Treatment Strategies and Quality-of-Care Indicators for Patients With Parkinson’s Disease

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Faculty Disclosures

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Off-Label Use

Droxidopa has orphan status for the treatment of orthostatic hypotension and
is currently not approved for this use in the United States. Currently, donepe-
zol is not FDA approved for treatment of dementia in patients with Parkinson’s
disease. While fludrocortisone has been used to treat orthostatic hypotension,
it does not have FDA approval. Selegiline does have FDA approval for use as an
adjunct to levodopa treatment; however, it is not approved for monotherapy to
 treat Parkinson’s disease. Additionally, tamsulosin and terazosin are approved for
the treatment of benign prostatic hyperplasia but have been used to treat urinary
dysfunction, which is a symptom of prostatic hyperplasia.

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Target Audience
The target audience for this activity is managed care pharmacists and managed care physicians. This is an application-based learning activity.

Learning Objectives
Upon completion of this program, participants will be able to:
1. Assess current challenges in the management of Parkinson’s disease in managed care.
2. Outline measures used to characterize quality of care for patients with Parkinson’s disease.
3. Identify the impact of quality indicators on Parkinson’s disease management.
4. Describe the role of the managed care pharmacist in each quality domain to improve management and resulting outcomes in Parkinson’s disease.

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Treatment Strategies and Quality-of-Care Indicators for Patients With Parkinson’s Disease

Jack J. Chen, PharmD, BCPS, CGP, FASCP; Mark F. Lew, MD; and Andrew Siderowf, MD, MSCE

ABSTRACT

BACKGROUND: Parkinson’s disease (PD) is a chronic, progressive, and debilitating disease, which affects over 1 million people in the United States. PD is characterized by a loss of voluntary and involuntary muscle control. As the disease progresses, additional complications can arise in the form of nonmotor and neurobehavioral symptoms. The traditional pharmacologic treatment for PD has been levodopa. While levodopa is effective for reducing the symptoms of PD, it is associated with long-term complications such as motor fluctuations and dyskinesias. More recently, several pharmacological agents have been implemented for the treatment of PD at various stages in the disease course. Specific indicators have been developed that will allow health care practitioners to improve the diagnosis, treatment, and quality of care for patients with PD.

OBJECTIVES: To familiarize managed care professionals with treatment options in the management of PD based on current practice guidelines and clinical evidence, and to consider a set of quality-of-care indicators to improve symptom assessment and treatment strategies for patients with PD.

SUMMARY: A variety of treatment options should be evaluated on an individual basis to optimize management of PD at all disease stages. A set of quality-of-care indicators and treatment recommendations have been developed to assist health care providers and managed care professionals in improving and optimizing clinical outcomes for patients with PD.

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Epidemiology and Pathophysiology of PD

Parkinson’s disease (PD) presently affects over 1 million people in the United States. While PD can occur at younger ages, the disorder most commonly affects people over 50 years of age. Global epidemiologic studies have shown that PD affects approximately 1.5% of the population older than 60 years of age and approximately 4%-5% of those 85 years or older.1 Worldwide, PD medications alone cost an average of $11 billion per year.2 Additionally, statistics from 2002 indicate that there were more than 20,000 hospital discharges as a result of PD, at an average cost of $17,000 per patient.3 Since PD affects such a large population and generates substantial health care costs, proper diagnosis and effective disease management are vital for improving outcomes at all levels of care.

PD is a chronic, progressive, and often debilitating disease. Many patients with PD will be significantly disabled 10 to 15 years after initial disease onset.4 While the exact cause, or causes, of PD are unknown, there is some understanding of the underlying pathophysiology. In the substantia nigra, dopaminergic neurons are responsible for the proper coordination and movement of muscle groups. In PD, this pathway is disrupted because of dysfunction and/or degeneration of these dopaminergic neurons. The result is loss of normal motor control in voluntary movement.5 Additionally, structures known as Lewy bodies are found within the remaining nigral neurons. Lewy bodies are cytoplasmic inclusions containing the protein α-synuclein. Storage of α-synuclein within these inclusion bodies disrupts normal neuronal function and contributes to the pathology of PD.6

Quality of Care for PD

The quality of general health care in the United States has been reported to fall below professional standards in many instances.7 Approaches to addressing the problem of low quality health care include the development of quality indicators and practice guidelines. Quality indicators measure either processes or outcomes of care that can be assessed by review of clinical records or administrative data. Quality indicators may be based on evidence from clinical studies or expert consensus. The main use of quality indicators is to determine whether health care providers are giving quality care to their patients and to identify variations between groups of providers. In contrast, practice guidelines are used to guide individual practitioners in the care of individual patients. They are almost always based on high-level evidence from clinical trials and are promulgated by professional organizations.

Cheng et al. have developed a set of PD-specific quality indicators with the Veterans Administration (VA) health care system that may have wider applicability in assessing the quality of

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PD care and guiding the design of future quality improvement efforts. In their analysis, a comprehensive set of 79 potential quality indicators for PD care were first identified based on an extensive review of the medical literature. An expert panel of 7 movement disorder specialists then rated each indicator for several different criteria: validity, feasibility, impact on outcomes, overall utility, and room for improvement. Using thresholds for consensus by the panel members, a subset of 29 quality indicators were identified as having the highest potential for future improvements in the quality of PD care, and 22 separate quality indicators were identified that met thresholds for validity and feasibility. These quality indicators spanned all domains of care in the diagnosis and treatment of patients with PD. Table 1 provides selected examples of key quality indicators that were identified for 4 distinct domains of care. Since a consideration of the entire published list of quality indicators for PD care is not feasible, this supplement will focus on key indicators that are shown in Table 1, as well as current practice parameters or guidelines from the American Academy of Neurology (AAN) as the framework for discussion of various aspects of diagnosis and management of patients with PD.

### Classification of Clinical Evidence and AAN Treatment Recommendations

In order to best inform clinicians and other health care providers, clinical studies are evaluated for outcomes in a certain patient population for a specific disease. The AAN has published recommendations for clinical practice based on the number and class of studies conducted. Clinical studies were evaluated based on overall design, scientific rigor, and potential bias, and given 1 of 3 different classifications from I-III, with level I having the best study design, highest rigor, and least potential for bias. Four different overall treatment recommendations have been developed: Level A—the treatment is established as effective, ineffective, or harmful; Level B—the treatment is probably effective, ineffective, or harmful; Level C—the treatment is possibly effective, ineffective, or harmful; and Level U—the data are inadequate or too conflicting to determine its effectiveness (Table 2).

#### Diagnosis of and Initial Treatment for PD

Since there are no definitive imaging techniques or biomarkers available for testing and detection purposes, diagnosis of PD relies on physical and neurological examination by physicians. The most commonly used diagnostic criteria are those developed by the United Kingdom PD Society Brain Bank. The characteristic, or cardinal, symptoms found in PD affect motor skills and include bradykinesia (or slowed movement), tremors when the patient is at rest, muscle rigidity, and postural instability. Bradykinesia is a required symptom for diagnosis of PD, and patients must display at least one of the other cardinal symptoms. Symptom onset is typically asymmetrical in patients with PD.

Additional motor and nonmotor symptoms can occur in patients with PD (Table 3). Nonmotor complications such as behavioral and autonomic disturbances may be observed; these will be discussed in more detail later in this supplement. However, it is important to note that many similar symptoms occur in a variety of other diseases, including essential tremor, multiple system atrophy (MSA), or corticobasal degeneration,
and that initial misdiagnosis occurs in about 5%-10% of patients with actual PD. Additionally, approximately 20% of patients originally diagnosed with PD are found to have an alternative disease upon autopsy such as progressive supranuclear palsy (PSP), MSA, or Alzheimer disease-type pathology. Due to overlapping symptoms, it is important to use a differential diagnosis based on a process of elimination to properly diagnose and treat patients with PD. Positive confirmation of PD usually requires a post-mortem diagnosis confirming the presence of Lewy bodies within residual neurons. Several alternative diseases are associated with the presence of Lewy bodies, including diffuse Lewy body disease and Alzheimer’s disease.

### Summary and Recommendations for the Diagnosis of PD

For purposes of diagnosis of PD, the AAN recommends (Level B recommendation) that both levodopa and apomorphine challenge tests should be considered if the diagnosis of PD is in doubt. Although there is a 30% chance of either a false positive or a false negative result, response to an acute levodopa challenge is strongly associated with a diagnosis of PD. Because PD has symptoms similar to other diseases, the AAN recommends (Level B recommendation) evaluation of a set of clinical features that are suggestive of other parkinsonian syndromes: (a) symmetry of motor signs, (b) lack of tremor, (c) poor response to levodopa, (d) falls occurring early in disease, (e) autonomic dysfunction occurring early, and (f) rapid progression of the disease (Hoehn & Yahr stage III within 1 year). Confirmation of PD can also be determined by assessing symptoms during long-term follow-up such as lack of autonomic symptoms and oculomotor or cognitive dysfunction.

### Treatment Strategies for PD

Following a diagnosis of PD, the general paradigm for disease management includes both pharmacological and nonpharmacological approaches. Nonpharmacological management of patients with PD prior to dopaminergic therapy should be considered. Generally, this approach includes adjustments to both nutritional and exercise regimens as well as patient education and support.

Several classes of pharmacologic agents are also available to treat PD (Table 4). Historically, levodopa has been the gold standard for treatment in patients requiring dopaminergic therapy. Carbipoda is now typically coadministered with levodopa in patients with PD to inhibit peripheral metabolism of levodopa. This reduces the side effects caused by dopamine in the periphery such as nausea and orthostasis, as well as increasing the concentration of both levodopa and dopamine in the brain. Additional dopaminergic or dopamine enhancing drugs can be used including catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase (MAO)-B inhibitors, and dopamine receptor agonists. Anticholinergic drugs may also be used for initial treatment of PD, especially in younger patients where tremor is predominant.

### Delaying the Use of Levodopa

While levodopa reduces parkinsonian symptoms, it is also associated with the development of motor complications, which may lead to additional significant disability and impairment of patient quality of life. These motor complications include involuntary movements (dyskinesia), involuntary muscle spasms (dystonia), freezing of gait, fluctuations of symptoms (on-off), and wearing off of the beneficial response to treatment. In a Parkinson Study Group report, levodopa effectively reduced the symptoms of PD in a dose-dependent manner, as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS); however, increasing the dose of levodopa positively correlated with the frequency of motor complications (Figure 1). The UPDRS is an
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**FIGURE 1** Levodopa Reduces Symptom Worsening in Early Parkinson’s Disease But Is Associated With Motor Complications

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=90)</th>
<th>150 mg per day (n=92)</th>
<th>300 mg per day (n=88)</th>
<th>600 mg per day (n=91)</th>
<th>P value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>3 (3.3)</td>
<td>3 (3.3)</td>
<td>2 (2.3)</td>
<td>15 (16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dystonia</td>
<td>19 (21.1)</td>
<td>19 (20.7)</td>
<td>14 (15.9)</td>
<td>12 (13.2)</td>
<td>0.300</td>
</tr>
<tr>
<td>Freezing of gait</td>
<td>13 (14.4)</td>
<td>9 (9.8)</td>
<td>6 (6.8)</td>
<td>5 (5.5)</td>
<td>0.150</td>
</tr>
<tr>
<td>On-off</td>
<td>3 (3.3)</td>
<td>1 (1.1)</td>
<td>0</td>
<td>3 (3.3)</td>
<td>0.260</td>
</tr>
<tr>
<td>Wearing off</td>
<td>12 (13.3)</td>
<td>15 (16.3)</td>
<td>16 (18.2)</td>
<td>27 (29.7)</td>
<td>0.060</td>
</tr>
</tbody>
</table>


In order to delay the development of motor complications, treatment with levodopa may best be utilized for more advanced stages of the disease, when the benefits of the treatment far outweigh the adverse reactions. Indeed, prolonging the period between initial treatment and the need for levodopa treatment was an efficacy endpoint in clinical trials of new therapies for PD. Accordingly, the AAN has made several recommendations for treatment based on the findings of these studies.15,16

**MAO-B Inhibitors as Initial Treatment for PD**

Several studies have evaluated MAO-B enzyme inhibitors (rasagiline or selegiline) as monotherapy in early PD management. Since MAO-B is primarily responsible for the metabolism of dopamine, these agents increase the concentration of available dopamine within the brain and reduce the symptoms associated with PD. Previously, selegiline was the only available MAO-B inhibitor on the market. Selegiline is an amphetamine pharmacophore; its amphetamine-derived metabolites are associated with neurotoxicity in experimental studies and, clinically, with adverse cardiovascular and psychiatric effects.19 Additionally, the traditional oral form of selegiline only has approximately 8% bioavailability and, at high doses, decreased selectivity for MAO-B. Use of orally dissolving selegiline tablets helps to increase bioavailability and decrease the levels of amphetamine metabolites by bypassing hepatic metabolism.19

A second generation oral MAO-B inhibitor, rasagiline, was developed as a non-amphetamine pharmacophore. Rasagiline is up to 15-fold more selective for MAO-B in the brain than selegiline.20 Its primary metabolite, aminodindan, is clinically inactive...

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instrument commonly used for measuring the rate of progression of PD over the course of the disease. The UPDRS evaluates mentation, behavior and mood, activities of daily living (ADL), and motor skills.11 It was initially thought that motor fluctuations could be reduced with the use of controlled-release (CR) carbidopa-levodopa rather than the immediate-release (IR) formulation of the drug. In 1 comparative study of the 2 levodopa formulations in 618 patients, the prevalence of motor fluctuations and/or dyskinesias after 5 years was 20.6% for the IR group versus 21.8% for the CR group (P value not reported), indicating that CR carbidopa-levodopa had no significant advantage over the IR formulation.18

In order to delay the development of motor complications, treatment with levodopa may best be utilized for more advanced stages of the disease, when the benefits of the treatment far outweigh the adverse reactions. Indeed, prolonging the period between initial treatment and the need for levodopa treatment was an efficacy endpoint in clinical trials of new therapies for PD. Accordingly, the AAN has made several recommendations for treatment based on the findings of these studies.15,16
and not associated with neurotoxicity or cardiovascular adverse effects. Additionally, rasagiline has an oral bioavailability that is approximately 4 times greater than that of conventional selegiline.

Two key studies evaluating selegiline in the treatment of early PD are shown in Figure 2. In a randomized, double-blind trial conducted by the Parkinson Study Group evaluating the efficacy and safety of selegiline for the initial treatment of PD, the primary objective was to determine if selegiline (10 mg per day) could delay the time until levodopa treatment was required. The study enrolled over 800 patients with idiopathic PD who had not previously undergone treatment. This clinical trial also evaluated tocopherol (i.e., vitamin E); however, there was no beneficial effect of tocopherol or interaction of tocopherol with selegiline. The left graph in Figure 2 shows that selegiline significantly delayed the onset of disability requiring levodopa therapy ($P<0.001$). The difference in the estimated median time to endpoint was approximately 9 months. Similar results were reported by Pålhagen et al. in a randomized study of selegiline as monotherapy in patients with early PD. Kaplan-Meier curves in Panel B of Figure 2 show that selegiline significantly delayed the need for levodopa therapy compared with placebo-treated subjects ($P=0.028$).

Another Parkinson Study Group clinical trial evaluated patients with early PD ($n=404$) who were randomized to receive placebo or rasagiline at doses of 1 mg or 2 mg daily. The primary endpoint, at the end of 12 months, was the change in total UPDRS. After 6 months of treatment, the placebo group was switched to a regimen of 2 mg of rasagiline (designated as delayed-start rasagiline), while the other 2 treatment groups continued with their initial treatment assignment (either 1 mg or 2 mg rasagiline) for 1 year. Figure 3 shows that in the first 26 weeks of treatment, the placebo group showed an increase in symptoms by almost 4 UPDRS points, while the 2 rasagiline treatment groups initially improved over this time frame and then gradually returned toward baseline. Patients receiving rasagiline (2 mg per day) for 1 year had a significantly smaller increase (i.e., worsening) in mean adjusted total UPDRS score compared with those treated with placebo for 6 months followed by rasagiline (2 mg per day) for 6 months ($P=0.010$). The difference between the placebo/rasagiline group and those receiving rasagiline (1 mg per day)
Dopamine Receptor Agonists in the Treatment of Early PD

For more than 10 years, dopamine agonists have been used as an alternative early therapy to levodopa. Dopamine agonists function by interacting with postsynaptic dopamine receptors in the brain, where they mimic ligand binding to the receptor. A benefit of dopamine agonists is that these agents interact directly with dopamine receptors, unlike levodopa (which requires conversion to dopamine). Although there are several dopamine agonists available worldwide, only 2 nonergot-derived oral dopamine agonists are currently available in the United States: ropinirole and pramipexole. These medications require several weeks of dosing to reach an optimal therapeutic dose; this slow titration is necessary to minimize such side effects as nausea and orthostatic hypotension.

The Parkinson Study Group conducted a 4-year, double-blind, randomized trial comparing levodopa and pramipexole as treatment for early PD. The objective of this study was to evaluate the development of motor complications and other adverse effects. Approximately 22 centers in the United States and Canada were involved in this study with a total of 301 participants. One group received carbidopa-levodopa (25-100 mg 3 times per day) with a pramipexole placebo, while the other group received pramipexole (0.5 mg 3 times per day) with a levodopa placebo. Figure 4 shows curves for the probability of developing motor complications that were measured as outcomes in this study. Significantly fewer patients receiving pramipexole developed dopaminergic motor complications (dyskinesias and wearing off) compared with the group treated with levodopa (52% vs. 74%, P<0.01). Reduced risk was reported for pramipexole for the individual motor complications of wearing off (hazard ratio [HR] = 0.68, P = 0.020) and dyskinesias (HR = 0.37, P < 0.001), but not for on-off fluctuations (HR = 0.64, P = 0.340). Patients in the pramipexole group had an increased risk of freezing compared with the levodopa group (HR = 1.7, P = 0.010). Freezing, the involuntary inability to move one’s feet, is generally seen in more advanced stages of PD. Both pramipexole and carbidopa-levodopa are good treatment options for PD; however, complications and adverse effects differ with each of these drugs and should be considered prior to choosing either of these agents.

Rascol et al. conducted a 5-year, prospective, double-blind trial to evaluate the efficacy and safety of ropinirole compared with levodopa for treating early PD. This trial included 268 patients randomized to receive ropinirole (n = 179) or levodopa (n = 89). Study medication doses were adjusted weekly, if needed, with 13 possible increasing dose levels. Ropinirole was initiated at 0.75 mg per day (0.25 mg 3 times per day) and levodopa at 50 mg once daily plus placebo 2 times daily. The maximal doses for ropinirole were 24 mg per day (8 mg 3 times daily), and for levodopa were 1200 mg per day (400 mg 3 times daily). Dyskinesias occurred in 45% of subjects treated with levodopa, while only 20% of participants receiving ropinirole experienced similar motor complications. Overall, the HR for remaining free from dyskinesia in the ropinirole group compared with the levodopa group was 2.82 (P < 0.001).

Hauser et al. subsequently conducted a 10-year, open-label follow-up to the blinded study by Rascol et al., evaluating the long-term effects of ropinirole and levodopa on motor complications. Subjects who were initially randomized to ropinirole (n = 42) had a significantly lower incidence of dyskinesias compared with those taking levodopa (n = 27). Figure 5 shows the proportion of patients remaining free from dyskinesias over time in this study. Dyskinesias occurred in 52.4% of subjects from the original ropinirole group compared with 77.8% from the original levodopa group (adjusted odds ratio [OR] = 0.3, P = 0.046). At any time point, patients originally randomized to levodopa were more than twice as likely to develop dyskinesias than those who had received ropinirole.28
**Treatment Strategies and Quality-of-Care Indicators for Patients With Parkinson’s Disease**

**FIGURE 4** Probability of Motor Complications in Patients With Early Parkinson’s Disease Treated With Levodopa or Pramipexole

![Graphs showing probability of motor complications](image)


**FIGURE 5** Incidence of Dyskinesia in PD Patients Receiving Levodopa or Ropinirole

![Graph showing incidence of dyskinesia](image)

Source: Hauser RA, et al. Mov Disord. 2007;22(16):2409-17.28

**Quality Improvement Indicators in the Diagnosis and Initial Treatment of PD**

Several key indicators have been identified that may improve the quality of care in the initial diagnosis and management of PD.8 Indicators with high potential with respect to the diagnosis of PD include the assessment of the patient’s functional status and the assessment for the possibility of drug-induced (e.g., neuroleptic) PD. In terms of initial treatment, indicators with high potential for improving quality of care include initiating treatment with a nondopaminergic or dopaminergic agent when functional impairment is present. If a dopaminergic agent is selected, a discussion with the patient about the use of a dopamine agonist versus carbidopa-levodopa should occur, as well as continuous reassessment for complications of PD.8

**Recommendations for Initial Treatment of PD**

Levodopa has been the traditional gold standard for treating PD. According to current AAN practice parameters developed from a critical evaluation of clinical trials, levodopa is usually the most effective of all drugs for symptoms of PD, but is associated with
a higher risk of developing motor fluctuations. Thus, initiating symptomatic treatment for patients with PD prior to the institution of dopaminergic therapy should be considered, particularly in younger patients with early stage disease. Agents such as MAO-B inhibitors and dopamine agonists may help to relieve symptoms in early PD, while also delaying the need for initiation of levodopa therapy and reducing the development of motor complications associated with levodopa.

For patients who require dopaminergic treatment, either levodopa or a dopamine agonist should be considered (Level A recommendation). As no evidence exists for an advantage of sustained-release levodopa over immediate-release formulations, either preparation can be utilized (Level B recommendation). As PD progresses, additional agents are usually required for optimal symptomatic control, with multi-drug therapy being the norm.

### Treatment Options for Later Stages of PD

#### Levodopa

Eventually, all patients with PD will be placed on levodopa as the disease progresses. While the non-levodopa agents previously discussed are associated with favorable outcomes in younger patients, it is more common for older patients (> 70 years old) to be placed on levodopa. As previously noted, while levodopa is an effective treatment to reduce many PD-related symptoms, long-term complications such as motor fluctuations and dyskinesias are a concern. Motor fluctuations and dyskinesias were found to occur in approximately 40% of patients receiving levodopa over a 5-year period. Additional complications include “wearing off” (a decrease in the length of time that levodopa is effective) and “on-off” (a fluctuation between the time that levodopa is working properly [on] and when the symptoms of PD reappear [off]). All of these complications can be severe and present a challenge in terms of disease management. Additionally, these complications are often associated with a further reduction in quality of life and increased disability for patients. Due to the complications that arise from levodopa treatment, adjunctive pharmacological treatments are commonly required to optimize quality of care and improve function.

#### Adjunctive Therapies for PD Patients Taking Levodopa

In 2007, Jankovic and Stacy devised a decision tree (Figure 6) to guide adjunctive treatment strategies for levodopa-induced motor complications. Clearly, as complications arise and advance, different approaches may be necessary to maintain both treatment efficacy and quality of life for patients with PD. While initial motor complications can be treated by adding either catechol-O methyltransferase inhibitors (COMT), MAO-B inhibitors, or a dopamine receptor agonist to levodopa treatment, severe motor fluctuations may require the use of a short-acting injectable dopamine agonist as rescue therapy or apomorphine in order to control symptoms. The AAN also has recommendations for treatment of PD patients with motor complications based on review of various classes of clinical studies. As discussed previously, the use of the CR formulation of carbidopa-levodopa showed no significant difference in the development of motor complications compared with IR.
formulations. Therefore, the AAN recommendation (Level C) is that sustained release carbidopa-levodopa, as well as bromocriptine, be disregarded to reduce “off” time.31

Figure 7 shows results from the Lasting effect in Adjunct therapy with Rasagiline Given Once daily (LARGO) study to evaluate the effect of rasagiline or entacapone on “off” time and daily on-time without dyskinesias.32 In total, 231 patients in the control group received rasagiline (1 mg per day), 227 received entacapone (200 mg per day), and 229 received placebo; all in addition to levodopa. Compared with levodopa plus placebo, patients receiving levodopa plus rasagiline or levodopa plus entacapone showed significant reductions in mean daily “off” time and significant increases in “on” time without dyskinesias32. With respect to daily “off” time, rasagiline plus levodopa had a mean reduction of 1.8 hours compared with the 0.4 hour reduction by levodopa alone (P=0.001).32 Entacapone plus levodopa reduced mean “off” time by 1.2 hours compared with 0.4 hours by levodopa alone (P<0.001).32 When “on” time without dyskinesias was the end point, levodopa alone showed an increase of 0.03 hours, while both entacapone plus levodopa and rasagiline plus levodopa increased “on” time by 0.85 hours (P<0.001).32 There were no significant differences between treatment groups with respect to on-time with dyskinesias.32

Several additional studies designated as class I and II by the AAN indicate that treatment with entacapone significantly reduces “off” time by 21% to 26% in patients taking levodopa compared with placebo.32-34 Similarly, 2 class I studies investigating rasagiline as adjunctive therapy to levodopa showed significant decreases in “off” time, ranging from 21% to 32%.32,33 Accordingly, the AAN recommendation (Level A recommendation) is that rasagiline or entacapone should be offered to levodopa-treated patients who are experiencing “off” time.31

Two class II clinical studies investigated ropinirole as adjunctive therapy to levodopa.36,37 Although these were somewhat smaller studies, significant reductions in “off” time were observed with ropinirole. Several studies evaluating adjunctive pramipexole have shown that this agent also significantly reduces “off” time.31

The effect of tolcapone (100 mg or 200 mg three times daily) as adjunctive therapy to levodopa was evaluated in a study of 202 Parkinson’s patients by Rajput et al.38 At the end of 1 year, subjects in the 200 mg tolcapone dose group had a significant decrease in “off” time of 48% (3.2 hours) compared with placebo (P<0.001).38 Based on evidence from these studies, the current AAN recommendation (Level B recommendation) is that ropinirole, pramipexole, and tolcapone may be considered for the reduction of “off” time in patients taking levodopa.31 However, due to the hepatotoxicity of tolcapone, this agent should be prescribed with caution and requires careful monitoring for liver abnormalities.31

Several other drugs may be considered as adjunctive therapy to ameliorate motor complications that are associated with levodopa treatment. The noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, amantadine, has received an AAN Level C
recommendation for patients with levodopa-induced dyskinesia, and selegiline has received an AAN Level C recommendation for management of fluctuations.31 The AAN gives a Level U recommendation for the use of clozapine in reducing levodopa-induced dyskinesia, as there is insufficient evidence to either support or refute its efficacy.31

Adverse Effects Associated With PD Therapies

Adverse effects vary among the available treatments and should be considered when managing patients with PD. A general overview of the major side effects associated with each class of medications used to treat PD is provided in Table 5. In addition to the motor complications that have been discussed, levodopa-levodopa treatment is commonly associated with nausea, somnolence, hypotension, or hallucinations.14 The COMT inhibitors can cause diarrhea and exacerbate the adverse dopaminergic effects of levodopa.14 The MAO-B inhibitor selegiline is associated with confusion, hallucinations, and insomnia; rasagiline is generally well tolerated and not associated with excessive dopaminergic side effects.14

Side effects that are commonly seen with the dopamine agonists pramipexole and ropinirole include nausea, sedation, edema, hallucinations, and hypotension.14 These symptoms can be minimized with slow titration of the drug upon initiation of therapy. Another set of adverse reactions associated with dopamine agonists, which has been reported with more frequency in recent years, consists of behavioral abnormalities. These are compulsive in nature and include inappropriate activities such as pathological gambling, compulsive shopping, spending excessive amounts of money, and hypersexuality.30,40

Quality Indicators for Management of Motor Complications

One of the main concerns for patients with PD receiving levodopa treatment is the occurrence of motor complications and fluctuations.8 One indicator with high potential to improve the quality of care is to evaluate if the initial or subsequent treatment is wearing off and to manage any problems appropriately (Table 1). Entacapone, rasagiline, or a dopamine agonist can be used as adjunctive therapy with levodopa for management of motor fluctuations. With respect to COMT inhibitors, entacapone should be used before tolcapone, and if tolcapone is given for adjunctive therapy, liver function testing should occur regularly as per the new labeling recommendations.8 Effective management of dyskinesias can also improve the quality of patient care.

Surgery for Management of Levodopa-Induced Motor Complications

While pharmaceutical agents can reduce levodopa-associated motor complications, more aggressive treatments must be considered when the best medical therapy fails. Recently, the use of surgical techniques such as deep brain stimulation (DBS) to relieve motor fluctuations has gained popularity. DBS is the most common surgery for PD performed in North America and involves the implantation of electrodes into the brain, which are then connected to an implantable pulse generator (IPG). Benefits of successful DBS surgery have been shown to persist for many years.31 As with any treatment, the goal is to provide the greatest benefit while at the same time reducing adverse effects. Surgery should generally be considered for levodopa-responsive patients who require more symptomatic control or patients who are experiencing severe motor complications despite optimized pharmacological therapies.16 An additional indication for surgery includes the development of medication-related adverse events, such as peak dose dystonia/dyskinesia or hallucinations that preclude optimizing medication dosing.

Summary and Recommendations for Treatment Options in Later Stages of PD

While motor fluctuations associated with levodopa treatment cannot be completely avoided, adjunctive treatment options are available to help minimize their effects. The MAO-B inhibitor rasagiline and the COMT inhibitor entacapone have similar efficacy and strong AAN recommendations for the reduction of “off” time in patients receiving levodopa.31,32 Dopamine agonists were found to also decrease “off” time in patients concurrently receiving levodopa but have less rigorous evidence. As with

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Dry mouth, dry eyes, constipation, cognitive impairment, sedation, urinary retention</td>
</tr>
<tr>
<td>Carbidopa-Levodopa</td>
<td>Nausea, somnolence, dyskinesia, hypotension, hallucinations</td>
</tr>
<tr>
<td>COMT Inhibitors</td>
<td>Diarrhea, exacerbates levodopa adverse effects, bright orange urine</td>
</tr>
<tr>
<td>Dopamine Agonists</td>
<td>Nausea, headache, dizziness</td>
</tr>
<tr>
<td>MAO-B Inhibitors</td>
<td>Confusion, insomnia</td>
</tr>
</tbody>
</table>

every prescribed medication, the occurrence of side effects should be carefully monitored, and treatment strategies adjusted accordingly. Analysis of clinical studies has led to several AAN recommendations for the surgical treatment of PD-associated complications. DBS of the subthalamic nucleus (STN) should be considered for PD patients in order to improve motor function and to reduce motor fluctuations and the use of medication (Level C recommendation).31 Patients should be carefully counseled on the possible risks and complications that can arise from the surgery. There is insufficient evidence for recommendation of DBS of the thalamus or globus pallidus (GPI) for the reduction of adverse motor effects.31

### Nonmotor Symptoms Associated With PD

There are 4 major categories of nonmotor symptoms observed in patients with PD associated with cognition, sleep disturbances, sensation, and autonomic dysfunction.49 Table 6 shows these general categories and the main symptoms within each category.

### Orthostatic Hypotension

Orthostatic hypotension (OH), sometimes referred to as postural hypotension, is defined as a reduction in systolic blood pressure (BP) of at least 20 mm Hg or diastolic BP of at least 10 mm Hg within 3 minutes of standing up.41 The physical symptoms include blurred vision, dizziness, fainting, and a feeling of being light-headed within seconds of standing up. Neurogenic OH is a commonly occurring autonomic dysfunction that can be a significant problem in patients with PD. Dopamine agonists and virtually all medications used to treat PD may contribute to the emergence of OH. Other medications, such as antihypertensives and diuretics, and neurological diseases other than PD, such as diabetic neuropathy, multiple system atrophy, and autonomic neuropathies, may also contribute to the development of OH.42

Several clinical studies have been conducted to investigate the prevalence of OH in patients with PD.43 All studies evaluated used a decrease in systolic BP equal to or greater than 20 mm Hg as the definition of OH. The prevalence of OH in these studies varied from 30% and 58%, with an average of 41%.43 These results did not necessarily correlate with disease duration or severity, and it was found that OH can occur at any disease stage.43 In normal elderly patients, however, the occurrence of OH is roughly 5% to 30%, indicating that there is an increased incidence of OH in patients with PD.42

### Management of Orthostatic Hypotension

The main goal in the management of OH is to improve orthostatic blood pressure, while avoiding the occurrence of excessive supine hypertension. By reaching this goal, the patient can regain the ability to participate in orthostatic activities (e.g., ambulation), which, in turn, can lead to an improved quality of life. Additionally, management of OH can help improve a patients’ standing time, relieve orthostatic symptoms, and prevent falls that could lead to further disability. There are several strategies available for the management of OH, including the use of pharmacological therapies, nonpharmacologic approaches such as increased intake of fluids and salt, use of support hose, and physical countermaneuvers (Table 7). While sympathomimetic agents

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### Table 6: Nonmotor Symptoms in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Cognitive/Psych</th>
<th>Sleep</th>
<th>Sensation</th>
<th>Autonomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowed reaction times</td>
<td>Daytime somnolence</td>
<td>Reduction or loss of sense of smell</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Dementia</td>
<td>Insomnia</td>
<td>Pain</td>
<td>Oily skin and seborrheic dermatitis</td>
</tr>
<tr>
<td>Psychosis</td>
<td>REM sleep behavior disorder</td>
<td>Impaired proprioception</td>
<td>Urinary incontinence or nocturia</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Sleep apnea</td>
<td>Impaired visual contrast sensitivity</td>
<td>Constipation and gastric dysmotility</td>
</tr>
<tr>
<td>Depression</td>
<td>Restless legs syndrome</td>
<td></td>
<td>Altered sexual function</td>
</tr>
<tr>
<td>Apathy and anhedonia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---

### Table 7: Strategies for Management of Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume Expansion</td>
<td>Fluid and NaCl</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td></td>
<td>Vasopressin analogs</td>
</tr>
<tr>
<td></td>
<td>Intermittent water bolus therapy</td>
</tr>
<tr>
<td>Sympathomimetic Agonists</td>
<td>Midodrine (selective for peripheral α adrenoreceptors)</td>
</tr>
<tr>
<td></td>
<td>Ephedrine</td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Supplementary Therapies</td>
<td>Adjust PD medications</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
</tr>
<tr>
<td></td>
<td>Droxidopa</td>
</tr>
<tr>
<td></td>
<td>Pyridostigmine</td>
</tr>
<tr>
<td></td>
<td>Yohimbine</td>
</tr>
<tr>
<td>Other Nonpharmacologic</td>
<td>Patient education</td>
</tr>
<tr>
<td></td>
<td>Compression stockings/support hose</td>
</tr>
<tr>
<td></td>
<td>Physical countermaneuvers (toe raising, leg crossing, thigh contracting, bending at waist, etc.)</td>
</tr>
</tbody>
</table>

*Approved by the FDA for orthostatic hypotension.*
*Orphan drug for neurogenic orthostatic hypotension.*
*Can worsen tremor in patients with PD.*

such as ephedrine and pseudoephedrine might be considered, midodrine is the only FDA-approved product for this indication. Droxidopa has orphan status for the treatment of OH and is currently in Phase 3 trials in the United States. Additionally, while fluodrocortisone had been used off-label for some time, there is very little evidence to support its use as a first-line agent.

Midodrine is a selective agonist for peripheral α1-adrenergic receptors that causes an increase in vascular tone and BP. One of the limitations of midodrine is the increased risk for supine hypertension, which must be considered when determining the proper management strategies for OH. A randomized, double-blind, dose-response study 44 was conducted to determine the effects of midodrine for treatment of neurogenic orthostatic hypotension (NOH). This 6-day trial included 25 non-PD patients randomized to receive either placebo or midodrine (2.5, 10 or 20 mg per day), and the endpoints were changes in supine systolic BP and standing systolic BP. Results showed that standing systolic BP increased in direct correlation with the midodrine dose but a minimal dose of 10 mg was required for statistical significance. 44 Similarly, a dose-dependent increase in supine systolic BP was also observed with midodrine. 44 Based on the published results, a 10 mg dose may provide the most clinical benefit (increase standing BP), while producing minimal side effects (increased supine BP).

**Sleep Abnormalities**

Approximately 80% to 90% of patients with PD experience some form of sleep disturbance. 45 The cause of sleep disturbances may be related to PD itself, treatments used, or due to underlying comorbidities such as cognitive dysfunction, dementia, or depression. Treatment for sleep dysfunction should first involve promotion and development of good sleep habits and hygiene. Additional sleep improvements may require a change in PD medications or doses. Treatment of comorbidities should also be considered for the management of sleep disorders.

Several types of sleep disturbances are recognized, including excessive daytime sleepiness (EDS), insomnia, restless legs syndrome (RLS), and REM behavioral sleep disorders (RBD). Each category has several pharmacological treatments that may be considered (Table 8). Assessment of the efficacy of modafinil, a psychostimulant, for treating EDS was based on the Epworth Sleepiness Scale (ESS), which is used to determine a propensity for daytime sleepiness. In a randomized, double-blind, placebo-controlled, crossover study by Adler et al., patients with PD (n=21) experiencing EDS, with an ESS ≥ 10, were treated with either 200 mg per day of modafinil or placebo for 3 weeks. 46 Overall, the study showed that while the placebo treated participants saw no relief for their EDS, modafinil reduced patients ESS by a mean of 3.4 points (P=0.039). 46

### Table 8: Pharmacologic Alternatives for Sleep Abnormalities in Patients With Parkinson’s Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive Daytime Sleepiness (EDS)</td>
<td>Modafinila, Methylphenidateb</td>
</tr>
<tr>
<td>REM Behavior Disorder (RBD)</td>
<td>Clonazepam, Melatonin</td>
</tr>
<tr>
<td>Insomnia and Sleep Fragmentation</td>
<td>Sedative-hypnotics, Benzodiazepines, Melatonin</td>
</tr>
<tr>
<td>Restless Legs Syndrome (RLS)</td>
<td>Gabapentin, Benzodiazepines, Opioids</td>
</tr>
</tbody>
</table>

*aHas not been extensively studied in patients with PD.  
*bRandomized clinical trials have been conducted in patients with PD.


Constitution

Another common nonmotor symptom in patients with PD is constipation, with a prevalence of 70% to 80%. 50 There is evidence to suggest that a potential cause of constipation in PD involves a loss of neurons and the presence of Lewy bodies very early in the disease within the myenteric plexus of the colon. These nerve cells are involved in the coordination of normal defecation. 47 Constipation can be managed by: (a) increasing daily fluid intake, dietary fiber, and physical activity; and (b) by using stool softeners, laxatives, or enemas. 45

Sexual Dysfunction

Sexual dysfunction is common in males with PD and also occurs in females. 47 In males, erectile dysfunction (ED) is the most common form of sexual dysfunction. 47 Comorbid issues, such as depression and anxiety, should be considered when treating ED in patients with PD. Because ED can also result as a side effect of pharmacological therapy (e.g., anticholinergics) for PD, a thorough review of each patient’s current medications is important.

In a study by Hussain et al., sildenafil was evaluated in patients experiencing erectile dysfunction, including patients with PD. 51 To measure treatment outcomes, the International Index of Erectile Function (IIIEF) questionnaire and a quality-of-life
on the management and reduction of the motor dysfunction associated with PD.

Neuropsychiatric Manifestations of PD
Psychiatric complications associated with PD include dementia, depression, and psychosis. Although the occurrence of these complications in PD patients is 20% to 50%, many physicians do not recognize the symptoms related to these complications, frequently due to a lack of valid criteria for assessment. Additionally, PD symptoms such as facial masking overlap with features of depression and dementia, so determining if they are the origin of comorbidity can be difficult.

Criteria and AAN Recommendations for the Diagnosis of Depression
The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) contains criteria for diagnosing mental or behavioral disorders. For a diagnosis of major depression, patients must display 5 of the following criteria, one of which must be a depressed mood, for a period of at least 2 weeks: depressed mood, diminished interest in daily activities, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness, an inability to concentrate or make decisions, and recurrent thoughts of death. However, there are currently several challenges when using these clinical criteria to diagnose depression associated with PD. One such challenge is that symptoms of depression can overlap with those of PD and apathy. Other challenges include the difficulty of assessing PD patients with impaired cognitive capabilities; the timing of assessment, which can influence results; and evaluating depression, which, in PD patients, can look different from depression in patients without PD.

There are several screening and rating systems that physicians can use to test for depression that consist of questions or statements that can be scored to determine the appropriate management of orthostatic hypotension. Clinicians and providers should also consider treatment for constipation, urological symptoms, swallowing difficulties, and speech dysfunction to improve the quality of life for PD patients.

The occurrence of nonmotor complications can occur in a variety of combinations and at varying degrees of severity that are unique to each patient. While treatment options vary with each patient and/or complication that arises, the objective of treatment is not only relief of symptoms, but also improvement in the overall quality of life for patients with PD. By alleviating these symptoms, patients and their physicians can concentrate

Quality Indicators and Summary for Management of Nonmotor Complications
Overall, there are a variety of nonmotor complications associated with PD that health care providers should be aware of in order to provide optimal care for their patients. While not every nonmotor complication was discussed in this supplement, some of the more common dysfunctions were addressed. One PD-specific quality indicator with high potential for quality improvement is the appropriate management of orthostatic hypotension.

Table 9: Antidepressants Used in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents (s)</th>
<th>Primary Adverse Events (for drug class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>Citalopram, Paroxetine, Fluoxetine, Duloxetine, Sertraline, Escitalopram</td>
<td>Insomnia, Jitteriness, Dizziness, Nausea, Diarrhea, Headache, Sexual dysfunction, Weight gain</td>
</tr>
<tr>
<td>Tricyclic Antidepressants (TCAs)</td>
<td>Nortriptyline, Amitriptyline</td>
<td>Dry mouth, Constipation, Urinary retention, Sedation, Sexual dysfunction, Orthostatic hypotension, Worsening cognition in PD</td>
</tr>
<tr>
<td>Other</td>
<td>Venlafaxine, Bupropion</td>
<td>Dry mouth, Sweating, Anxiety, Dizziness, Nausea</td>
</tr>
</tbody>
</table>

(NSRIs), and tricyclics (TCAs). While studies to determine the efficacy of many of these drugs have been conducted for idiopathic depression, studies conducted to gauge the efficacy of these drugs for PD-related depression are limited. Rampello et al. conducted a small study using 46 patients to investigate the efficacy of citalopram for treatment of depression associated with PD. All patients within the study were currently taking carbidopa-levodopa for PD, and several rating scales (e.g., BDI, HDRS) were utilized to gauge the changes in depression treated with citalopram (20 mg per day) compared with placebo. Results of the 4-month study indicate treatment with citalopram reduces the symptoms and/or the severity of symptoms of depression in patients with PD, regardless of the rating scale utilized. As expected, symptoms improved in direct relationship to the length of treatment. Another citalopram study of 37 PD patients with depression found no significant differences in depression scores (Ham-D and the Melancholia Scale) when treating with citalopram versus placebo. In this 52-week study, those patients under the age of 65 received 20 mg per day of citalopram, while patients over 65 years of age received 10 mg per day. Several adverse effects were noticed with citalopram treatment, including sweating, nausea/vomiting, and decreased sexual desire.

A study conducted by Antonini et al. determined the effects of the SSRI sertraline (50 mg) and the TCA amitriptyline (25 mg) on PD-related depression. This small study involved approximately 12 patients per group. The results were evaluated using the Ham-D scale. Sertraline and amitriptyline showed significant decreases in depression using the Ham-D scale after 3 months of treatment. Several other studies (reviewed in Chung et al.) were conducted to determine the effects of additional treatment options for managing PD-related depression. A 16-week study of nortriptyline (25 to 150 mg daily) versus placebo in 22 patients found significant improvements in depression (P<0.001), with nonsignificant effects in neurological signs and orthostatic hypotension. A study of 52 patients conducted by Menza et al. investigated the effects of nortriptyline (25 to 75 mg) and paroxetine CR (12.5 to 37.5 mg) for the treatment of PD-related depression. The results indicated that compared with placebo, nortriptyline significantly reduced depression (P=0.002) while paroxetine CR did not (P=0.165).

**AAN Recommendations for the Treatment of PD-Associated Depression**

Despite the high prevalence of depression among PD patients, very few clinical trials have been performed to assess the efficacy of common antidepressants. Additionally, the studies that have been done have several common flaws, such as poor design, an insufficient number of participants, and studies that were open-label or not well controlled. Since the AAN uses study design rigor as a component of their guidelines, recommendations for the treatment of depression in patients with PD are minimal. The level C recommendation is to consider amitriptyline for PD-related depression as long as dementia is not present. However, this should not necessarily be the first choice for treatment. There was insufficient evidence (Level U) to make recommendations for other pharmacological treatments, transcranial magnetic stimulation, or electroconvulsive therapy for the treatment of PD-related depression.

**Psychosis Symptoms and Treatment Options**

Psychosis in PD is characterized by hallucinations and paranoid delusions, such as delusions of spousal infidelity. Hallucinations are usually formed visual hallucinations rather than the auditory hallucinations more common in schizophrenia. Psychosis is associated with dopaminergic treatment for PD and is often a marker of dementia. Once psychosis has been effectively treated, significant cognitive dysfunction or decline may become apparent. The assessment scales used to measure psychosis in patients with PD include the Neuropsychiatric Inventory, the Parkinson Psychosis Rating Scale, the Brief Psychiatric Rating Scale (BPRS), and the Schedule for Assessment of Positive Symptoms (SAPS). As none of these scales have been validated, the AAN has no specific recommendations for which psychosis screening scale should be used in patients with PD. However, the AAN has made recommendations for the pharmacological treatment of psychosis in patients with PD.

The Parkinson Study Group investigated low doses of clozapine (6.25 to 50 mg per day) in the treatment of Parkinson-related psychosis. This randomized, double-blind, placebo-controlled study involved 60 subjects, all of whom were diagnosed with idiopathic Parkinson's disease and psychosis due to pharmacological treatment for PD. This 14-month study assessed the efficacy of clozapine in terms of its effects on symptoms of PD as measured by the UPDRS, and symptoms of psychosis using several rating scales including BPRS and SAPS. Clozapine was found to reduce tremors and psychosis scores in patients with PD. A 12-week study conducted by Morgante et al. determined the effects of quetiapine (25 to 200 mg per day) versus clozapine (12.5 to 50 mg per day) in the treatment of dopaminergic psychosis in patients with PD. In this controlled, open-label study, 10 patients were monitored for each treatment regimen. The endpoints measured baseline versus endpoint scores of several neuropsychological and PD rating scales. Both medications caused a significant decrease (P<0.001) in rating scores for psychosis as measured by BPRS and the Clinical Global Impression (CGI) scale. While clozapine showed a significant decrease (P<0.050) in Parkinson's symptoms, as measured by UPDRS, quetiapine did not. Both drugs significantly (P<0.050) reduced the occurrence of dyskinesias as measured by the Abnormal Involuntary Movement Scale (AIMS). More recently, controlled studies of quetiapine have failed to show that it is efficacious for hallucinations. While these studies are small, they suggest that both clozapine and quetiapine are efficacious in the treatment of Parkinson-related psychosis without any adverse effects on symptoms of
PD. Additionally, quetiapine may be tried for hallucinations due to possible efficacy and better safety profile than clozapine, but the evidence supporting clozapine’s efficacy is clearly stronger. The AAN recommends clozapine (Level B recommendation) and quetiapine (Level C recommendation) for the treatment of psychosis in PD patients. Additionally, the AAN recommends that olanzapine not be routinely considered (Level B recommendation), as it can worsen motor functions in PD patients.

**Dementia Diagnosis and Treatments**

Dementia is another common psychological disturbance associated with PD. Compared with age-matched controls, patients with PD show a 4-fold increased risk of developing dementia. Delayed diagnosis is common due to the masking of symptoms by the slowing of thought processes (bradyphrenia) and loss of motivation due to the progression of PD. The AAN recognizes 2 screening tools for the assessment of dementia in patients with PD. The Level B recommendations include the Mini-Mental State Examination (MMSE) and the Cambridge Cognitive Examination (CAMCog). Electroencephalography (EEG) has also been used to detect dementia, however, the AAN appoints a Level U recommendation for this procedure because of insufficient evidence to either refute or support its use.

Studies have been conducted with several medications, including donepezil and rivastigmine, for the treatment of dementia in PD. Donepezil is a cholinesterase inhibitor that reduces the metabolism of acetylcholine in the brain. Acetylcholine is a neurotransmitter that is believed to affect cognition and memory. In a 26-week, double-blind, randomized, placebo-controlled study, Ravina et al. studied the efficacy and safety of donepezil (5-10 mg per day) for treating dementia in patients with PD (n = 222). The primary effects on dementia were measured by the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog), and the UPDRS was used to measure any changes in PD symptoms. There was a nonsignificant decrease in ADAS-cog scores (1.9 points) with donepezil compared with placebo (P = 0.18). Secondary dementia outcomes were measured with the MMSE and the MADRS; donepezil significantly reduced (2.0 points) MMSE scores compared with placebo (P = 0.004), but results were not significant as assessed by the MDRS (P = 0.098). Treatment with donepezil was safe and well tolerated by subjects in this study.

Rivastigmine, like donepezil, functions to reduce the metabolism of acetylcholine in the brain. In a 24-week study conducted by Emre et al., the efficacy of rivastigmine (3 to 12 mg per day) for the treatment of mild to moderate dementia in PD was determined utilizing the ADAS-cog and Alzheimer’s Disease Cooperative Study–Clinician’s Global Impression of Change (ADCS-CGIC). A total of 490 participants were divided into 2 study groups: 329 patients received the study drug, and 161 were given a placebo. Compared with placebo, rivastigmine significantly improved scores for dementia as measured by both rating scales. Overall, the improvements were moderate compared with previously reported results. The scores for rivastigmine measured on the ADAS-cog scale improved by 2.5-3 points compared with placebo (P < 0.001), while analysis with the ADCS-CGIC scale indicates that 19.8% of participants had a noticeable improvement in scores with rivastigmine compared with placebo (P = 0.007). As both drugs modestly decrease the symptoms of dementia, the AAN recommends that donepezil and rivastigmine should be considered as treatment options (Level B recommendation). While rivastigmine is FDA approved for the treatment of dementia associated with PD, donepezil is not.

**Quality Indicators for the Management of Dementia, Depression, and Psychosis**

In order to improve treatment for the neurobehavioral manifestations that arise with PD, indicators have been developed to measure the quality of care provided to patients with PD and neurobehavioral problems. Based on an expert consensus process, the indicators with the highest potential to improve the management of PD include conducting a proper assessment for depression, using quetiapine or clozapine to treat persistent hallucinations, and the possibility of withdrawal or reduction of medications that can cause hallucinations. It is highly recommended to monitor white blood cell counts (WBCs) in patients receiving clozapine to check for agranulocytosis. Additionally, an assessment of the decision-making capacity should be done for PD patients with dementia.

**Summary of Management for Depression, Dementia, and Psychosis**

Neuropsychological disturbances can go undetected due to overlap with motor features of PD and the lack of valid criteria to recognize them. Although there are few specific recommendations for the treatment of neuropsychological problems in PD, it is widely acknowledged that it is important, clinically, to recognize and address them in order to provide an increased quality of care for patients with PD and for those who care for them.

**Managed Care Pharmacy Considerations in Domains of PD Care**

**Initial Diagnosis and Treatment of PD**

The number of PD cases is expected to dramatically increase in the future. Accurate diagnosis of PD ensures that the patient is being prescribed an effective initial therapy, which may lead to reduced patient disability over time, with reduced direct and indirect health care costs. Optimization and maintenance of symptom control in PD often requires continuous titration of medications and addition of other therapies over the disease course. Adherence to prescribed medications is important for both symptom control and maximizing therapeutic efficacy. However, adherence can be compromised by numerous factors, including complex dosing regimens,
have been previously discussed. For example, midodrine is currently the only FDA-approved product for OH. Pharmacologic agents may also be prescribed for other non-motor complications, such as sleep abnormalities, urinary dysfunction, and sexual dysfunction, although not all agents have been specifically evaluated in patients with PD.

The comorbid neuropsychiatric nonmotor symptoms of PD, such as depression, dementia, psychosis, and cognitive impairment are particularly important considerations, as these may be more disabling to the patient than their motor symptoms. Despite the high prevalence of depression in patients with PD, there is a paucity of quality clinical trials that have evaluated antidepressants in this population. However, antidepressants continue to be prescribed for depression associated with PD and can be effective, although there currently is insufficient evidence to make high level recommendations for specific agents. Pharmacists should be aware of potential interactions of certain drug classes with antiparkinson agents. For example, some tricyclic antidepressants may decrease the effectiveness of levodopa.

Conclusions

Parkinson’s disease is a complex disorder that not only involves disruption of the voluntary motor system, but is also associated with significant nonmotor and neurobehavioral manifestations. Clinicians should be familiar with the signs and symptoms of PD in order to better evaluate a patient and initiate treatment protocols at the early stages of the disease. The main goal of initial treatment is to reduce the symptoms of PD, while minimizing any long-term side effects.

Nonpharmacological therapies, such as exercise and physical therapy may be considered prior to initiation of or as an adjunct to pharmacological agents, but little controlled data exists to support this therapeutic modality. While levodopa remains the gold standard of treatment, additional pharmacological agents, such as dopamine agonists, and MAO-B and COMT inhibitors, have become available in recent years; these can help reduce the occurrence of motor complications associated with levodopa use. Individualized treatment plans are essential to assist patients in maintaining the best quality of life. An awareness of potential nonmotor and neurobehavioral symptoms can assist clinicians in the improved management of PD as the disease progresses. Throughout the course of this disease, AAN evidence-based recommendations for treatment should be considered. The quality indicators discussed describe considerations with potential to improve the quality of care available to patients with PD. Achieving this goal may help cut costs associated with hospitalizations and medications, while also increasing the quality of life of those afflicted. Managed care pharmacists play an integral role in optimizing management of PD by understanding current treatment options, enhancing opportunities to improve clinical outcomes, and optimizing resource utilization.

Management of Motor Complications. One of the major challenges faced in PD is recognition and management of motor complications. As previously noted, younger patients with early-onset PD may be more prone to develop motor fluctuations with chronic levodopa treatment. These individuals are candidates for initial therapy with nondopaminergic agents. For patients taking levodopa who develop motor fluctuations, adjunctive agents may need to be added to their regimen to optimize treatment. Whether a patient is in early or later stages of treatment, maintaining functionality as long as possible is the goal of clinical management. This not only improves patient health-related quality of life (HRQOL), but may also reduce direct costs associated with the need for office visits and lessen indirect costs by mitigating dependence on caregivers and allowing less time off from work.

Data on the cost-effectiveness of treatments for motor symptoms in PD are somewhat limited. However, in a retrospective study, health care costs (indirect and direct) can be up to 3 times higher in patients with PD who develop motor fluctuations. The number of daily “off” periods was reported to have the greatest impact on cost, such that medical costs are reduced by 5% for every 10% reduction in off time. Thus, effective treatment to minimize or delay “off” periods should result in cost savings.

Management of Nonmotor Symptoms. Pharmacologic strategies available for the management of selected nonmotor symptoms of PD have not been previously discussed. For example, midodrine is currently the only FDA-approved product for OH. Pharmacologic agents may also be prescribed for other non-motor complications, such as sleep abnormalities, urinary dysfunction, and sexual dysfunction, although not all agents have been specifically evaluated in patients with PD.

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REFERENCES


41. No authors listed. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. 

42. Low PA. Prevalence of orthostatic hypotension. 

43. Goldstein DS. Orthostatic hypotension as an early finding in Parkinson’s disease. 


47. Dubow JS. Autonomic dysfunction in Parkinson’s disease. 


49. Adler CH. Nonmotor complications in Parkinson’s disease. 


51. Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to pathologic gambling and other compulsions among Parkinson’s disease patients taking dopamine agonists. 


76. Dowding CH, Sahentorn CL, Salk SS. A review of the health-related quality of life and economic impact of Parkinson’s disease. 

77. Young LR, Justice LN. Parkinson’s disease: focus on management alternatives. 

78. Freeman R. Current pharmacological treatment for orthostatic hypotension. 


80. Freedman T. Sleep and Parkinson’s disease.
Treatment Strategies and Quality-of-Care Indicators for Patients With Parkinson’s Disease

Pharmacists
This is an application-based learning activity.

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The posttest worksheet is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:
1. Posttest form for this program, “Treatment Strategies and Quality of Care Indicators for Patients With Parkinson’s Disease” is accessible at the AMCP.org CME/CE Center or at PRIME® at www.primeinc.org/jmcp/pd. To receive credit, you must receive a score of 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be archived and tracked for you on the AMCP.org CME/CE Center site or at www.primeinc.org. All information is kept confidential.

Posttest Worksheet: Treatment Strategies and Quality-of-Care Indicators for Patients With Parkinson’s Disease

1. A 65-year-old male visits his primary care physician’s office for an examination because he has been experiencing some disconcerting physical symptoms since his last check-up more than a year ago. Which of the following symptoms would LEAST likely be a sign of Parkinson’s disease (PD)?
   a. Slowness of movements (bradykinesia)
   b. Tremor that increases with voluntary movement
   c. Rigidity and increased muscle tone
   d. Postural instability in later disease stages

2. Which of the following observations would be most characteristic of PD that would facilitate the differentiation of PD from other parkinsonian or neurodegenerative disorders?
   a. Response to levodopa
   b. Symmetry of motor signs
   c. Falls early in disease course
   d. Rapid disease progression

3. Which of the following is NOT a typical motor symptom of PD?
   a. Hypophonic speech
   b. Swallowing difficulties
   c. Frequent blinking
   d. Postural instability

4. A 52-year-old female has been diagnosed with early onset PD based on clinical symptoms. In discussing her options for initial treatment, which of the following statements is correct?
   a. Since her symptoms are minor, only physical therapy is indicated at her relatively young age.
   b. Surgery should be considered as a first option for young patients because of their more rapid recovery time.
   c. The patient should consider an alternative to levodopa as initial therapy to prolong the time to when levodopa may be needed.
   d. An anticholinergic agent should be used as initial therapy based on the patient’s age.

To complete this activity, go to www.amcp.org (CE/CME Center) or http://primeinc.org/jmcp/pd to access the posttest and evaluation form.
5. A 70-year-old, right-handed female was previously diagnosed with idiopathic PD. She has been taking carbidopa-levodopa (25 mg-100 mg) 3 times a day for the last 4 years with adequate control of her symptoms. Recently, the patient began experiencing a return of her motor symptoms (slowness and tremor) 1 hour prior to her next scheduled carbidopa-levodopa dose. Which of the following steps would be most appropriate for optimizing treatment of this patient?
   a. Discontinue levodopa and switch to another class of agent
   b. Switch to controlled release carbidopa-levodopa formulation
   c. Increase the frequency of the current carbidopa-levodopa dose
   d. None of the above

6. Which of the following statements regarding motor complications during levodopa therapy in patients with PD is INACCURATE?
   a. Motor fluctuations generally increase with each year of levodopa therapy
   b. Motor complications may occur as early as several months after initiation of levodopa therapy
   c. Motor fluctuations and dyskinesias can occur together
   d. Management of fluctuations and dyskinesias are similar

7. The presence of Lewy bodies in PD is usually confirmed:
   a. At the time of diagnosis of PD
   b. At a postmortem autopsy
   c. With neurological examination
   d. Using a blood toxicology screen for α-synuclein

8. Based on AAN Practice Parameters for PD, which of the following agents has the strongest clinical evidence that supports its use as an adjunct to levodopa to reduce "off" time?
   a. Ropinirole
   b. Pramipexole
   c. Rasagiline
   d. Selegiline

9. At a routine follow-up visit, a 64-year-old male previously diagnosed with PD reports having experienced orthostatic hypotension soon after rising from a seated position. He also reports daytime sleepiness, impotence, and being depressed all the time. In discussing his various symptoms and potential options for intervention, which of the following statements would be correct?
   a. Although treatments for orthostatic hypotension have been evaluated, none are currently FDA approved.
   b. While selected stimulants are approved for improving wakefulness in patients with somnolence, these agents have not been effective in patients with PD.
   c. His depression is most likely related to his erectile dysfunction.
   d. The American Academy of Neurology currently has no high-level (Level A) recommendations regarding specific agents for treatment of depression in patients with PD.

10. Which of the following medications has FDA approval for the treatment of orthostatic hypotension?
   a. Clonidine
   b. Methylphenidate
   c. Midodrine
   d. Pyridostigmine

11. During a visit with her physician, a 69-year-old female previously diagnosed with PD complains that her symptoms occur more frequently than before. Upon further inquiry, the physician discovers that the patient has not been taking her medication as prescribed. She informs the physician that she takes so many medications all at different times of the day, that she has a hard time remembering if she has taken them all. The physician advises the patient to set up an appointment with her local pharmacist in order to better assist her with all of her medications. The pharmacist should assist this patient in all of the following ways EXCEPT:
   a. Obtain a full medication history for the patient
   b. Assist patient in the proper utilization of a weekly medication organizer
   c. Educate the patient about the importance of adherence to medication regimens and the progression of PD
   d. Determine if the patient has cognitive impairment

12. All of the following have been identified as quality indicators with high potential for improving PD care EXCEPT:
   a. Timing of levodopa therapy
   b. Management of dyskinesias
   c. Treatment of orthostatic hypotension
   d. Treatment of dementia

13. Based on diagnostic criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), which symptom MUST be present for a diagnosis of major depression?
   a. Feelings of worthlessness
   b. An inability to concentrate
   c. Depressed mood
   d. Suicidal thoughts

14. AAN practice recommendations are based on evaluation of published clinical studies. Which of the following is NOT used for classification of the strength of the evidence in a particular study?
   a. Scientific rigor
   b. Potential bias
   c. Study findings
   d. Overall design

15. Based on current AAN recommendations, which of the following pharmacological agents has the strongest (Level B) clinical evidence supporting its use for the treatment of psychosis?
   a. Clozapine
   b. Quetiapine
   c. Olanzapine
   d. Chlorpromazine

To complete this activity, go to www.amcp.org (CE/CME Center) or http://primeinc.org/jmcp/pd to access the posttest and evaluation form.