selegiline, and rasagiline are being investigated for putative neuroprotectant (disease-modifying) properties,\textsuperscript{3,5,8,12,22,23} which implies the ability to spare or salvage dopaminergic cells from the progressive neurodegenerative processes in PD and slow disease progression.\textsuperscript{8} However, based on a recent evidence-based review by the American Academy of Neurology\textsuperscript{38} and a review by Jankovic,\textsuperscript{12} no therapeutic agent has unequivocally demonstrated neuroprotection in PD.

**Managed Care Considerations**

**Cost-effectiveness of Therapies for PD.** Although use of the most effective therapy for PD—and optimization of that therapy—can facilitate improved outcomes over time, initial costs of such treatment remain a concern to managed care. Will the initial costs of a therapeutic modality, especially more expensive drugs and surgery, be offset by improved long-term outcomes and reduced total patient care costs?

Data on the cost-effectiveness of treatments for motor or nonmotor symptoms in PD remain limited. However, it is known that healthcare costs are up to 3 times higher in patients with PD who develop motor fluctuations compared with those PD patients who do not develop fluctuations.\textsuperscript{29} Costs have been shown to double with each Hoehn and Yahr stage.\textsuperscript{29} The number of daily off periods has been reported to have the greatest impact on cost, such that medical costs are reduced by 5% for every 10% reduction in off time.\textsuperscript{29} Thus, effective treatment to minimize or delay off periods should result in cost savings.

Results of available pharmacoeconomic analyses suggest that the following regimens for PD are cost-effective over time, primarily by reducing motor fluctuations and dyskinesias, and improving functionality:

- Bromocriptine was better than levodopa\textsuperscript{29}
- Entacapone plus levodopa was better than levodopa alone or usual care\textsuperscript{29,39-41}
- Levodopa/carbidopa controlled-release was better than standard levodopa/carbidopa\textsuperscript{29}
- Levodopa/carbidopa/entacapone was better than standard care\textsuperscript{42}
- Pramipexole was better than levodopa or bromocriptine\textsuperscript{29,37}
- Rasagiline as levodopa adjunct was better than standard care\textsuperscript{40}
- Ropinirole was better than levodopa\textsuperscript{43}
Most of these analyses evaluated quality-adjusted life-years gained, and most assessed costs from a societal perspective. Assessments of HRQOL with cost-effectiveness were infrequent. Although further cost-effectiveness studies are needed, including comparative cost-effectiveness, available data do suggest that effective treatment of PD with entacapone, dopamine agonists, and MAO-B inhibitors results in improvements that favor costs savings and may offset the initial costs of individual drug therapy.

Surgery Costs. DBS-STN for PD appears cost-effective, with several investigators reporting that the initial cost of surgery is more than offset by savings in direct medical costs and long-term overall care.\textsuperscript{24,29} However, well-conducted cost-effectiveness studies utilizing appropriate end points, such as a valid HRQOL tool to enable calculation of cost-utility scores, are lacking. In one of the better studies to date assessing HRQOL, DBS-STN was considered superior to standard medical management in late-stage PD; it was suggested that cost-effectiveness of the procedure would be realized if HRQOL improved by >18%.\textsuperscript{29} However, the UPDRS was used to measure outcomes, and the investigators incorrectly assumed this would correlate with HRQOL. Further evaluation of the cost-effectiveness of surgical treatments is needed.

In a retrospective study of surgeries for PD from 1996 to 2000, the median total hospital charge for DBS was $36,000, which was higher than for other surgical techniques (eg, pallidotomy).\textsuperscript{44} Total charges for DBS were significantly lower, and short-term outcomes were better when DBS was performed at higher-volume hospitals.

**Conclusion**

Costs of care for PD are rising. Greater recognition of PD in the community, use of the most effective modalities for its treatment, and optimization of this treatment can lead to improved functionality and HRQOL of the patient, which will likely reduce costs over time. Choice of initial symptomatic therapy is an important determination of long-term function. This can be achieved with proper use of levodopa/carbidopa, dopamine agonists, MAO-B inhibitors, and COMT inhibitors, as well as effective treatment of nonmotor symptoms. In particular, delaying the need for levodopa therapy in early disease with dopamine agonists and controlling levodopa-related motor complications in more advanced disease with COMT inhibitors, MAO-B inhibitors, and dopamine agonists can have a major positive impact on patient disability and long-term healthcare costs.

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