



Practice Parameter: Diagnosis and prognosis of new onset Parkinson disease (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

O. Suchowersky, MD; S. Reich, MD; J. Perlmutter, MD; T. Zesiewicz, MD; G. Gronseth, MD; and W.J. Weiner, MD

Abstract—Objective: To define key issues in the diagnosis of Parkinson disease (PD), to define features influencing progression, and to make evidence-based recommendations. Two clinical questions were identified: 1) Which clinical features and diagnostic modalities distinguish PD from other parkinsonian syndromes? 2) Which clinical features predict rate of disease progression? **Methods:** Systematic review of the literature was completed. Articles were classified according to a four-tiered level of evidence scheme. Recommendations were based on the evidence. **Results and Conclusions:** 1. Early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction are probably useful in distinguishing other parkinsonian syndromes from Parkinson disease (PD). 2. Levodopa or apomorphine challenge and olfactory testing are probably useful in distinguishing PD from other parkinsonian syndromes. 3. Predictive factors for more rapid motor progression, nursing home placement, and shorter survival time include older age at onset of PD, associated comorbidities, presentation with rigidity and bradykinesia, and decreased dopamine responsiveness. Future research into methods for earlier and more accurate diagnosis of the disease and identification and clarification of predictive factors of rapid disease progression is warranted.

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Statement of purpose. The Quality Standards Subcommittee (QSS) develops scientifically sound, clinically relevant practice parameters to aid in the practice of neurology based on available evidence. This article addresses diagnostic and prognostic issues important for the management of Parkinson disease (PD). These recommendations are meant to

address the needs of specialists and nonspecialists caring for people with PD.

Background and justification. PD is a neurodegenerative disorder caused by a loss of dopaminergic neurons in the substantia nigra, as well as other dopaminergic and nondopaminergic areas of the brain. It has an estimated prevalence of up to 329/100,000.¹ Although PD is common, it can be difficult to diagnose clinically, particularly in early stages, and approximately 5 to 10% of patients with PD are

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From the University of Calgary (O.S.), AB, Canada; University of Maryland Hospital (S.R.), Baltimore; Division of Radiation Sciences (J.P.), St. Louis, MO; Movement Disorder Center (T.Z.), Tampa, FL; University of Kansas (G.G.), Kansas City; and University of Maryland School of Medicine (W.J.W.), Baltimore. Quality Standards Subcommittee Members are listed in appendix E-5 on the *Neurology* Web site at www.neurology.org.

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Address correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116.

misdiagnosed.² Conversely, up to 20% of patients diagnosed with PD reveal alternative diagnoses at autopsy, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), AD-type pathology, and cerebrovascular disease.²⁻⁶ Based on these studies, diagnostic criteria have been developed, with the most commonly used being the UK PD Society Brain Bank criteria² (see appendix E-1 on the *Neurology* Web site at www.neurology.org). However, it has been suggested that an accuracy of 90% is the best that can be achieved with clinical assessment and clinical diagnostic criteria.⁴

Although symptomatic therapy can provide benefit for many years, PD is a progressive disorder that will eventually result in significant morbidity. Knowledge of the features that predict the rate of progression would empower clinicians to better counsel patients regarding prognosis and life expectancy. Improvement in diagnostic accuracy and the ability to predict the rate of progression would also impact on the ability to assess neuroprotective therapies that may delay the progression of the disease (see Practice Parameter on neuroprotective strategies).

Clinical question statement. This practice parameter addresses the following two clinically relevant questions regarding the diagnosis and prognosis of PD: 1. Which clinical features and diagnostic modalities distinguish PD from other parkinsonian syndromes? 2. Which clinical features predict rate of disease progression?

Description of the analytical process. The QSS of the American Academy of Neurology identified five movement disorder specialists and a general neurologist with methodologic expertise. For the literature review, the following databases were searched: MEDLINE, EMBASE, CINHALL, and Cochrane Database of Systematic Reviews for the years 1997 to 2002. Only articles written in English were included. A second MEDLINE search covered 1966 through August 2004, followed by another search using the bibliographies of retrieved articles and knowledge from the expert panel extending to January 2005. At least two panel members reviewed each article. If a panelist was an author of one of the articles, at least two other panelists reviewed that article. If a disagreement was identified, consensus was reached by discussion with the whole group. The risk of bias for each study was determined using the classification of evidence scheme in appendix E-2. The strength of the practice recommendation was linked directly to the level of evidence (appendix E-3). Conflicts of interest were disclosed. Support was provided by the American Academy of Neurology. Writing meetings were funded by the Michael J. Fox Foundation. Panelists were not compensated.

Results, key words, and inclusion/exclusion criteria. For question 1: Search terms: Parkinson disease, neurologic examination, clinical characteristics, neuroimaging, radionuclide imaging, ultrasonography, differential diagnosis, autopsy, SPECT, PET, (levo-

dopa or dopamine or apomorphine) challenge, olfactory. The search resulted in 176 articles. Inclusion criteria: At least 10 subjects with PD and 10 in the comparison group. Categories found: clinical, acute challenge testing, radiologic evaluation, neurophysiologic testing, biochemical testing, CSF examination, olfactory testing. Data presented in sufficient detail to allow calculation of sensitivities and specificities.

Results: Of the original 176 articles identified, 48 were found to be unrelated to the topic or were review articles. A total of 128 articles were reviewed; 31 articles satisfied inclusion criteria.

For question 2: Search terms: Parkinson disease, disease progression, muscle rigidity, tremor, hypokinesia, equilibrium, posture, gait. The search resulted in 59 articles. Inclusion criteria: Longitudinal data to assess putative factors, with an outcome measure that included motor progression measured by a validated rating scale, motor fluctuations, dementia, quality of life, and death. Articles were excluded if published before 1990 because of changes in the case definition of PD.

Results: Of the original 59 articles, 32 were not related to the topic or were review articles. Twenty-seven articles were reviewed, and seven fulfilled inclusion criteria.

Analysis of the evidence.

Question 1: Which clinical features and diagnostic modalities distinguish PD from other parkinsonian syndromes? We identified four articles that addressed the diagnostic accuracy of clinical features that were helpful in differentiating PD from other forms of parkinsonism (table E-1).⁷⁻¹⁰ A Class II case control study of 77 patients with pathologic diagnoses of different parkinsonian conditions including corticobasal degeneration (CBD), dementia with Lewy bodies (DLB), MSA, PD, and PSP revealed that falling within 1 year of diagnosis was a strong predictor of other forms of parkinsonism.⁹ Recurrent falling within the first year was a strong predictor of PSP, whereas time to onset of falling was more delayed in CBD, DLB, and MSA and most prolonged in PD.

A Class II retrospective study of 100 autopsy-confirmed cases of PD and 38 with MSA¹⁰ used a multivariate logistic regression analysis to construct a model of clinical features which help to distinguish PD from MSA. Based on features present until death, and assigning point values to each, the following variables yielded the best prediction: poor response to levodopa (two points); autonomic dysfunction, consisting of symptomatic postural hypotension, urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, and persistent erectile dysfunction (two points); speech or bulbar dysfunction (two points); absence of levodopa induced confusion (four points); and falls (four points). A point score of ≥ 11 yielded a sensitivity of 90.3% and specificity of 92.6% in predicting patients had MSA rather than PD. It is perhaps

more important to make a distinction between PD and MSA earlier in the disease course. In that setting, within the first 5 years, the following variables and point values were most predictive: poor response to levodopa (two points), early motor fluctuations (two points), autonomic dysfunction (two points), and rigidity (two points). A score of ≥ 4 had a sensitivity of 87.1% and specificity of 70.5% of predicting MSA.

A Class II retrospective cohort study of 800 patients diagnosed with PD by movement disorder specialists and enrolled in DATATOP found that 65 individuals (8.1%) were ultimately determined to have an alternative diagnosis.⁸ Clinical features that distinguished the two groups at baseline included higher Hoehn and Yahr stage, higher Unified PD Rating Scale (UPDRS) scores for bradykinesia, postural instability and gait difficulty, and a lower tremor score in the group with other forms of parkinsonism.

In a Class III case control study of 20 people with PD and 32 with either PSP or MSA identified pathologically, only 5% of patients with PD had orthostatic hypotension and all cases of PD were levodopa responsive.⁷ Lack of tremor, symmetry, and rapid progression were more likely to be associated with PSP or MSA, rather than PD.

Drug challenge: Response to levodopa or apomorphine. As the response to chronic levodopa therapy is an important factor in distinguishing PD from a parkinsonian syndrome, it follows that an acute dopaminergic challenge with either levodopa or apomorphine may have similar predictive value. Several meta-analyses of levodopa and apomorphine challenge tests have been published.¹¹⁻¹³ A review of studies of either levodopa or apomorphine challenge tests yielded two articles that met our inclusion criteria.

A Class I double-blind study of 82 patients presenting with parkinsonian symptoms were given an acute levodopa challenge of 250/50 mg of levodopa-carbidopa orally (table E-2).¹⁴ A blinded rater assessed the UPDRS; improvement of 30% or greater was felt to be positive and supportive of a diagnosis of PD. At 24 months, the patients were retested and the diagnosis of PD made clinically in 55 of the patients, based on the UK Parkinson Brain Bank criteria⁶ (appendix E-1). The test had a sensitivity of 70.9% and a specificity of 81.4% for predicting the eventual diagnosis of PD.¹⁴ When the patients were divided into three groups based on UPDRS scores, the sensitivity for those with scores ≤ 10 was similar to the entire group (71.4%), but the specificity increased to 100%. In those patients with more advanced signs at presentation (UPDRS ≥ 21), the sensitivity dropped to 36.4% and the specificity was 87%.

In a Class II cohort survey of a levodopa and apomorphine challenge to 134 consecutive patients with parkinsonism, the response to a single oral dose of levodopa (250 mg) had a sensitivity of 77.1% and a specificity of 71.1% for distinguishing PD from other forms of parkinsonism (table E-2).¹⁵ Comparable val-

ues were observed with varying doses of apomorphine (1.5 to 4.5 mg) given subcutaneously. Results ranged from 65.9% sensitivity and 70.5% specificity with a 1.5 mg dose, to 66.7% sensitivity and 76.5% specificity with a 4.5 mg dose. The specific diagnosis (PD, PSP, MSA, or parkinsonism not otherwise specified) was based almost exclusively on clinical rather than pathologic criteria.

It should be noted that patients in both studies were pretreated with domperidone 2 to 3 days prior to administration of the challenge to prevent peripheral dopaminergic side effects (nausea, emesis, and hypotension).

Drug challenge: Stimulation of growth hormone (GH) with clonidine. The ability of clonidine, a centrally acting α_2 adrenergic receptor agonist, to stimulate the release of GH has been proposed as a method to distinguish PD from MSA. Of the studies reviewed, only one met inclusion criteria. In this Class II study, 32 patients with early parkinsonism were followed for 2 years, until a diagnosis could be made using clinical criteria and IBZM-SPECT. Of the 21 patients with PD and 11 with MSA, the frequency of positive and negative responses did not differ between the two groups.¹⁶

Olfaction. Olfaction is frequently impaired in PD, suggesting smell may be a potentially useful test to distinguish PD from related disorders.¹⁷ Three Class II studies were identified that met inclusion criteria. In a controlled but unblinded study using the University of Pennsylvania Smell Identification Test (UPSIT), patients with PSP (n = 21) had similar olfaction to normal controls (n = 21), but differed from patients with PD (n = 21) ($p < 0.001$).¹⁸ In a prospective study of 50 patients with parkinsonism evaluated with "Sniffin' Sticks," all 37 patients determined to have PD had moderate to severe hyposmia or anosmia, while the 13 patients with other causes of parkinsonism (MSA, PSP) and essential tremor (ET) had normal or only mild to moderate hyposmia.¹⁹ Wenning et al.²⁰ compared olfaction in patients with PD (n = 118), MSA (n = 29), PSP (n = 15), CBD (n = 7), and normal controls (n = 123) using the UPSIT. Patients with PD scored significantly worse than all other patient groups, as well as controls. Patients with PSP and CBD achieved normal values. Patients with MSA scored worse than controls, but significantly better than PD. A cutoff score of 25 (out of possible 40) yielded a sensitivity of 77% and specificity of 85% in distinguishing PD from other parkinsonian syndromes.

Diagnostic neurophysiologic testing. A variety of noninvasive or minimally invasive procedures have been proposed to distinguish PD from parkinsonian syndromes. Twelve Class III articles²¹⁻³¹ were identified (table E-3). In these studies, diagnosis of PD or other parkinsonian syndromes were based on clinical criteria.

In one Class III study, electrooculography was used to determine the frequency of square wave jerks in 118 patients with PD, PSP, and MSA (table

E-3).²⁷ Using a cutoff of >10 square wave jerks/minute as indicative of impaired gaze holding, positive results were observed in 7/8 (87.5%) patients with PSP, 16/25 (64%) with MSA, but only 13/85 (15.3%) with PD. These results suggest that frequent square wave jerks in this population may assist in the diagnosis of PSP or MSA. Vidailhet et al.³⁰ performed eye movement recordings in 14 patients with PD, 14 with MSA, 10 with CBD, and 10 with PSP (table E-3). Latency of horizontal saccades was significantly slower in CBD than PD and other parkinsonian syndromes. Horizontal saccade gain was significantly slower in PSP than PD and other parkinsonian syndromes. The percentage of errors on the anti-saccade task was significantly greater in PSP compared to PD and MSA, but not CBD. Square wave jerks were present as follows: PD 18%, MSA 7%, CBD 20%, and PSP 60%.

Six Class III studies of autonomic testing in parkinsonism met inclusion criteria. One study compared urodynamics in 21 patients with PD and 27 with MSA.²⁸ All of the MSA patients had abnormal results, compared to 13/21 (61.9%) of patients with PD.

Sympathetic skin responses (SSR) and R-R interval variability (RRIV) were compared in 26 PD and MSA patients.²¹ Nine of 13 (69.2%) MSA patients had an abnormal SSR compared to only 1/13 (7.7%) PD patients for a sensitivity of 69% and a specificity of 92%. RRIV after deep breathing was abnormal in 8/9 (89%) patients with MSA compared to only 3/11 (27.3%) patients with PD ($p = 0.02$).

In another study of autonomic function, heart rate variability (HRV) was reduced during forced respiration in patients with MSA, but not PD or PSP as compared to controls ($p < 0.01$).²⁴ However, pathologic HRV occurred in all groups: 27/45 (60%) of MSA, 12/31 (38.7%) of PD, and 4/14 (28.6%) of PSP patients. During tilt table testing, mean arterial pressure decreased significantly in MSA and PD, but not PSP. A pathologic tilt table response was seen in all groups; (28/47) 59.6% of MSA, (17/33) 51.5% of PD, and (2/15) 13.3% of PSP patients.

Cardiac sympathetic innervation assessed using Iodine-123 meta-iodobenzylguanidine (MIBG) revealed that the heart to mediastinum average count ratio for both early and late images was significantly lower in PD compared to normal controls, MSA, and PSP.³¹ These results indicate that patients with PD have an abnormality of cardiac sympathetic function.

Autonomic testing (Quantitative Sodomotor Axon Reflex Test; tilt table testing; heart rate response to deep breathing; Valsalva ratio; beat to beat BP during Valsalva, tilt, deep breathing) in 20/124 patients diagnosed with dementia with Lewy bodies referred for autonomic testing was compared to 20 patients with PD and 20 with MSA.²⁹ Using the Composite Autonomic Severity Score (CASS), patients with DLB had dysautonomia intermediate between MSA and PD.

Using motor clinical criteria, 47 patients referred for autonomic testing with diagnoses of PD, parkin-

sonism, and MSA were classified as having probable PD ($n = 19$), probable MSA ($n = 14$), and uncertain diagnosis ($n = 14$).²⁶ Subsequent results of formal autonomic testing (deep breathing, Valsalva, tilt table, sudomotor axon reflex, sweat test) failed to distinguish between probable MSA and probable PD patients.

One electromyography study demonstrated that urethral sphincter motor units in MSA are of greater duration than in PD and that the percent of abnormal motor units is greater than in PD (table E-3).²² Using a cutoff of >20% motor unit prolongation, urethral sphincter EMG had a sensitivity of 62% and a specificity of 92% for predicting probable MSA. If the cutoff for the percent of abnormal units was set lower than 20%, the gain in sensitivity led to overlap with PD, decreasing specificity.

In a blinded study of anal sphincter EMG, no significant differences were observed between PD and MSA.²³ In another study, anal sphincter EMG could distinguish MSA from normal controls, but not from patients with PD²⁵ (table E-3).

Diagnostic neuroimaging.

MRI. Two Class III articles evaluated the ability of MRI to differentiate PD from MSA (table E-4).^{32,33} In the first study, 27 patients with PD and 24 patients with MSA had an MRI 1.5 T upon presentation.³² Diagnoses were confirmed clinically at least 1.5 years later. Putaminal hypointensity on T2-weighted images was seen in 21/24 patients with MSA (87.5% sensitivity) compared to only 3/27 patients with PD (88% specificity). Putaminal hyperintensity on proton density weighted images was seen in 20/24 MSA patients compared to none of the PD patients (100% specificity). Fast spin echo (FSE) protocol images had putaminal abnormalities in 9/20 MSA patients (45% sensitivity) and none of the PD patients. The second study evaluated diffusion-weighted MRI in 11 PD patients, 10 MSA patients, and 7 healthy controls.³³ Clinical diagnosis was made based on published criteria. Putaminal regional apparent diffusion coefficients were higher in MSA (median $0.791 \times 10^3/\text{mm}^2/\text{second}$) patients than PD patients ($0.698 \times 10^3/\text{mm}^2/\text{second}$) ($p < 0.001$) or healthy volunteers ($0.727 \times 10^3/\text{mm}^2/\text{second}$) ($p < 0.001$).

Sonography. One Class III study compared brain parenchyma sonography in 25 patients with atypical parkinsonian syndromes (16 with MSA and 9 with PSP) to 25 patients with PD (table E-4).³⁴ Diagnosis was made based on clinical criteria. Ninety-six percent (24/25) of the PD patients had hyperechogenicity of the substantia nigra compared to only 2/23 (9%) of the patients with other parkinsonian syndromes ($p < 0.001$).

SPECT. Using clinical evaluation as the gold standard, five class III studies³⁵⁻³⁹ demonstrated that IBZM or B-CIT SPECT had 8% to 100% specificity in identifying clinically diagnosed PD patients, as compared to other parkinsonian syndromes. Sensitivity varied from 30 to 100% (table E-4).

PET. One Class III article reported the results of

quantitative ^{18}F Fluorodeoxyglucose (FDG) PET in 48 patients with atypical parkinsonian syndromes and 56 patients with likely PD (table E-4).⁴⁰ Both groups were diagnosed based on clinical criteria. A linear combination of regional metabolic data of the caudate, lentiform, and thalamic values distinguished atypical parkinsonism from PD ($p < 0.0001$). No studies using fluoro-dopa PET fulfilled inclusion criteria.

Conclusions. Falls at presentation or early in the disease course, poor response to levodopa, symmetry of motor signs, rapid progression (to Hoehn and Yahr stage 3 in 3 years), lack of tremor, and early dysautonomia (urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, persistent erectile failure, and symptomatic orthostatic hypotension) are signs that are probably useful in identifying patients with forms of parkinsonism other than PD in patients with mild disease (three Class II and one Class III studies). The signs are particularly useful when several are present.

Levodopa and apomorphine challenge tests are probably useful in distinguishing PD from other parkinsonian syndromes (one Class I and one Class II studies). The diagnostic yields appear to be comparable between the two tests. However, using clinical diagnosis as the gold standard, at least 30% of patients with PD will not be diagnosed by either test (false negative) and 20 to 30% of patients ultimately diagnosed with other forms of parkinsonism will have a positive test (false positive). The acute levodopa challenge appears to be a reliable predictor of the chronic response to levodopa. Pretreatment with domperidone in drug naïve patients is recommended to prevent peripheral side effects.

GH stimulation by clonidine may not be useful to distinguish PD from MSA (one Class II study).

Olfaction testing, using either the UPSIT or “Sniffin’ Sticks,” is probably useful in differentiating PSP and CBD from PD (three Class II studies). Although PD patients have decreased smell as compared to MSA, these differences are not as pronounced. Thus, a significant loss of smell is suggestive of PD rather than other parkinsonian syndromes.

Formal eye movement recordings may not be useful to distinguish PD from other forms of parkinsonism, due to significant overlap in the abnormalities observed (two Class III studies).

There is insufficient evidence to determine if urodynamic testing or urethral or anal sphincter EMG are useful in distinguishing PD from MSA (one Class III study for each modality).

Testing of autonomic function may not be useful to distinguish PD from other forms of parkinsonism (four Class III studies).

There is insufficient evidence to determine if iodine-123 meta-iodobenzylguanidine cardiac imaging is useful in differentiating PD from MSA or PSP (one Class III study).

MRI is possibly useful in distinguishing PD from

MSA (two Class III studies using different MRI techniques).

There is insufficient evidence to determine if brain parenchyma sonography is useful in distinguishing PD from atypical parkinsonian syndromes (one Class III study).

β -CIT and IBZM SPECT are possibly useful in distinguishing PD from ET and subjects (five Class III studies). There is insufficient evidence to determine if these modalities are useful in distinguishing PD from other forms of parkinsonism.

There is insufficient evidence to determine if FDG PET is useful for diagnosing PD (one Class III study).

Recommendations. Determining the presence of the following clinical features in early stages of disease should be considered to distinguish PD from other parkinsonian syndromes: 1) falls at presentation and early in the disease course, 2) poor response to levodopa, 3) symmetry at onset, 4) rapid progression (to Hoehn and Yahr stage 3 in 3 years), 5) lack of tremor, and 6) dysautonomia (urinary urgency/incontinence and fecal incontinence, urinary retention requiring catheterization, persistent erectile failure, or symptomatic orthostatic hypotension) (Level B) (appendix E-4).

Levodopa and apomorphine challenge should be considered for confirmation when the diagnosis of PD is in doubt (Level B).

Olfaction testing should be considered to differentiate PD from PSP and CBD, but not PD from MSA (Level B).

There is insufficient evidence to determine whether levodopa and apomorphine challenge or olfaction testing have any advantage over the clinical diagnostic criteria of PD (Level U). Additionally, there is insufficient evidence to determine the optimal combination or sequence of these tests (Level U).

The following may not be useful in differentiating PD from other parkinsonian syndromes: GH stimulation with clonidine, electrooculography, and SPECT scanning (Level C).

There is insufficient evidence to support or refute the following as a means of distinguishing PD from other parkinsonian syndromes: urodynamics, autonomic testing, urethral or anal EMG, MRI, brain parenchyma sonography, and FDG PET (Level U).

Question 2: Which clinical features predict rate of disease progression? The ability to predict rate of progression of disease can benefit planning for long term patient care as well as permit the development of neuroprotective strategies. We identified seven studies (six Class II, one Class III) that evaluated whether factors such as age at disease onset, sex, and cognitive and motor symptoms can predict the progression of PD (table E-5).⁴¹⁻⁴⁷

One Class II, single blind, retrospective, matched double cohort study found that PD patients with an older age at onset (≥ 78) had greater motor impairment than patients with middle age onset (43 to 66) after a comparable disease duration of approxi-

mately 5 years (33.3 vs 21.2 on total UPDRS; $p < 0.001$).⁴² The group with older age at onset had more rigidity (5.2 vs 4.3, $p = 0.03$), bradykinesia (13 vs 9.6, $p = 0.001$), and axial impairment (12.8 vs 5.2, $p < 0.001$) than their younger onset counterparts as measured by UPDRS motor scores. Comorbidities including stroke, auditory deficits, and visual impairments were also more common in PD patients with an older age at onset. The increase in motor impairment in the older onset group was still evident after adjusting for comorbidities.

A single blind, Class II, retrospective cohort survey followed 297 consecutive PD patients at various stages of disease for at least 3 years (mean 6.4) and determined the rate of PD progression by the percent change in yearly total UPDRS scores.⁴⁴ Patients were categorized as having either tremor-dominant or postural instability/gait difficulty (PIGD) dominant PD. Patients with an older age at onset (>57 years) had more progression in freezing and in parts I and II of the UPDRS score (mentation and activities of daily living) compared with patients with middle age onset disease. Rate of progression as measured by the total UPDRS was greater in the group with age at onset >57 years as compared to the group with age at onset <57 years (slopes 2.65 vs 0.89). The slopes (annual rate of decline) in UPDRS scores were steeper for the PIGD group compared to the tremor-dominant group when adjusted for age at the initial visit (slopes 2.82 vs 1.59). UPDRS parts I and II subscores progressed more quickly in men than women.

A Class II, single blind, retrospective cohort study demonstrated that PD patients with rigidity/hypokinesia as a first symptom reached Hoehn and Yahr stage III sooner than patients who experienced tremor alone at disease onset ($p = 0.001$).⁴⁷ Patients with tremor at disease onset developed dementia less frequently ($p = 0.05$) and later ($p = 0.001$) than patients with rigidity/hypokinesia at onset ($p = 0.05$).

A Class II, single blind, historical cohort study of 89 PD patients examined predictors of nursing home placement and survival.⁴⁶ Predictors included age at onset of PD, dementia, and responsiveness to levodopa. Early nursing home placement was associated with older age at onset (RR 3.1), presence of dementia (RR 2.3), and unresponsiveness to dopaminergics (RR 2.0). Longer survival was associated with dopaminergic responsiveness (relative risk of death 0.4), absence of dementia (RR 0.4), and younger age at onset (RR 0.3). Multivariate analysis revealed that older age at onset was the sole independent predictor of both nursing home placement and death.

A Class II, single blind, prospective cohort survey examined whether clinical characteristics could predict cognitive decline.⁴³ A total of 104 PD patients at various stages of disease and 60 healthy volunteers of comparable age and education underwent 14 tests of memory, language, frontal lobe, and visuospatial capacity. Eighty percent of participants had more than one test session, and the repeat testing was

completed over a period of 1 to 10 years (mean 3.6 years). A delay in cognitive decline was associated with a younger age at onset of PD. Severity of motor impairment, as measured by the Hoehn and Yahr scale, was related to impairment on almost all cognitive tests. Once cognitive decline began, it occurred at a similar rate in all age groups.

One Class II prospective cohort study evaluated the progression of PD in 34 patients using levodopa half-life kinematic-dynamic modeling in an attempt to assess residual neuronal function.⁴¹ The study proposed that a reduction in levodopa half-life with disease progression could signify abnormal nigrostriatal turnover, possibly due to the loss of dopamine storage capacity. Levodopa half-life values correlated negatively with the severity of symptoms ($r = -0.652$, $p < 0.0001$) and progressively decreased along with the patients' clinical stage (annual reduction of 37 minutes in H&Y 1 vs 6.5 minutes in H&Y III). PD patients without tremor had a larger annual reduction in levodopa half-life compared to patients with tremor, 28 minutes vs 11 minutes.

A Class III, case control study using a subset of the DATATOP cohort found that patients with early onset of disease (first symptom at ≤ 40 years) had a slower progression of disease and better cognitive function than patients with late onset symptoms (≥ 70).⁴⁵ Early onset patients reached the same level of disability in 2.9 years, vs 1.7 years for late onset patients. Patients with late onset disease were also more occupationally disabled than their early onset counterparts. Patients with PIGD had a more rapid rate of disease progression and greater subjective, intellectual, motor, and occupational impairment than tremor dominant patients. Patients in the benign group of PD (duration of PD symptoms at least 4 years before study entry) had an earlier age at onset (55.4 years) compared to the malignant group (68.2 years). The malignant group was defined as PD patients with symptoms for ≤ 1 year who progressed during this period of time to a stage of 2.5 on the Hoehn and Yahr scale. Tremor was the initial disease symptom in 74% of patients in the benign group compared with 55% of patients in the malignant group. Although not significant, a trend was suggested when adjusted for age ($p = 0.06$).

Conclusions. Older age at onset (variably defined as over age 57 to 78 years) (two Class II and one Class III studies) and rigidity/hypokinesia as a presenting symptom (two Class II studies) are factors which are probably useful in predicting a more rapid rate of motor progression of PD.

The presence of associated comorbidities (one Class II study), features of PIGD (one Class II and one Class III studies), and male sex (one Class II study) are factors that are possibly useful for predicting a more rapid rate of motor progression of PD.

Tremor as the initial presentation is a factor that is possibly useful in predicting slower progression and a longer response to levodopa therapy (one Class II and one Class III studies).

Older age at onset and initial manifestations of hypokinesia/rigidity are factors that are probably useful in predicting earlier development of cognitive decline and dementia (two Class II and one Class III studies).

Older age at onset, dementia, and decreased dopamine responsiveness are factors that are possibly useful in predicting an increased risk for nursing home placement and shorter survival after diagnosis (one Class II study).

Recommendations. In patients with newly diagnosed PD, older age at onset and rigidity/hypokinesia as an initial symptom should be used to predict more rapid rate of motor progression (Level B).

The presence of associated comorbidities (stroke, auditory deficits, and visual impairments), PIGD, and male sex may be used to predict faster rate of motor progression (Level C).

Tremor as a presenting symptom may be used to predict a more benign course and longer therapeutic benefit to levodopa (Level C).

Older age at onset and initial hypokinesia/rigidity should be used to predict earlier development of cognitive decline and dementia (Level B).

Older age at onset, dementia, and decreased dopamine responsiveness may be used to predict earlier nursing home placement as well as decreased survival (Level C).

Recommendations for future research. Although PD is a common disorder, accurate diagnosis remains a challenge in early stages of the disease. Clinical examination with long-term follow-up appears to be the best method for confirmation of diagnosis during the patient's lifetime. Further studies are needed to identify other techniques, such as neuroimaging and levodopa challenge tests, that may improve diagnostic accuracy and adequately address disease progression, and to determine superiority to the clinical examination.

In the future, there may be an increasing role for genetic testing to make the diagnosis of PD. However, the development of any new diagnostic test (e.g., neuroimaging, genetic screening) will require long-term follow-up and autopsy confirmation to determine its accuracy. Methods for presymptomatic testing to identify patients who are at risk of developing PD are also critical, particularly for testing of neuroprotective strategies. Similarly, knowledge of disease progression will play a key role, not only in providing useful clinical information, but in assessing the benefit of neuroprotective interventions. Funding agencies need to recognize the necessity of supporting long term studies to answer these questions.

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Practice Parameter: Evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

J.M. Miyasaki, MD; K. Shannon, MD; V. Voon, MD; B. Ravina, MD, MSCE; G. Kleiner-Fisman, MD; K. Anderson, MD; L.M. Shulman, MD; G. Gronseth, MD; and W.J. Weiner, MD

Abstract—Objective: To make evidence-based treatment recommendations for patients with Parkinson disease (PD) with dementia, depression, and psychosis based on these questions: 1) What tools are effective to screen for depression, psychosis, and dementia in PD? 2) What are effective treatments for depression and psychosis in PD? 3) What are effective treatments for PD dementia or dementia with Lewy bodies (DLB)? **Methods:** A nine-member multispecialty committee evaluated available evidence from a structured literature review using MEDLINE, and the Cochrane Database of Health and Psychosocial Instruments from 1966 to 2004. Additional articles were identified by panel members. **Results:** The Beck Depression Inventory-I, Hamilton Depression Rating Scale, and Montgomery Asberg Depression Rating Scale should be considered to screen for depression in PD (Level B). The Mini-Mental State Examination and the Cambridge Cognitive Examination should be considered to screen for dementia in PD (Level B). Amitriptyline may be considered to treat depression in PD without dementia (Level C). For psychosis in PD, clozapine should be considered (Level B), quetiapine may be considered (Level C), but olanzapine should not be considered (Level B). Donepezil or rivastigmine should be considered for dementia in PD (Level B) and rivastigmine should be considered for DLB (Level B). **Conclusions:** Screening tools are available for depression and dementia in patients with PD, but more specific validated tools are needed. There are no widely used, validated tools for psychosis screening in Parkinson disease (PD). Clozapine successfully treats psychosis in PD. Cholinesterase inhibitors are effective treatments for dementia in PD, but improvement is modest and motor side effects may occur.

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Statement of purpose. The Quality Standards Subcommittee (QSS) develops scientifically sound, clinically relevant practice parameters to guide the

practice of neurology. This article discusses treatments for the management of patients with depression, psychosis, and dementia in Parkinson disease (PD). These recommendations address the needs of neurologists and other clinicians caring for people with PD, patients and caregivers, research funding agencies, and researchers in movement disorders.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the April 11 issue to find the title link for this article.

Editorial, see page 966
See also pages 968, 976, and 983

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From the University of Toronto (J.M.M.), Canada; Rush University Medical Center (K.S.), Chicago, IL; NIH (V.V.), Bethesda, MD; University of Rochester (B.R.), NY; University of Pennsylvania (G.K.-F.), Philadelphia; University of Maryland (K.A., L.M.S., W.J.W.), Baltimore; and University of Kansas (G.G.), Kansas City. Quality Standards Subcommittee Members are listed in appendix E-4 on the *Neurology* Web site at www.neurology.org.

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Address correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116.

This guideline provides answers to the following questions:

1. In patients with PD, what are the most accurate tools to screen for depression, psychosis, and dementia?
2. In patients with PD, what are the best treatments for depression and psychosis?
3. What is the most effective treatment of dementia in PD or dementia with Lewy bodies (DLB)?

Background and justification. PD is the second most common neurodegenerative disease.¹ Characterized by the cardinal signs of bradykinesia, rigidity, tremor at rest, and abnormalities of balance, posture, and gait, the etiology of PD remains unknown in most patients.² Nonmotor symptoms in PD, an increasingly recognized intrinsic feature of PD, may affect three domains: autonomic, neuropsychiatric, and sensory, including pain.² The prevalence of nonmotor symptoms is high. For instance, a survey of 99 patients with PD using validated questionnaires for nonmotor symptoms including anxiety, depression, sensory disturbance, fatigue, or sleep problems revealed that 88% of patients had at least one nonmotor symptom and 11% had five nonmotor symptoms.³ With improved treatment of motor symptoms, it is also now evident that the nonmotor features of PD such as dementia, depression, and psychosis may result in significant disability.^{2,4} Yet, despite the high prevalence and associated disability of nonmotor symptoms in PD, physician recognition of these important clinical features is low.⁵ Furthermore, many PD symptoms overlap with features of depression and dementia including symptoms of withdrawal, lack of motivation, flattened affect, decreased physical activity, or bradyphrenia, thus confounding the identification of these behavioral and cognitive disorders. It should be noted that validated criteria for depression, psychosis, and dementia in PD do not exist. Hence, the identification of clinically relevant screening and diagnostic tools for depression, psychosis, and cognitive decline validated specifically in the PD population is necessary.

In this parameter, the focus in the section on validation studies will be on the diagnostic accuracy of specific measures for behavioral disorders and dementia in PD. The mechanisms underlying nonmotor symptoms are poorly understood, and may be related to abnormalities of dopaminergic, serotonergic, adrenergic, cholinergic, and other peptidergic pathways.⁶⁻⁹ This complex pathophysiology reflects the resistance of nonmotor symptoms to dopamine replacement strategies. Therefore, specific treatments for autonomic, behavioral, and cognitive complications need to be employed.

Converging evidence suggests that the behavioral symptoms in PD may be pathophysiologically different from the behavioral symptoms observed in the general population. For instance, several lines of evidence suggest that PD depression may be related to

the underlying pathology of PD itself rather than general psychiatric vulnerabilities and psychosocial associations. This suggests that reliance on the psychiatric treatment literature in the general population may not be sufficient and that specific treatment studies are required in PD.

The etiology of dementia in PD is unclear. Whether PD dementia represents a discrete categorical entity from DLB or exists on a spectrum is not known. For the purposes of this parameter, we will consider the treatments of both entities, presuming a similar underlying pathophysiology.¹⁰

Throughout this parameter, the term depression will be used to refer to major depression unless otherwise specified; there are no validation or treatment studies investigating forms of depression such as dysthymia or minor depression.

This parameter reviews the available evidence assessing diagnostic screening tools and the most effective treatments for dementia, depression, and psychosis in PD.

Description of the analytical process. The QSS of the American Academy of Neurology (AAN) identified a panel of six experienced movement disorder specialists, two psychiatrists, and a general neurologist with methodologic expertise. For the literature review, the following databases were searched: MEDLINE, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews and Health and Psychosocial Instruments from 1966 to 2004. This was followed by a secondary search using the bibliography of retrieved articles and knowledge of the expert panel. Two authors reviewed each abstract for topic relevance. Two authors reviewed each full article to rate the level of evidence (Class I–IV) (appendices E-1 and E-2 on the *Neurology* Web site at www.neurology.org). If there was disagreement, the entire panel reviewed the article and the level of evidence was decided by consensus. The panel reviewed all articles cited in the evidence below. If a panelist was an author of one of the articles, at least two other panelists reviewed that article. Conflicts of interest were disclosed according to AAN guidelines. The AAN provided support and the Michael J. Fox Foundation funded the writing meetings. Panelists were not compensated.

Description of literature review. *Search terms.* Psychosis scale OR depression scale OR psychosis diagnosis OR depression diagnosis OR psychosis treatment OR depression treatment OR cognitive treatment OR dementia diagnosis OR psychoses OR hallucinations OR psychotic OR delusion OR depression OR depressive disorder OR adjustment disorder OR experimental drug therapy OR dementia treatment AND Parkinson disease OR diffuse Lewy body disease OR dementia with Lewy bodies.

Inclusion and exclusion criteria. For depression scales and treatment, Diagnostic and Statistical Manual (DSM) criteria for depression were the gold

standard. DSM-IV criteria for major depression were used unless otherwise stated in the study reviewed. Various criteria for the diagnosis of PD were allowed. Class IV studies were not considered if Class III studies were available. Similarly, Class III studies were not considered if Class II studies were available. All Class I and II studies were included.

Depression screening tools. The search identified 37 articles. Thirty-four were rejected; 31 did not examine diagnostic accuracy and in 3 the patients did not have PD. Three articles were accepted (Class I, Class II).

Depression treatment (pharmacologic). The search identified 31 articles. Twenty were excluded because the populations studied were not PD patients with depression. Two were excluded because they were not randomized controlled trials. Nine articles were reviewed. An additional 27 articles were identified, 19 of which had been identified through the Cochrane bibliography. Of the 36 articles reviewed, 30 were rejected as they were Class IV articles. Six articles were accepted that were Class I, II, or III.

Depression treatment (nonpharmacologic). The search identified six studies: one Class II and five Class IV because of a high risk of bias. Class IV studies were not considered. One Class II study was accepted.

Psychosis screening tools. The search identified 31 articles. Eighteen did not examine diagnostic accuracy. Twelve articles did not include patients with PD. One Class IV article was accepted.

Psychosis treatment. The search identified 63 articles. Twenty-five were rejected because the patients did not have PD. Fifteen were rejected because the articles did not address psychosis treatment. Twenty-three articles received a full review. Eleven were rejected because they were Class III or IV. Three did not include patients with PD. Three were excluded because they were review articles, and one was excluded because it was an epidemiologic study. Four Class I and II articles were accepted.

Cognitive screening tools in PD. Twenty-four studies were identified. Ten were rejected because they did not examine diagnostic accuracy. One did not include patients with dementia. Thirteen articles received a full review; five did not examine diagnostic accuracy, five were Class IV, and one did not include PD patients with dementia. Two articles were accepted (Class I, III).

Cognitive treatment in PD or dementia with Lewy bodies. The search identified 331 articles. A total of 146 were excluded because they did not include patients with PD. A total of 115 were not randomized controlled trials. Forty-eight did not examine treatment for dementia. Twenty-two articles received a full review. An additional article was identified by the panelists and reviewed. Ten were Class III or IV. Five were excluded because they were review articles, and two articles were excluded because they included PD patients without dementia or criteria

for dementia were not adequately defined. Three did not include cognitive treatment in PD. Three Class II articles were accepted.

Analysis of evidence. *Question 1a: In patients with PD, which are the most accurate tools to screen for depression?* **Evidence.** One Class I and two Class II articles compared the accuracy of depression screening tools to an independent reference standard based upon DSM criteria.¹¹⁻¹³ These studies reported results of the Beck Depression Inventory (BDI),¹¹ which is a self completion questionnaire (21 items, range 0–63), the Hamilton Depression Rating Scale (HDRS-17) (17 items, range 0–52),^{12,13} and the Montgomery Asberg Depression Rating Scale (MADRS) (10 items, range 0–60).¹² Both the HDRS-17 and MADRS require a trained administrator and take 15 to 25 minutes each to administer. No studies examining the diagnostic accuracy of the Geriatric Depression Scale, Hospital Anxiety and Depression Scale, or Zung Self-Rating Depression Scale were identified.

All three studies were of prospective, cohort design. One employed a double masked methodology (Class I).¹¹ The other two studies were not double masked (Class II).^{12,13} The authors reported various cut points and corresponding sensitivities and specificities for each screening tool. For the purposes of this article, we chose the cutpoint providing the greatest diagnostic accuracy for major depression (best specificity and sensitivity). For the BDI-I, a score of greater than 13 indicated depression, with a sensitivity of 67% (95% CI 39 to 86) and a specificity of 88% (95% CI 75 to 95). For the HDRS-17 (pooled results from two studies), a score of greater than 13 indicated depression, with a sensitivity of 83% (95% CI 67 to 92) and specificity of 95% (95% CI 89 to 98). For the MADRS, the cut point was greater than 14 for patients indicating depression, with a sensitivity of 88% (95% CI 64 to 97) and specificity of 89% (95% CI 77 to 95). Although these data suggest that the HDRS-17 and MADRS are superior to the BDI, the studies were underpowered to determine superiority. In addition, the BDI is more easily administered, requiring at most 10 minutes.

Conclusions. For patients with PD, the BDI (one Class I) and HDRS (two Class II) are probably useful to screen for depression associated with PD. Based on one Class II study, MADRS is possibly useful to screen for depression associated with PD. Based on the available evidence, we cannot recommend one screening test over another.

There is insufficient evidence to support or refute the usefulness of other rating scales for depression in PD (Level U) (appendix E-3).

Recommendation. The BDI- I and HDRS should be considered for depression screening in PD (Level B). MADRS may be considered for screening for depression associated with PD (Level C).

Question 1b: In patients with PD, which are the most accurate tools to screen for psychosis? Evidence. There is no gold standard for the diagnosis of psychosis in PD. There was one Class IV study¹⁴ in which an expert-derived Parkinson Psychosis Rating Scale (PPRS) was administered to 29 patients with PD and psychosis, and compared with two scales that have been validated in the general population: the Brief Psychosis Rating Scale (BPRS) and the Nurses Observation Scale for Inpatient Evaluation (NOSIE-Psychotic). The PPRS demonstrated good interrater reliability and internal consistency. There was good diagnostic accuracy between the PPRS and BPRS ($p < 0.01$) and the PPRS and the NOSIE-Psychotic ($p < 0.01$). PD patients without psychosis were not included in the study, and therefore, the specificity of this screening tool in PD cannot be determined.

Conclusion. Based on one Class IV study, there is insufficient evidence to support or refute PPRS as a screening tool for psychosis in PD (Level U).

Recommendation. No recommendation is made.

Question 1c: In patients with PD, which are the most accurate tools to screen for dementia? Evidence. There was one Class I¹⁵ and one Class III¹⁶ study. In the Class I study, the Cambridge Cognitive Examination (CAMCog) and Mini-Mental State Examination (MMSE) were administered to 126 patients older than 60 years treated for PD in the community and institutions. Forty-four percent of this population had dementia by DSM-IV criteria. Both the CAMCog and MMSE had similar sensitivities (95% and 98%). However, the CAMCog was more specific (94%) than the MMSE (77%). The CAMCog includes all items of the MMSE and covers additional domains (orientation, concentration, expression, memory, abstract thinking, drawing, understanding, and writing), requiring approximately 20 minutes to administer by a trained rater.

In addition to scales, procedures are proposed to screen for PD dementia. In a case control EEG study (Class III) of 10 patients with PD dementia and 10 patients with PD without dementia, no significant differences in the amplitude of delta and theta activities were observed between the groups.¹⁶

Conclusion. The MMSE and CAMCog are probably useful for screening patients with PD and DSM-defined dementia (one Class I). The MMSE is as sensitive as the CAMCog and quicker to administer, but less specific.

Based on one Class III study, there is insufficient evidence to support the use of EEG as a screening tool for dementia in PD (Level U).

Recommendation. The MMSE and the CAMCog should be considered as screening tools for dementia in patients with PD (Level B).

Question 2: In patients with PD, what is the best pharmacologic treatment for depression? Evidence. Six studies were identified: one Class I,¹⁷ two Class II,^{18,19} and three Class III.²⁰⁻²² All were randomized controlled trials. Interventions included amitriptyline, nortriptyline, citalopram, fluoxetine, sertraline,

pergolide, pramipexole, and nefazodone. Three of the studies used placebo comparators.¹⁷⁻¹⁹ One study compared nefazodone to fluoxetine,²² one amitriptyline to fluoxetine,²⁰ and one pramipexole to pergolide.²¹ In four studies, depression was defined by DSM criteria. One study²¹ employed ICD-10 criteria for depression. In another study, the author's ad hoc scale was used.¹⁸ In all but one study, the severity of the depression was mild to moderate; depression was severe in the study of amitriptyline.²⁰ Outcome measures varied and included BDI, HAM-D, MADRS, Zung Self Rating Depression Scale, and a unique rating scale.²⁰

Five of the six studies used masked outcome assessment. The nefazodone vs fluoxetine study utilized independent but not masked outcome assessment (Class III).²² Three studies lacked allocation concealment of treatment groups (the attempt to prevent selection bias by concealing the assignment sequence until allocation to avoid maneuvering a patient to a particular assignment, either intentionally or unintentionally),²⁰⁻²² one had nonstandard inclusion criteria,¹⁹ and one had less than 80% completers without an intent to treat analysis.²⁰ Despite randomization, there were confounding differences in the severity of depression between groups in the pramipexole vs pergolide study (Class III).²¹ Follow-up ranged from 6 weeks to 12 months. The single Class I study, citalopram vs placebo, had the shortest duration of follow-up and used the HAMD for assessment.¹⁷

No significant benefit of treatment was observed in the studies of citalopram and sertraline.^{17,19} However, neither study was sufficiently powered to exclude a clinically important benefit. Fluoxetine and nefazodone revealed equal efficacy for depression, but this study lacked a placebo control, and consequently, we could not conclude whether either drug was effective.²²

Patients treated with pramipexole improved significantly more than patients treated with pergolide on measures assessing depression.²¹ However, there were important confounding differences in the severity of depression at baseline, which compromised these results.

In the study comparing the treatment of severely depressed patients with amitriptyline or fluoxetine, patients randomized to amitriptyline significantly improved (change in HAM-D of 14), while those treated with fluoxetine did not.²⁰ Dropout rates were greater in the amitriptyline group due to adverse events.

In the nortriptyline study, the authors report a significant improvement in depression compared to placebo.¹⁸ However, it is impossible from the publication to determine if this difference was significant.

Conclusions. Based on one Class II study, amitriptyline is possibly effective in treating depression associated with PD. There is insufficient evidence to support or refute the efficacy of other specific antidepressants in the treatment of PD depression. Anti-

cholinergic side effects, especially problematic with tricyclics, are an important consideration in the PD population due to concerns regarding potential worsening of cognition, as is the concern about orthostatic hypotension increasing the risk of falls.

Although the age at onset of PD is generally in adulthood, it should be noted that the Food and Drug Administration issued a drug labeling change in 2004 for a black box warning of the increased risk of suicidal ideation and suicide in adolescents and children with all antidepressants.

Recommendations. Amitriptyline may be considered in the treatment of depression associated with PD (Level C). Although the highest level of evidence is for amitriptyline, it is not necessarily the first choice for treatment of depression associated with PD. There is insufficient evidence to make recommendations regarding other treatments for depression in PD. Absence of literature demonstrating clear efficacy of non-tricyclic antidepressants is not the same as absence of efficacy.

Question 2b: In patients with PD and depression, what are the best nonpharmacologic treatments?

Evidence. No published trials of psychotherapy for depression associated with PD were available. The single Class II study randomized patients to transcranial magnetic stimulation (TMS) or fluoxetine.²³ Outcomes were assessed in a blinded fashion using HAM-D. Completion rate was 100%. A primary outcome measure was not specified. Both groups improved, but there was no difference in the magnitude of improvement in the treatment groups. The study was insufficiently powered to exclude a moderate difference in efficacy between the two therapies. Additionally, because of the absence of a placebo comparator, we cannot determine whether either intervention was effective. Due to these study design weaknesses, this study was downgraded to Class III evidence.

Only Class IV studies were available regarding ECT, which were not further evaluated.

Conclusion. There is insufficient evidence to support or refute the efficacy of TMS (single Class III) or ECT (Class IV) in the treatment of depression associated with PD (Level U).

Recommendation. No recommendations were made.

Question 2c. In patients with PD and psychosis, what is the best treatment? **Evidence.** There were four randomized, double blind, controlled trials (one Class I²⁴ and three Class II²⁵⁻²⁷). One study compared clozapine to quetiapine (Class II).²⁵ Psychosis was defined using various criteria. Three studies were placebo controlled.

One Class I study demonstrated superiority of clozapine compared to placebo using the Clinical Global Impression Scale (CGI) ($p < 0.001$).²⁴ This study also demonstrated improvement on the Brief Psychiatric Rating Scale (BPRS) ($p = 0.002$) and the Scale for the Assessment of Positive Symptoms (SAPS) ($p =$

0.01). Parkinsonism did not worsen and tremor improved. One patient discontinued due to leukopenia.

Two Class II studies compared olanzapine to placebo.^{26,27} In both studies, psychosis failed to improve and motor symptoms worsened.

One 12-week Class II study was randomized, open label, and used a blinded rater. Eleven patients received quetiapine and 12 received clozapine.²⁵ Endpoints were change in BPRS, CGI, Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore, and the Abnormal Involuntary Movement Scale (AIMS). BPRS improved by 9.1 ($p < 0.001$) for quetiapine and 10.7 for clozapine ($p < 0.001$). For CGI, quetiapine improved by 1.5 ($p < 0.001$) and clozapine by 1.9 ($p < 0.001$). UPDRS motor worsened by 1.6 ($p = \text{NS}$) for quetiapine and improved by 2.1 for clozapine ($p < 0.005$). AIMS improved by 1.6 for quetiapine ($p < 0.05$) and 1.8 for clozapine ($p < 0.05$).

Conclusions. For patients with PD and psychosis, one Class I study and one Class II study demonstrated that clozapine is probably an effective treatment. Clozapine improved psychosis and resulted in improved motor function in some cases.

One Class II study demonstrated that quetiapine possibly improves psychosis in PD.

Two Class II studies demonstrated that olanzapine probably does not improve psychosis and worsens motor function.

There is a concern that all atypical neuroleptics have a small increased risk of mortality particularly in elderly patients with dementia who are treated for behavioral disorders. The mechanism for increased mortality is not clear. This must be balanced by the high morbidity and mortality associated with psychosis.²

Recommendations. For patients with PD and psychosis, clozapine should be considered (Level B). Clozapine use is associated with agranulocytosis that may be fatal. The absolute neutrophil count must be monitored. Monitoring requirements may vary according to country.

For patients with PD and psychosis, quetiapine may be considered (Level C).

For patients with PD and psychosis, olanzapine should not be routinely considered (Level B).

Question 3: what is the most effective treatment for dementia in PD or DLB? **Evidence.** One Class I study was identified.²⁸ The Class I study was a randomized, double-masked, placebo-controlled, crossover study in 22 subjects with PD and dementia. Each treatment period was 10 weeks separated by a 6-week washout period. Donepezil was administered at 5 to 10 mg/day. The primary outcome measure was the AD Assessment Scale–Cognitive Subscale (ADAScog). Donepezil was not significantly better than placebo based on ADAScog. Secondary endpoints (MMSE and CGI) were significantly better with donepezil. UPDRS scores did not deteriorate with donepezil.

Four Class II studies were identified.²⁹⁻³² All stud-

ies were randomized, controlled trials with blinded outcome assessments lasting 10 to 24 weeks. Three studies examined cholinesterase inhibitors (donepezil,³⁰ rivastigmine^{29,31}). One study examined piracetam, a compound of unknown mechanism of action.³² These studies employed DSM criteria for dementia. Primary outcome measures were change in the MMSE, ADAScog, AD Cooperative Study–Clinicians Global Impression of Change (ADCS-CGIC), the Clinicians Interview Based Impression of Change Plus Caregiver Input (CIBIC+), and a computerized cognitive assessment system speed score. Only one study focused on patients with DLB.³¹

When compared with placebo, piracetam did not show a significant benefit on any measure.³² However, the study was insufficiently powered to exclude a moderate benefit of piracetam.

When rivastigmine (n = 362) was compared with placebo (n = 179), the ADAScog score improved 2.1 ± 8.2 in the treatment group, but decreased by 0.7 ± 7.5 in the placebo group ($p < 0.001$).²⁹ The number needed to treat for any improvement as defined by the ADCS-CGIC was nine. The number needed to treat to obtain clinically meaningful (moderate or marked) improvement on the ADCS-CGIC was 19. Tremor increased in 10.2% vs 3.9% ($p = 0.01$) in the treatment group. Sixty-two (17.1%) patients on rivastigmine dropped out due to adverse events such as nausea, vomiting, and tremor. For every eight patients receiving rivastigmine, one patient dropped out due to adverse events. The number needed to harm was eight. This means that eight patients must experience worsening of parkinsonism as assessed by the UPDRS for each patient experiencing clinically meaningful improvement, as measured by the ADCS-CGIC.

Rivastigmine was evaluated in a randomized, double blind, placebo controlled trial of 120 patients with DLB,³¹ as defined by the DLB consensus guidelines.³³ The intention to treat analysis of the primary outcome (computerized cognitive assessment system speed score) at week 20 revealed a benefit in the treatment group ($p = 0.048$). At week 20, there was no significant improvement in the MMSE or the Clinical Global Change–Plus. In the donepezil cross-over design study (n = 14), the MMSE improved by 2.1 (SD 2.7) compared to only 0.3 (SD 3.2) for placebo ($p = 0.013$).²⁸ No change occurred in the UPDRS motor subscale scores. Two patients dropped out due to adverse events. On the CIBIC+, the number needed to treat to obtain any improvement was four. Number needed to harm was seven.

Conclusion. For patients with PD dementia or DLB, rivastigmine is probably effective in improving cognitive function. However, the magnitude of the benefit is modest and tremor may be exacerbated (two Class II studies).

For patients with PD dementia, donepezil is probably effective in improving cognitive function. However, the magnitude of the benefits is modest (one Class I and one Class II study).

There is insufficient evidence to support or refute the efficacy of piracetam (Level U). **Recommendations.** Donepezil should be considered for the treatment of dementia in PD (Level B).

Rivastigmine should be considered for the treatment of dementia in PD or DLB (Level B).

Recommendations for future research. Despite advances in treatment that improve motor symptoms for many patients, PD remains a progressive disease with complex, long-term, nonmotor symptoms that are often unrecognized. In order to identify the impact of depression, psychosis, and dementia, validated diagnostic questionnaires and rating scales are needed.

Depression rating scales. Current studies using the Beck Depression Inventory, Hamilton Scale for Depression, and the Montgomery Asberg Depression Rating Scale are underpowered to establish their diagnostic accuracy in this patient population. Other scales, such as the Geriatric Depression Scale and Zung Self-Rating Depression Scale, are not formally evaluated in PD. Future research is required to determine the best (sensitive, specific, but also practical for clinicians to rapidly administer) depression screening tool for patients with PD. DSM-IV criteria have not been validated for depression in PD.

Psychosis screening tools. Psychosis in PD is characterized by visual hallucinations and delusions (often paranoid).³⁴ Screening tools for psychosis should be sensitive to hallucinations as well as other psychosis features such as delusions. Only one study evaluated the PPRS,¹⁵ which may be appropriate for patients with PD.¹⁵ However, in order to determine its specificity, the PPRS needs to be evaluated in nonpsychotic and psychotic PD patients. DSM-IV criteria for psychosis have not been validated in PD.

Cognition screening tools. Screening tools must be easy and quick to administer. Cognitive decline in PD is characterized by impaired executive function, visuospatial abnormalities, impaired memory, and language deficits.³⁵ An appropriate scale that reliably incorporates executive function (e.g., frontal assessment battery and other practical tests of executive function) should be incorporated into a screening test for PD dementia. When evaluating new screening tools, the DSM-IV criteria for dementia may not be the most appropriate gold standard for patients with PD. DSM-IV criteria for dementia have not been validated in PD. In PD patients, it may be difficult to assess impairments in domains other than memory.

Depression treatment. There is a need for randomized, double-blinded, placebo-controlled studies of adequate size and duration of follow-up to assess antidepressants, psychotherapies, and other somatic therapies such as ECT and TMS.

Psychosis treatment. Due to rare but possible agranulocytosis and concerns about increased mortality associated with clozapine, other treatments should be identified for patients with PD and psycho-

sis. Class I studies are required to evaluate the efficacy of quetiapine. Evidence for efficacy of novel antipsychotics without dopaminergic blocking effects is needed for effective treatment of psychosis in PD.

Dementia treatment. The cognitive benefits of donepezil and rivastigmine were small in PD dementia or DLB, and tremor increased with rivastigmine. Therefore, future research should include more Class I studies to assess the role of cholinesterase inhibitors and other medications in the treatment of dementia associated with PD. Additional treatments need to be developed that alleviate cognitive symptoms without worsening parkinsonism.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

R. Pahwa, MD; S.A. Factor, DO; K.E. Lyons, PhD; W.G. Ondo, MD; G. Gronseth, MD;
H. Bronte-Stewart, MD; M. Hallett, MD; J. Miyasaki, MD; J. Stevens, MD; and W.J. Weiner, MD

Abstract—Objective: To make evidence-based treatment recommendations for the medical and surgical treatment of patients with Parkinson disease (PD) with levodopa-induced motor fluctuations and dyskinesia. To that end, five questions were addressed. 1. Which medications reduce off time? 2. What is the relative efficacy of medications in reducing off time? 3. Which medications reduce dyskinesia? 4. Does deep brain stimulation (DBS) of the subthalamic nucleus (STN), globus pallidus interna (GPI), or ventral intermediate (VIM) nucleus of the thalamus reduce off time, dyskinesia, and antiparkinsonian medication usage and improve motor function? 5. Which factors predict improvement after DBS? **Methods:** A 10-member committee including movement disorder specialists and general neurologists evaluated the available evidence based on a structured literature review including MEDLINE, EMBASE, and Ovid databases from 1965 through June 2004. **Results, Conclusions, and Recommendations:** 1. Entacapone and rasagiline should be offered to reduce off time (Level A). Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B). Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C). 2. The available evidence does not establish superiority of one medicine over another in reducing off time (Level B). Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C). 3. Amantadine may be considered to reduce dyskinesia (Level C). 4. Deep brain stimulation of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C). There is insufficient evidence to support or refute the efficacy of DBS of the GPI or VIM nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function. 5. Preoperative response to levodopa predicts better outcome after DBS of the STN (Level B).

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Statement of purpose. The Quality Standards Subcommittee (QSS) develops scientifically sound, clinically relevant practice parameters to aid in the

practice of neurology. This article addresses medical and surgical treatments for the management of patients with Parkinson disease (PD) with levodopa-

Editorial, see page 966
See also pages 968, 976, and 996

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From the University of Kansas Medical Center (R.P., K.E.L., G.G.), Kansas City; Emory University School of Medicine (S.A.F.), Atlanta, GA; Baylor College of Medicine (W.G.O.), Houston, TX; Stanford University Hospital (H.B.-S.), San Francisco, CA; National Institutes of Health (M.H.), Bethesda, MD; Toronto Western Hospital (J.M.), Canada; Fort Wayne Neurological Center (J.S.), Fort Wayne, IN; and University of Maryland School of Medicine (W.J.W.), Baltimore.

Quality Standards Subcommittee Members are listed in appendix E-4 on the *Neurology* Web site at www.neurology.org.

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Address correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116.

induced motor fluctuations and dyskinesia. These recommendations address the needs of specialists and nonspecialists caring for patients with PD.

Background. PD is a progressive neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity. Although initially effective, dopaminergic therapies are eventually complicated by motor fluctuations, including off time (periods of return of PD symptoms when medication effect wears off) and dyskinesia (drug-induced involuntary movements including chorea and dystonia) in most patients. These motor complications can impair quality of life and cause significant disability.¹ Risk factors for motor complications include younger age at onset of PD, disease severity, higher levodopa dosage, and longer disease duration.²⁻⁴ These problems are often addressed with levodopa adjustments and the addition of adjunctive medications. The first part of this article addresses the effectiveness of adjunctive medications in this situation.

Motor fluctuations and dyskinesia can be resistant to medical therapy. This, along with advances in the understanding of basal ganglia circuitry, surgical techniques, neuroimaging, and intraoperative microelectrode recording, has led to a resurgence in surgical approaches for medically refractory disabilities. Initially, ablative procedures like thalamotomy and pallidotomy were used to treat PD symptoms. However, due to concerns about morbidity,⁵ especially with bilateral procedures, deep brain stimulation (DBS) has become the most commonly performed surgery for PD in North America.

DBS is a stereotactic surgical procedure that uses an implanted electrode connected to an implantable pulse generator (IPG) that delivers electrical current to a targeted nucleus in the brain.⁶ The three primary targets for DBS for PD are the ventral intermediate (VIM) nucleus of the thalamus, globus pallidus interna (GPi), and the subthalamic nucleus (STN). The IPG is programmed externally from several days to 4 to 6 weeks after implantation. Adjustable stimulation parameters include amplitude, frequency, and pulse width. The device is generally left on but patients can turn the device off when desired.

Although the criteria are evolving, currently patients with PD who are considered candidates for DBS include levodopa-responsive, non-demented, and neuropsychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor.

This practice parameter addresses five questions:

1. Which medications reduce off time?
2. What is the relative efficacy of medications in reducing off time?
3. Which medications reduce dyskinesia?

4. Does DBS of the STN, GPi, or VIM reduce off time, dyskinesia, and antiparkinsonian medication usage and improve motor function?
5. Which factors predict improvement after DBS?

The conclusions and recommendations addressing these questions are based only on the evidence available in the literature and are limited by the quality of the studies reviewed. An inherent problem with this process is that treatments may receive a recommendation lower than what may be expected based on clinical experience. This can be due to many factors including the possibility that older treatments may not have been studied as rigorously as newer therapies; published manuscripts may not have included sufficient details or used a study design that would eliminate potential bias; or a particular issue related to a specific treatment may not have been addressed in the literature.

Description of the analytical process. The QSS of the AAN identified an expert panel of experienced movement disorder specialists and general neurologists with methodologic expertise. For the literature review, a research librarian searched MEDLINE, EMBASE, and Ovid databases. This was supplemented by a secondary search using the bibliography of retrieved articles and knowledge from the expert panel. Panel members reviewed abstracts and titles for relevance. Then, at least two panel members reviewed articles meeting inclusion criteria. If a panelist was an author of one of the articles, at least two other panelists reviewed that article. Disagreements were arbitrated by an additional panel member. The risk of bias was determined using the classification of evidence for each study (appendix E-1 the *Neurology* Web site at www.neurology.org). The strength of the practice recommendations was linked directly to the level of evidence (appendix E-2). Conflicts of interest were disclosed. Support was provided by the AAN. Writing meetings were funded by the Michael J. Fox Foundation. Panelists were not compensated.

Medical treatment. For questions 1, 2, and 3, the authors used the following search terms: Parkinson disease, advanced Parkinson disease, dyskinesia, motor fluctuations, double masked trials, randomized trials, placebo controlled trials, clinical trials, medical treatment, human studies, adenosine A2A antagonists, amantadine, apomorphine, bromocriptine, cabergoline, controlled release carbidopa/levodopa, entacapone, pergolide, pramipexole, rasagiline, ropinirole, selegiline, tolcapone, clozapine, rotigotine (search restricted to English language and medications available in the United States or those having an approvable letter from the Food and Drug Administration). The initial search included articles from 1965 to June 2004 and a supplemental search was performed in 2005 to include the latest clinical trials.

The authors considered randomized masked trials that included at least 20 patients with motor fluctuations or dyskinesia followed for greater than 3

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months. If no articles met the 3-month criterion for a specific drug, the authors included articles with shorter durations of therapy and this led to a drop in class level.

The initial search identified 730 articles, of which 670 were excluded during the abstract review. An additional 34 articles were excluded during the article review, leaving 26 articles for consideration. Of the 704 articles eliminated, 172 were not related to the drugs examined, but instead looked at alternative agents, alternative modes of administration such as infusions, and a variety of surgical procedures. A total of 151 of the articles were reviews; 99 were studies of early PD or non-fluctuators; 75 were open label studies; 72 were about mechanisms of action, pharmacokinetics, or animal studies; 69 evaluated other uses of the drugs; 30 had fewer than 20 subjects; 17 were primarily about adverse effects; 11 had a study duration less than 3 months; and 8 were not peer reviewed. The supplemental search identified three additional articles. From each article the authors abstracted the following methodologic characteristics: trial design, method of allocation concealment, mechanism of masking, number of enrollees, comparative baseline characteristics of subjects, number of completers, trial duration, measure of "off" time or "on" time and dyskinesia, magnitude of response, adverse events, and levodopa dose change.

Surgical treatment. For questions 4 and 5, the authors used the following search terms: deep brain stimulation AND Parkinson disease; DBS AND Parkinson disease; subthalamic stimulation AND Parkinson disease; pallidal stimulation AND Parkinson disease; and thalamic stimulation AND Parkinson disease for all articles from 1965 through June 2004. All non-English language articles, review articles, and animal studies were excluded. A total of 478 articles resulted. The authors included studies of DBS for PD reporting postsurgical outcome in terms of motor improvement or reduction of motor complications that had a sample size of at least 20 subjects and a follow-up duration of at least 6 months post-DBS. Twenty articles met all inclusion criteria; 13 for subthalamic stimulation; 1 for subthalamic and pallidal stimulation; 2 for pallidal stimulation; and 4 for thalamic stimulation. A total of 458 articles were excluded for the following reasons: 200 had less than 20 patients in the study; 152 were not motor function outcome studies of DBS in PD; 41 were review articles; 26 were comments; 18 had less than 6 months follow-up; 9 were not from peer-reviewed sources; 4 were animal studies; 6 were redundant reports of included data; 1 did not differentiate results of PD vs essential tremor; and 1 did not use standard outcome measures for PD. The authors abstracted the following characteristics from the 20 articles meeting inclusion criteria: study design, patient selection criteria, follow-up duration, number, age, sex and disease duration of subjects, baseline Unified PD Rating Scale (UPDRS) activities of daily living (ADL) and motor scores in the medication on and medica-

tion off conditions at baseline and during follow-up evaluations in the stimulation on condition, specific measures of dyskinesia and motor fluctuations, adverse events, and medication reduction.

Brief summaries of the medical studies examining off time and the surgical studies can be found in tables 1 and 2, and complete evidence tables describing the methodologic details of the medical (table E-1) and surgical (table E-2) studies are available on the *Neurology* Web site.

Results. *Question 1: Which medications reduce off time?* Dopamine agonists. Pergolide. One Class I, 24-week, multicenter, placebo controlled, parallel group, double masked study compared 189 in the active group (mean dose 2.9 mg/day) and 187 in the control group.⁷ More than 80% of the patients completed the study (84% on pergolide and 82% on placebo). The active group had a 32% decrease (1.8 hours) in off time compared to a 4% decrease (0.2 hours) in the control group ($p < 0.001$). There were also differences in level of improvement in UPDRS ADL and motor scores in the on state in favor of pergolide ($p < 0.001$). However, 62% of the active group had a new onset or worsening of dyskinesia, compared to only 25% of the placebo group. Levodopa dose decreased 24.7% in the pergolide group compared to 4.9% in the placebo group ($p = 0.001$).

Pramipexole. One Class I study⁸ and one Class II study⁹ compared pramipexole to placebo. The Class I multicenter, double masked, parallel group study randomized 360 patients (181 active, 179 control) for 32 weeks.⁸ Eighty-three percent of the active group and 78% of the control group completed the study. Off time decreased by 31% in the active group (mean dose 3.4 mg/day) compared to 7% in the placebo group ($p = 0.0006$). UPDRS ADL in the on and off states, and motor examination in the on state all improved with pramipexole vs placebo ($p < 0.01$). Levodopa dose was reduced in the active group (27%) compared to the placebo group (5%) ($p = 0.0001$). There was a significant difference with regard to dyskinesia in the active group (61%) compared to the placebo group (40%).

In the Class II, multicenter, double masked, randomized, parallel group study, 79 patients received pramipexole (mean dose 3.4 mg/day) and 83 received placebo for 40 weeks.⁹ There were 80% completers in the active group and 60% in the control group. The active group had a 15% (2.5 hour) decrease in off time vs a 3% reduction in the control group ($p = 0.007$). In the on state, the active group also experienced improvements in the UPDRS ADL and motor scores ($p < 0.0006$). Levodopa reduction was not reported. Dyskinesia was reported in 40% of pramipexole patients and 27% of controls.

Ropinirole. Two Class II studies compared the effect of ropinirole vs placebo on off time.^{10,11} The first was a multicenter, randomized, parallel group, double masked, placebo controlled, 12-week study with 23 patients randomized to each group.¹⁰ The

Table 1 Summary of medication studies examining off time changes

Ref	Drug	Class	N*	Age,† y	Disease duration,† y	Study duration, wk	Decrease off time active	Decrease off time placebo
Placebo-controlled studies								
7	Pergolide	I	189/187	62.5	11.4	24	32% (1.8 h)‡	4% (0.2 h)
8	Pramipexole	I	181/179	63.3	9	32	31%‡	7%
9	Pramipexole	II	79/83	62.9	6§	40	15% (2.5 h)‡	3%
10	Ropinirole	II	23/23	62	8	12	23%‡	4%
11	Ropinirole	II	95/54	NR	8.6	26	11.7%‡	5%
12	Apomorphine	II	20/9	66	9.2	4	34% (2.0 h)‡§	0
9	Bromocriptine	II	84/83	61.5	7.2§	40	8%	3%
13	Cabergoline	III	19/18	60.8	13.6	24	40% (2.0 h)‡	18% (0.7 h)
14	Cabergoline	III	17/10	67.5¶	12.3	24	59% (3.3 h)‡	NS
15	Selegiline	III	50/46	61.4	9.5	6	NR	NR
16	Orally disintegrating selegiline	II	94/46	66	6.3	12	32% (2.2 h)‡	9% (0.6 h)
17	Rasagiline (0.5 mg)	I	164/159	62.6	9.3	26	23% (1.4 h)‡	15% (0.9 h)
17	Rasagiline (1.0 mg)	I	149/159	62.9	8.8	26	29% (1.8 h)‡	15% (0.9 h)
18	Rasagiline	I	231/229	63.9	8.7	18	21% (1.2 h)‡	7% (0.4 h)
19	Tolcapone (100 mg tid)	II	69/66	63	11	12	32% (2.3 h)	20% (1.4 h)
19	Tolcapone (200 mg tid)	II	67/66	64	11	12	48% (3.2 h)‡	20% (1.4 h)
20	Tolcapone (100 mg tid)	II	60/58	62	9	12	31.5%‡	11%
20	Tolcapone (200 mg tid)	II	59/58	63	10	12	26.2%	11%
21	Entacapone	I	103/102	63.9	10.8	24	NR	NR
18	Entacapone	I	227/229	63	9.2	18	21% (1.2 h)‡	7% (0.4 h)
22	Entacapone	II	197/104	60.7	8.3	24	25.8% (1.6 h)‡	13.4% (0.9 h)
23	Entacapone	II	85/86	62.6	10.2	24	23.6% (1.3 h)‡	1.9% (0.1 h)
24	Entacapone	II	99/63	63.5	NR	12	0.9 h	0.4 h
Crossover studies (carbidopa/levodopa CR vs carbidopa/levodopa IR)								
26	Carbidopa/levodopa CR/IR	III	20	61.1	8.3	16	NS	
27	Carbidopa/levodopa CR/IR	III	21	67.2	10.2	24	NS	
28	Carbidopa/levodopa CR/IR	III	28	NR	NR	16	NS	
29	Carbidopa/levodopa CR/IR	III	24	66.2	9.3	16	NS	
Comparator studies (not placebo-controlled)								
30	Cabergoline [c]/bromocriptine [b]	II	22/22	71	10	36	50% [c]	31.3% [b]
31	Ropinirole [r]/bromocriptine [b]	II	88/51	64	9	24	17.7% [r]	4.8% [b]
32	Tolcapone [t]/entacapone [e]	II	75/75	NR	NR	3	NR	NR
33	Tolcapone [t]/pergolide [p]	III	101/102	65	8	12	19% [t]	20% [p]

* Active/placebo.

† Data for active group, placebo not significantly different from active group.

‡ $p < 0.05$.

§ Median values.

¶ Significantly older than placebo.

NR = not reported; NS = not significant; CR = controlled release; IR = immediate release.

ropinirole group had 87% completers and the control group had 65%. There was a greater reduction in off time per day (from 47% to 24%) in the active group (mean dose 6.8 mg/day) compared to controls (44% to 40%) ($p = 0.08$). Clinical Global Impression (CGI) favored ropinirole ($p = 0.004$). Levodopa dose change and dyskinesia were not reported.

The second multicenter, randomized, double masked, placebo controlled study randomized 95 subjects to ropinirole (maximum allowed dose 24 mg/day) and 54 to placebo for 26 weeks.¹¹ In the ropinirole group, 78% were completers, and in the placebo group, 65% were completers. Ropinirole decreased off time by 11.7% compared to 5.1% with placebo ($p = 0.04$). The ropinirole group had a 31%

decrease in levodopa dose compared to 6% in the placebo group ($p = 0.001$). Dyskinesia occurred in 33.7% taking ropinirole and 13% taking placebo ($p = 0.006$).

Apomorphine. A single Class II study evaluated subcutaneously injected apomorphine (mean dose 5.4 mg/injection) in a double masked, parallel group, randomized study of 29 patients for 4 weeks (20 active, 9 placebo).¹² There were over 80% completers (85% active, 88% placebo). The active group experienced a 34% decrease (2 hours) in off time compared to 0% in the placebo group ($p = 0.02$). Dyskinesia occurred in 35% of the active group compared to 11% of the controls. UPDRS motor score in the off state improved more in the apomorphine group ($p = 0.001$).

Table 2 Summary of deep brain stimulation studies

Ref	Ther. Class	Prog. Class	Follow-up	Site	N	Age, y	PD duration	Baseline UPDRS motor*	Follow-up UPDRS motor†	Dyskinesia/ off time improvement	Meds reduction
36	III	IV	6 mo	B-STN	96	59	NA	56%	52%	Rush dyskinesia: 58%; Diary: dyskinesia reduced 23 to 7%; off time decreased 49 to 19%	37%
37	III	IV	1 y	B-STN	26	59	15	54%	64% (1 y)	UPDRS (item 32) dyskinesia 86%; UPDRS (item 39) off time 83%	20%
38	III	IV	1 y	B-STN	33	58	12	40% (1 y)	32% (1 y)	Diary: dyskinesia 18% to 4% (1 y), 19% to 11% (2 y)	54% (1 y)
39	III	IV	2 y		19			37% (2 y)	28% (2 y)	Off time 44% to 20% (1 y), 43% to 17% (2 y)	57% (2 y)
39	III	IV	6 mo	B-STN	20	61	12	59%	49%	Dyskinesia UPDRS (item 32) 50%; dyskinesia UPDRS (item 33) 100%	33%
42	IV	II	6 mo	B-STN	41	56	16	71%	65%	Duration fluctuations 87%; duration dyskinesia 69%; UPDRS IV 78%	68%
45	IV	II	2 y	B-STN	25	57	13	55%	48% (1 y)	Dyskinesia Rating Scale 48% (1 y), 50% (2.5 y)	38% (1 y)
									41% (2.5 y)	UPDRS (#33) 83% (1 y), 82% (2.5 y); UDPRS (#32) 58% (1 y), 80% (2.5 y)	36% (2.5 y)
40	IV	IV	1 y	B-STN	22	57	15	51% (1 y)	63% (1 y)	Dyskinesia significantly reduced	32% (1, 2 y)
			2 y		9			51% (2 y)	48% (2 y)	Data not shown in manuscript	
41	IV	IV	6 mo	B-STN	38	56	13	43%	44% (6 mo)	Off time reduced 35% (10–60%)	53%
			1 y						48% (1 y)	Dyskinesia 72% (6 mo, 1 y)	
43	IV	IV	6 mo	B-STN	23	58	NA	NA	53% (6 mo)	Dyskinesia 77% (6 mo) 60% (1 y)	56% (6 mo)
			1 y		14				61% (1 y)	Off time 71%	53% (1 y)
44	IV	IV	2 y	B-STN	48	60	15	57.70%	51% (6 mo)	UPDRS (#32) 77% (6 mo), 83% (1 y), 73% (2 y)	49% (6 mo)
									57% (1 y)	UPDRS (#33) 92% (6 mo, 1 y, 2 y)	42% (1 y)
									57% (2 y)		68% (2 y)
46	IV	IV	5 y	B-STN	42	55	15	74.30%	66% (1 y)	UPDRS (#32) Dyskinesia 71% (1, 3, 5 y)	59% (1 y)
									59% (3 y)	UPDRS (#33) 63% (1 y), 68% (3 y), 50% (5 y)	63% (3 y)
									54% (5 y)		63% (5 y)
47	IV	IV	1 y	B-STN	25	57	14	59.40%	50%	UPDRS (#32) dyskinesia 80% (1 y); UPDRS (#33) dyskinesia 86% (1 y); UPDRS (#39) off duration 95% (1 y)	66% (1 y)
48	IV	IV	30 mo	B-STN	24	58	14	65%	38%	UPDRS IV (item 39) 16%; dyskinesia 69% (1 y) 71% (30 mo); fluctuations 52% (1 y) 50% (30 mo)	39% (1 y) 30% (30 mo)
49	IV	IV	4 y	B-STN	20	61	NA	56%	43%	NA	47% (4 y)
36	III	IV	6 mo	B-GPi	36	56	NA	53%	33%	Rush dyskinesia: 67%; Diary: dyskinesia reduced 35 to 12%; off time reduced 37 to 24%	3% more
51	IV	IV	33 mo	U-GPi	26	56	13	60%	-8%	Dyskinesia: 28% (UPDRS IVA); off time: 3.5% worsening (UPDRS IVB)	53% more
50	IV	IV	6 mo	GPi	30	58	8	32%	49% (6 mo)	UPDRS (#32–35) dyskinesia	NA
			1 y	U-10				(total UPDRS)	46% (1 y)	93% (6 mo)	
				B-20					(total UPDRS)		
52	IV	IV	6 mo	TS	80	NA	NA	NA	NA	NA	49% (3 mo) 15% (6 mo)
53	IV	IV	1 y	U-TS	24	65	NA	NA	NA	NA	NA
54	IV	IV	21 mo	U-TS	18	66	10	NA	29%	NA	NA
55	IV	IV	1 y	TS	73	62	10	NA	31%	NA	None
				U-56							
				B-16							

* % Improvement baseline meds OFF vs meds ON.

† % Improvement follow-up meds OFF/Stim ON vs baseline meds OFF.

Ther = therapeutic; Prog = prognostic; PD = Parkinson disease; UPDRS = Unified PD Rating Scale; STN = subthalamic nucleus; B-STN = bilateral STN; Gpi = globus pallidus interna; B-GPi = bilateral GPi; U-GPi = unilateral GPi; NA = not available; TS = thalamus; U-TS = unilateral TS.

Bromocriptine. In a single Class II multicenter, randomized, double masked study, bromocriptine was compared to pramipexole and placebo for 40 weeks.⁹ Eighty-four patients received bromocriptine (mean dose 22.6 mg/day) and 83 received placebo. Eighty percent of the bromocriptine patients completed compared to 60% of the placebo group. There was an 8% decrease in off time for bromocriptine compared to 3% in placebo, which was not different ($p = 0.2$). Maximum improvement occurred at 8 weeks. Bromocriptine therapy led to an improvement in the primary end points, UPDRS ADL and motor scores, compared to placebo ($p < 0.02$). Change in levodopa dose was not reported. Dyskinesia occurred in 45% of bromocriptine patients and 27% of controls.

Cabergoline. Two Class III studies evaluated whether cabergoline can reduce off time without a significant increase in dyskinesia.^{13,14} In a Class III, single center, 24-week placebo controlled study of 37 patients (19 active, 18 placebo), the active group (cabergoline mean dose 5.4 mg/day) had a 40% decrease in off time (2 hours/day) compared to 18% (0.7 hours/day) for the placebo group ($p < 0.05$).¹³ However, there were confounding differences at baseline; the active group had an off time duration of 5 hours compared to only 4 hours for the placebo group. Fewer than 80% of the patients completed the study (58% active, 39% placebo), and there was no information provided on allocation concealment. Levodopa dose decreased 8% in the cabergoline group and 5% in the placebo group. Neither group had worsening of dyskinesia. CGI was improved in the cabergoline group ($p < 0.05$).

A Class III, single center, 24-week, double masked, parallel group study compared 17 patients (mean age 67.5 years) on cabergoline (mean dose 4.9 mg/day) to 10 patients (mean age 57.9 years) on placebo.¹⁴ No information on allocation concealment was provided, and there were less than 80% completers (76% active, 70% placebo). Neither group had a change in dyskinesia. The active group had a 30% (2.7 hours) increase in on time and a 59% decrease (3.3 hours) in off time. No information was provided for the placebo group. UPDRS motor scores improved ($p = 0.006$). Levodopa dose decreased by 28% with cabergoline and 10% with placebo ($p = 0.004$).

Dopamine agonists adverse effects. The adverse effects associated with dopamine agonists are similar for all the agents. In the clinical trials reviewed, the following side effects were reported in the accompanying ranges in the actively treated groups: nausea 18 to 36%; symptomatic orthostatic hypotension 5 to 48% (highest with cabergoline and pramipexole); dizziness 11 to 37%; somnolence 10 to 35% (highest with apomorphine); and hallucinations 10 to 19%. Two studies reported pedal edema, cabergoline 8% and apomorphine 10%. Two studies reported confusion, pramipexole 14% and cabergoline 16%. Rare cases of cardiac valvular fibrosis have been reported with pergolide although this was not reported in the

clinical trials. Screening for valvular disease is recommended with pergolide use. Similarly, problems with impulse control have also been recently reported but not in the clinical trials.

MAO B inhibitors. Selegiline. One Class III multicenter, double masked, parallel group study randomized 50 patients to selegiline (mean dose 10 mg/day) and 46 to placebo for 6 weeks.¹⁵ There were greater than 80% completers (100% active, 93% controls). Fifty-eight percent of the selegiline group had improved "mean hourly overall symptom control" scores compared to 26% of the placebo group ($p = 0.002$). CGI change also favored selegiline ($p < 0.001$). Dyskinesia initially worsened in 60% of the selegiline patients and 30% of the placebo patients.

Orally disintegrating selegiline. One Class II, 12-week, multicenter, randomized, parallel group, double masked study randomized 94 patients to orally disintegrating selegiline (mean dose 2.5 mg/day) and 46 to placebo.¹⁶ Information on allocation concealment was not provided. Off time was reduced by 32% (2.2 hours) in the active group vs 9% (0.6 hours) in the placebo group ($p = 0.001$). Hours on were increased 20% (1.8 hours) for the active group and 5% (0.4 hours) for the control group ($p = 0.006$). Dyskinesia did not significantly worsen with active treatment and was not reported in the placebo group. There was no report on change in levodopa dose.

Rasagiline. Two Class I, double masked, placebo controlled, parallel group studies compared rasagiline with placebo. In the Parkinson's Rasagiline: Efficacy & Safety in the Treatment of OFF (PRESTO) study, rasagiline 1.0 mg/day or rasagiline 0.5 mg/day was compared with placebo for 26 weeks.¹⁷ There were 87.5% completers. The total daily off time decreased by 29% (1.8 hours) for rasagiline 1 mg/day and 23% (1.4 hours) for rasagiline 0.5 mg/day, which were both more than the decrease of 15% (0.9 hours) with placebo ($p < 0.0001$ for 1.0 mg/day; $p = 0.02$ for 0.5 mg/day). Compared to placebo, global impression, UPDRS ADL off, and UPDRS motor scores also improved significantly. Significant increases in on time corresponded to decreases in off time. However, for the 1.0 mg group, 32% of the increase in on time included troublesome dyskinesia ($p = 0.048$).

In the Lasting effect in Adjunct therapy with Rasagiline Given Once daily (LARGO) study,¹⁸ rasagiline 1.0 mg/day was compared to entacapone 200 mg with each dose of levodopa (up to eight per day) and placebo in a double dummy paradigm (each drug compared to placebo; not directly compared to each other). A total of 687 patients were randomized: 231 to rasagiline, 227 to entacapone, and 229 to placebo. There were 87% completers (90% rasagiline, 87% entacapone, and 85% placebo). The total daily off time decreased by 21% (1.18 hours) for rasagiline 1.0 mg/day and 21% (1.2 hours) for entacapone, both of which were more than the decrease of 7% (0.4 hours) with placebo ($p \leq 0.0001$ for both rasagiline and entacapone). Compared to placebo, global impression, UPDRS ADL off, and UPDRS motor score on

also improved significantly. Significant increases in on time corresponded to decreases in off time. There was no change in on time with troublesome dyskinesia and the percent of subjects with dyskinesia as an adverse effect was similar for all three groups.

MAO-B inhibitor adverse effects. Adverse effects with selegiline in the reviewed study¹⁶ included nausea 20%, symptomatic orthostatic hypotension 12%, hallucinations and confusion 6% each. There was no mention of insomnia. In the article on orally disintegrating selegiline, 6% reported dizziness and 4% reported hallucinations. The incidence of other adverse events was not disclosed. In PRESTO,¹⁷ rasagiline was associated with weight loss in 2.4 to 9.4%, vomiting in 3.7 to 6.7%, anorexia in 1.8 to 5.4%, balance difficulties in 3.4 to 5.5%, and three cases of melanoma (0.6%). In LARGO¹⁸ the primary side effects were postural hypotension (2%), nausea (3%), peripheral edema (2%), depression (3%), dizziness (3%), hallucinations (2%), dyskinesia (5%), and sleep disorders (3%) but none were significantly more common than in controls.

COMT inhibitors. Tolcapone. Two Class II studies evaluated tolcapone vs placebo.^{19,20} The first was a double masked, randomized, placebo controlled, multicenter 12-week trial with three treatment groups; tolcapone 100 mg TID, tolcapone 200 mg TID, and placebo.¹⁹ There were 136 active and 66 placebo patients. No concealment allocation information was provided. Tolcapone 100 mg TID decreased off time 32% (2.3 hours), tolcapone 200 mg TID decreased off time 48% (3.2 hours), and placebo decreased off time 20% (1.4 hours) ($p < 0.01$ for the tolcapone 200 mg TID group). At both tolcapone doses, a significant improvement in investigator global score occurred, as well as a significant decrease in levodopa dose (≤ 200 mg) and number of levodopa doses per day (decreased by approximately one). Dyskinesia increased in the first 30 days but was treated effectively with reductions in levodopa dose.

The second Class II study was multicenter, double masked, and placebo controlled with follow-up ranging from 3 to 12 months.²⁰ Patients were randomized to one of three groups: tolcapone 100 mg TID ($n = 60$), tolcapone 200 mg TID ($n = 59$), and placebo ($n = 58$). There were 81% completers in the active groups and 93% in the control group. Off time decreased by 26.2% on tolcapone 200 mg TID, 31.5% on tolcapone 100 mg TID, and 10.5% on placebo ($p < 0.01$). There was a corresponding increase in on time by 20.6% in the 200 mg TID group and 21.3% in the 100 mg TID group. Levodopa doses dropped 16% for the tolcapone 100 mg TID group and 18% in the tolcapone 200 TID group compared to 4% for the placebo group. Dyskinesia developed or worsened in 37% at 100 mg TID of tolcapone, 52.5% at 200 mg TID of tolcapone, and in 21% of the placebo group.

Entacapone. Two Class I^{18,21} and three Class II studies²²⁻²⁴ evaluated entacapone vs placebo. In one Class I double masked, parallel group, multicenter

trial, 103 patients received entacapone (200 mg with each dose of levodopa) and 102 received placebo for 24 weeks.²¹ On time increased by 5% in the entacapone group. Patients who had the smallest percent of on time at baseline ($< 55\%$) had the largest increase in on time with entacapone. Dyskinesia developed in 53% of the entacapone patients vs 32% of the placebo patients ($p = 0.002$). Masking may have been compromised due to urine discoloration by entacapone. The other Class I study was the LARGO study.¹⁸ In this study, rasagiline 1 mg/day was compared to placebo and entacapone 200 mg with each dose of levodopa (up to eight per day) was also compared to placebo in a double dummy paradigm. The active groups were compared to placebo, not each other. A total of 687 patients were randomized: 231 to rasagiline, 227 to entacapone, and 229 to placebo. There were 87% completers (90% rasagiline, 87% entacapone, and 85% placebo). The total daily off time decreased by 21% (1.2 hours) for entacapone, which was more than the decrease of 7% (0.4 hours) with placebo ($p < 0.0001$). Compared to placebo, global impression, UPDRS ADL off, and UPDRS motor score on also improved significantly. Significant increases in on time corresponded to decreases in off time. There was no change in on time with troublesome dyskinesia and the percent of subjects with dyskinesia as an adverse effect was similar for all three groups.

In a Class II multicenter, parallel group, randomized, placebo controlled double masked study, 197 patients received entacapone (200 mg/dose) and 104 received placebo in addition to their daily dose of levodopa.²² Only 78% of patients randomized completed the trial. Off time decreased by 25.8% (1.6 hours) with entacapone compared to 13.4% (0.9 hours) with placebo. Thirty-four percent of patients reported dyskinesia as an adverse event on entacapone compared to 26% on placebo.

A Class II, multicenter, parallel group, randomized, double masked study evaluated 171 patients on entacapone 200 mg/dose ($n = 85$) or placebo ($n = 86$) for 6 months.²³ Allocation concealment was not described. There were 90% completers in both groups. Patients taking entacapone had a decrease in off time that was 22% more than the decrease with placebo ($p < 0.001$) and a concomitant increase in on time of 13% ($p < 0.001$). Worsening of dyskinesia was more common in the entacapone group (8.2%) than the placebo group (1.2%) ($p < 0.05$).

A Class II, multicenter, double masked, placebo controlled study of 162 patients randomized 3:2 to entacapone 200 mg/dose or placebo failed to show a benefit in favor of entacapone.²⁴ Allocation concealment was not described. Seventy-seven percent completed the 3-month study. Patients on entacapone had more dyskinesia (31%) than those on placebo (13%).

COMT inhibitor adverse effects. The adverse effects associated with tolcapone and entacapone were similar but more frequent with tolcapone in the stud-

ies reported; however, it is important to stress that these studies cannot be directly compared. Diarrhea occurred in 20 to 34% of tolcapone treated patients in the reviewed trials and 8 to 20% with entacapone. Other side effects included nausea in 28 to 50% with tolcapone and 10 to 20% with entacapone; somnolence in 16 to 32% with tolcapone and 4% with entacapone; and hallucinations in 24% with tolcapone and 4 to 9% with entacapone. Symptomatic orthostasis was reported with tolcapone in 24% of patients in one study. Finally, an elevation of liver enzymes ALT and AST occurred in 1% of patients taking tolcapone 100 mg TID and 3% of patients taking tolcapone 200 mg TID. Rare cases of fatal hepatotoxicity have been reported with tolcapone leading to a recommendation of more stringent liver function monitoring.²⁵ Tolcapone should only be used in PD patients taking levodopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapy. If the patient does not have a substantial clinical benefit within 3 weeks of initiation of tolcapone, they should be withdrawn from the drug. In appropriate candidates for tolcapone, liver function monitoring should be done at baseline and then periodically (i.e., every 2–4 weeks) for the first 6 months and thereafter as clinically necessary.

Sustained release carbidopa/levodopa. Four Class III single center, double masked, crossover studies examining 97 total patients failed to demonstrate any difference in off time with sustained release carbidopa/levodopa compared to the immediate release preparation.^{26–29} Baseline characteristics and allocation concealment were not described for any of the studies. The daily dose of levodopa was higher with the sustained release preparation, but there was a significant decrease in the number of doses per day with sustained release. Dyskinesia was only described in one study,²⁷ which was similar in the sustained release and immediate release groups. The adverse effects of both drugs were the same.

Conclusions. Entacapone (two Class I studies) and rasagiline (two Class I studies) are established as effective in reducing off time.

Pergolide (one Class I study), pramipexole (one Class I and one Class II study), ropinirole (two Class II studies), and tolcapone (two Class II studies) are probably effective in reducing off time.

Apomorphine subcutaneously injected (one Class II study), cabergoline (two Class III studies), and selegiline (one Class II study, one Class III study) are possibly effective in reducing off time.

Based on four Class III studies, sustained release carbidopa/levodopa does not decrease off time compared to immediate release. The doses of sustained release carbidopa/levodopa were higher, but given less frequently. Based on one Class II study, bromocriptine does not decrease off time compared to placebo.

Recommendations. For patients with PD with

motor fluctuations the available evidence suggests the following (see appendix E-3):

- Entacapone and rasagiline should be offered to reduce off time (Level A).
- Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B). Tolcapone (hepatotoxicity) and pergolide (valvular fibrosis) should be used with caution and require monitoring.
- Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level c).
- Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C).

Question 2: What is the relative efficacy of medications in reducing off time? There was one Class I study,¹⁸ four Class II studies,^{9,30–32} and one Class III study³³ that compared the efficacy of antiparkinsonian medications in reducing off time. In one Class I study, there was no significant difference between rasagiline 1 mg/day and entacapone 200 mg with each levodopa dose in reducing off time (reduction of 0.8 hours relative to placebo for both; not powered to compare rasagiline to entacapone directly). There was no difference in dyskinesia or other adverse events.

In one Class II study, there was no significant difference between pramipexole mean dose 3.4 mg/day and bromocriptine mean dose 22.6 mg/day in the reduction in off time (15% vs 8%).⁹ The study was not powered to show a difference between the two active groups. There were no differences in adverse events in the two groups.

In another Class II study, there was no statistical difference between reduction in off time with cabergoline mean dose 3.2 mg/day compared to bromocriptine 22.1 mg/day (50% vs 31.3%).³⁰

In a Class II study comparing ropinirole mean dose 10 mg/day with bromocriptine mean dose 18 mg/day, ropinirole reduced off time by 17.7% compared to 4.8% with bromocriptine.³¹ Adverse events were similar, except ropinirole caused more nausea and bromocriptine caused more hallucinations.

A three-week Class II study compared tolcapone 100 mg TID and entacapone 200 mg/dose.³² Increase in on time showed a trend but was not statistically different between the two groups (tolcapone 1.3 hours vs entacapone 0.6 hours). Adverse events were similar.

In a Class III study, there was no significant difference in change in off time between tolcapone 100 to 200 mg TID and pergolide mean dose 2.2 mg/day (17.9% vs 18.2%).³³ Adverse events leading to withdrawal from the study were more common with pergolide (15% vs 5%).

Conclusions. Six studies (one Class I, four Class II, one Class III study) compared the efficacy of antiparkinsonian medications in reducing off time: rasagiline was similar to entacapone; bromocriptine was similar to pramipexole; tolcapone was similar to per-

golide; cabergoline was similar to bromocriptine; tolcapone was similar to entacapone; and ropinirole was possibly superior to bromocriptine. Many of these studies were not powered to demonstrate superiority of one drug over another. Other than comparisons of ropinirole and bromocriptine, there is insufficient evidence to conclude which one agent is superior to another in reducing off time.

Recommendations. Ropinirole may be chosen over bromocriptine for reducing off time (Level C). Otherwise, there is insufficient evidence to recommend one agent over another (Level U).

Question 3: Which medications reduce dyskinesia? Two studies, one Class II and one Class III, evaluated the efficacy of medications in reducing dyskinesia.^{34,35}

A Class II single center, double masked, placebo controlled, randomized, crossover trial enrolled 24 subjects for 3 weeks of treatment with amantadine (100 mg BID) and placebo.³⁴ Ninety-two percent of the subjects completed the trial. Total dyskinesia score (Goetz scale) decreased 24% after amantadine ($p = 0.004$). In addition, there was a 17% decrease in maximal dyskinesia score ($p = 0.02$) and a significant decrease in percentage of time with dyskinesia (UPDRS part IVa) ($p = 0.02$) on amantadine compared to placebo. UPDRS motor off state score improved ($p = 0.04$) and the on state score was unchanged. No adverse effects were reported in this study.

A Class III double masked, placebo controlled, parallel group study evaluated the effect of clozapine on the treatment of levodopa-induced dyskinesia in patients with severe PD for 10 weeks.³⁵ There were 76% completers. Clozapine treatment (mean dose 39.4 mg/day) resulted in a decrease in hours on with dyskinesia per day of 1.7, while hours on with dyskinesia increased in the placebo group by 0.7 hours (overall 2.4 hours difference between groups). Onset of change was noted at 4 weeks. Duration of on and off time and UPDRS motor scores were not different between groups. The most common adverse effects reported in this study were somnolence (100%), hypersalivation (38%), and asthenia (62%).

Studies of other drugs, including bupidine, dextromethorphan, idazoxan, istradefylline, memantine, nabilone, quetiapine, remacemide, riluzole, sarizotan, and talampanel did not meet the inclusion criteria.

Conclusions. Amantadine is possibly effective in reducing dyskinesia (one Class II study).

There is insufficient evidence to support or refute the effectiveness of clozapine in reducing dyskinesia (single Class III study).

Recommendations. Amantadine may be considered for patients with PD with motor fluctuations in reducing dyskinesia (Level C).

There is insufficient evidence to support or refute the efficacy of clozapine in reducing dyskinesia (Level U). Clozapine's potential toxicity including agranulocytosis, seizures, myocarditis, and ortho-

static hypotension with or without syncope, and required white blood cell count monitoring must be considered.

Surgical therapy. *Question 4: For patients with PD, does DBS of the STN, GPi, or VIM reduce off time, dyskinesia, and antiparkinsonian medication usage, and improve motor function?* Patients undergoing DBS surgery are evaluated with the UPDRS ADL and motor sections before surgery in the medication off and medication on states to determine maximum improvement with medication. The improvement with DBS, except for the possibility of increased tremor control, is generally equivalent to the best improvement seen with medications; however, this benefit persists for a longer amount of time resulting in a decrease in off time. Follow-up evaluations are generally performed in the medication off and on states with the stimulators turned on. The baseline medication off scores are then compared to the follow-up medication off/stimulation on scores to determine the effect of stimulation. In order to reach an evidence class of III, an objective measure of symptoms must be used such as timed tapping or walking tests, patient symptom diaries, or patient self report questionnaires. The effect of stimulation on dopaminergic medication use is examined by converting daily dosages of these medications, with a formula which varies slightly across sites, to a single value referred to as the levodopa equivalence dose.

Subthalamic nucleus stimulation. Fourteen articles met inclusion criteria for STN stimulation. There were 4 Class III studies³⁶⁻³⁹ and 10 Class IV studies.⁴⁰⁻⁴⁹ All studies examined bilateral DBS of the STN. Only the Class III studies are discussed in detail. Details of the Class IV studies can be found in the evidence tables (see table 2 and table E-2).

A Class III, 6-month, prospective, multicenter trial examined 102 PD patients with 96 patients receiving bilateral implants (mean age 59.0 ± 9.6 years) and 91 patients completing a 6-month follow-up.³⁶ At 6 months, off medication with stimulation on, there was a mean improvement of 52.4% in UPDRS motor scores ($p < 0.001$) and a 43.7% improvement in UPDRS ADL scores compared to the baseline off medication state ($p < 0.001$). Patient diaries indicated an increase in on time without dyskinesia from 27% to 74% of the waking day ($p < 0.001$), a decrease in on time with dyskinesia from 23% to 7%, and a decrease in off time from 49% to 19% ($p < 0.001$). The Rush Dyskinesia scale improved 58% ($p < 0.001$) and there was a decrease in daily levodopa equivalence dose of 37.3% ($p < 0.001$). Adverse events included infections in 3.9% of patients, intracranial hemorrhage leading to hemiparesis in 2.9%, seizures in 2.9%, increased dyskinesia in 2.0%, diplopia in 2.0%, lead migrations in 2.9%, device infections in 2.9%, improper lead placement in 2.0%, and brachial plexus injury, dysarthria, headache, paresthesia, confusion, paralysis, pulmonary embolus, abnormal healing, seroma, device erosion,

broken lead, and device with intermittent function each in 1.0% of the patients.

A second Class III study of 26 PD patients (mean age 59 ± 8 years) one year after DBS of the STN reported similar results.³⁷ There was a 66.3% improvement in UPDRS ADL scores ($p < 0.0001$) and a 64.3% improvement in UPDRS motor scores with stimulation in the medication off condition compared to baseline ($p < 0.0001$). Timed walking improved 37.6% ($p < 0.001$) and number of steps to walk 4.5 meters improved 46.6% ($p < 0.003$). Similarly, tapping scores increased by 45.1% ($p < 0.0001$). There was also an 86% improvement in dyskinesia (UPDRS item 32; $p < 0.0001$) and an 83% improvement in motor fluctuations (UPDRS item 39; $p < 0.0001$). Levodopa equivalence dose was decreased by 19.5% ($p < 0.001$). Adverse events included worsening of dysarthria in 15.4% of patients; depression in 7.7%; memory worsening in 7.7%; misplaced leads in 7.7%; scalp infection requiring system removal leading to the development of meningitis in 3.8%; seizures, hallucinations, confusion, dysphagia, eyelid apraxia, and lead fracture each in 3.8%.

A Class III study of 33 PD patients with a mean age of 58.5 ranging from 35 to 75 years 1 year after DBS of the STN also showed improvements in motor function.³⁸ UPDRS ADL (32.3%; $p < 0.001$) and motor (38.1%; $p < 0.003$) scores in the medication-off/stimulation on condition were significantly improved compared to baseline medication off scores. Finger tapping scores increased by 45.3% ($p < 0.001$) in the right hand and by 36.2% ($p < 0.002$) in the left hand. Patient diaries showed an increase in daily on time without dyskinesia from 38% at baseline to 76% at 1 year ($p < 0.002$). On time with dyskinesia was reduced from 18% to 4% and off time was also reduced from 44% to 20%. Levodopa equivalence dose was decreased by 44.2% ($p < 0.004$). Similar improvements were maintained in 19 patients 24 months after surgery. Surgical adverse events included transient confusion in 14.3% of patients, seizures in 8.6%, infection in 8.6%, visual disturbances in 2.9%, and hemiballismus in 2.9%. Stimulation related events included dysarthria in 28.6%, gait problems in 8.6%, paresthesia in 5.7%, depression in 2.9%, and muscle spasms in 2.9%. Adverse events related to the devices included lead replacements due to lack of benefit or misplacement in 25.7% of patients, IPG malfunctions in 22.9%, lead revisions in 20%, extension fractures in 5.7%, lead fracture in 2.9%, and extension erosion in 2.9%.

The final Class III study compared patients randomized to pallidotomy or DBS of the STN.³⁹ For purposes of this article, only the results of the 20 DBS patients (mean age 61, ranging from 55 to 66 years) are discussed (p values not included). The median change in UPDRS ADL scores in the medication off and stimulation on condition compared to baseline medication off was 46.3%, and for UPDRS motor scores was 48.5%. The duration of dyskinesia decreased by 50% (UPDRS item 32) and the severity of

dyskinesia decreased 100% (UPDRS item 33). Patients also completed the PD Quality of Life questionnaire that showed a median improvement of 23.2%. Levodopa equivalence dose was reduced by 33%. Adverse events included emotional lability in 30.0% of patients; increased drooling in 10.0%; postural instability in 10.0%; severe cognitive deterioration in 5.0%; CSF leakage requiring drainage in 5.0%; mild dysphasia, dysarthria, and dysphagia in 5.0%; transient confusion in 5.0%; extension strain in the neck (discomfort due to extension wire pulling with or without neck movement) in 5.0%; and displaced electrodes in 10%.

All 10 Class IV studies reported results similar to the Class III studies. All studies showed significant improvements in motor function and significant reductions in motor fluctuations, dyskinesia, and anti-parkinsonian medication.

Globus pallidus stimulation. Three articles met inclusion criteria for GPi stimulation. There was one Class III study³⁶ and two Class IV studies.^{50,51} Only the Class III study is discussed in detail; however, the details of the Class IV studies are available in the evidence tables (see table 2 and table E-2). The Class III study³⁶ was a 6-month, prospective, multicenter trial of 41 PD patients, 38 of whom received DBS (mean age 55.7 ± 9.8 years), with 36 patients completing the 6-month follow-up. At 6 months, there was a 33.3% improvement in UPDRS motor scores ($p < 0.001$) and a 35.8% improvement in UPDRS ADL scores ($p < 0.001$) with stimulation on compared to the baseline medication off condition. Patient diaries indicated an increase in on time without dyskinesia from 28% to 64% of the waking day ($p < 0.001$), a decrease in on time with dyskinesia from 35% to 12%, and a decrease in off time from 37% to 24% ($p < 0.01$). The Rush Dyskinesia scale showed an improvement of 67% ($p < 0.01$). There was no change in daily levodopa equivalence dose. Adverse events included intracranial hemorrhage in 9.8% of patients (7.3% leading to hemiparesis); increased dyskinesia in 7.3%; dystonia in 4.9%; lead migrations in 4.9%; and dysarthria, seizure, infection, broken lead, seroma, and abdominal pain each in 2.4%.

One Class IV study⁵⁰ of 20 patients receiving bilateral and 10 patients receiving unilateral DBS of the GPi (mean age 57.7, range 42 to 77 years) had results similar to the Class III study with a significant improvement $>40\%$ in UPDRS off medication with stimulation on at 6 and 12 months post surgery ($p < 0.005$) and a 92.9% reduction in dyskinesia at 6 months $p < 0.05$). The second Class IV study⁴⁹ included 26 PD patients (mean age 56.2 ± 8.6 years) with unilateral DBS of the GPi after 32.7 months of follow-up. In contrast to the other two studies, at long-term follow-up, UPDRS medication off and stimulation on motor scores worsened by 8.3%, UPDRS motor fluctuations worsened by 3.5%, and medication usage increased by 53.8%. On the other

hand, dyskinesia scores were improved by 28% at long-term follow-up (no *p* values included).

Thalamic stimulation. Four articles met inclusion criteria for thalamic stimulation.⁵²⁻⁵⁵ All four articles were Class IV. Due to the low quality of evidence, thalamic stimulation is not discussed.

Adverse events. Given the importance of understanding the risk/benefit ratio for DBS surgery, four additional articles focusing specifically on adverse events from large series of patients with DBS are discussed.⁵⁶⁻⁵⁹ The results from these studies are combined to include 360 total patients undergoing DBS, of which 288 were PD patients. Adverse events are categorized as surgical (during or within 1 month of surgery), hardware related, and stimulation related. Of the 360 patients undergoing DBS, death resulted in two patients due to pulmonary embolism and aspiration pneumonia (0.6%) and 2.8% had permanent neurologic sequelae. Other surgical complications not resulting in permanent neurologic sequelae included infection in 5.6% of patients, hemorrhage in 3.1%, confusion/disorientation in 2.8%, seizures in 1.1%, pulmonary embolism in 0.6%, CSF leak in 0.6%, peripheral nerve injury in 0.6%, and venous infarction in 0.3%. Complications related to the DBS hardware included lead replacement due to fracture, migration, or malfunction in 5% of patients; lead repositioning due to misplacement in 2.8%; extension wire replacement due to fracture or erosion in 4.4%; IPG replacement due to malfunction in 4.2%; IPG repositioning for cosmetic purposes or due to skin growth in 1.7%; and allergic reaction to the hardware in 0.6%. Stimulation-related adverse effects are generally mild and can be resolved with reprogramming of the stimulation parameters. The most common stimulation adverse effects are paresthesia, dysarthria, eyelid opening apraxia, hemiballismus, dizziness, dyskinesia, and facial contractions.

Conclusions. Based on four Class III studies, DBS of the STN is possibly effective in improving motor function and reducing motor fluctuations, dyskinesia, and antiparkinsonian medication usage in PD patients. Adverse events may limit application of this therapy.

Based on one Class III study and two Class IV studies, data are insufficient to determine if DBS of the GPi is effective in reducing motor fluctuations, dyskinesia, and antiparkinsonian medications or in improving motor function.

There is insufficient evidence to support or refute the efficacy of DBS of the VIM nucleus of the thalamus in reducing motor fluctuations, dyskinesia, and medication usage or to determine if DBS of the VIM improves motor function.

Recommendations. DBS of the STN may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C). Patients need to be counseled regarding the risks and benefits of this procedure.

There is insufficient evidence to make any recom-

mendations about the effectiveness of DBS of the GPi or VIM nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients (Level U).

Question 5: Which factors predict improvement after DBS? Of the 14 articles that met inclusion criteria for DBS of the STN, there were two prognostic Class II studies^{42,45} and 12 Class IV studies.^{36-41,43,44,46-49} Only the Class II studies are discussed in detail. Although these studies were rated Class IV relative to Question 4 regarding efficacy, they earned grades of Class II relative to prognosis for Question 5. Efficacy in these two studies was similar to the Class III studies reported above.

One Class II study was designed to examine factors predictive of outcome after DBS of the STN in 41 PD patients (mean age 56.4 ± 8.6).⁴² Regression analyses indicated that age ($p < 0.005$) and disease duration ($p < 0.007$) had a relationship with outcome. Therefore, patients were stratified by mean age, examining those 56 and older separately from those younger than 56 years. It was reported that the younger group had greater improvements in medication off UPDRS ADL (70.6% vs 53.3%; $p < 0.05$) and UPDRS motor (70.6% vs 60.0%; $p < 0.05$) scores with stimulation compared to baseline. Similarly, the group was stratified by mean disease duration and those with disease duration less than 16 years had greater improvements than those with disease duration 16 years or greater in medication off UPDRS ADL (64.5% vs 57.0%; $p < 0.05$) and UPDRS motor (67.6% vs 61.6%; $p < 0.05$) scores with stimulation compared to baseline. Levodopa responsiveness, defined as low residual motor disability on drug compared to the off state, correlated strongly with benefit from STN DBS (correlation coefficient 0.74). In addition to age and disease duration, it was concluded that levodopa responsiveness is the strongest predictor of outcome ($p < 0.002$).

The second Class II study⁴⁵ included 25 patients with a mean age of 57.2 years, ranging from 34 to 76 years at the time of DBS implantation. The study examined age, sex, disease duration, baseline drug usage, baseline dyskinesia, age at onset, and baseline levodopa responsiveness by stratifying each variable at the median. Levodopa responsiveness was the only factor that was shown to be related to postsurgical outcome ($p < 0.004$). The smaller size of this study reduced the ability to detect the association between age and disease duration and outcome.

There were no studies of GPi or VIM DBS examining predictive factors.

Conclusions. Based upon two Class II studies, preoperative response to levodopa is probably predictive of postsurgical improvement. Based on one Class II study, younger age and shorter disease duration (less than 16 years) are possibly predictive of greater improvement after DBS of the STN.

Data are insufficient to reach a conclusion on predictive factors influencing improvement after DBS of the GPi and VIM DBS.

Recommendations. Preoperative response to levodopa should be considered as a factor predictive of outcome after DBS of the STN (Level B).

Age and duration of PD may be considered as factors predictive of outcome after DBS of the STN. Younger patients with shorter disease durations may possibly have improvement greater than that of older patients with longer disease durations (Level C).

There is insufficient evidence to make any recommendations about factors predictive of improvement after DBS of the GPi or VIM nucleus of the thalamus in PD patients (Level U).

Recommendations for future research. *Medical treatment.* Comparative, randomized, double masked, controlled trials are needed to determine which drugs are the most effective in reducing off time and dyskinesia in patients with moderate to advanced PD. Uniform and more specific inclusion criteria need to be reported in these series. Outcome measures should also be standardized to include a specific diary form for measuring on/off/dyskinesia. Non-motor fluctuations, PD-specific quality of life measures, and neuropsychiatric features require greater assessment and reporting. Additional novel drug classes need further investigation.

Surgical treatment. Further research in DBS of the STN, GPi, and VIM nucleus of the thalamus should include objective clinical measures such as finger tapping, walking times, patient diaries, or patient global assessments and include the effect of DBS on disability status. Raters should be masked to whether surgery was performed for evaluations of motor function. Currently, most DBS series include a homogeneous young, fluctuating population, based on the clinical impression that this group most robustly responds to DBS. Additional studies should systematically examine which factors are predictive of a positive outcome and evaluate the optimal timing for surgery. Long duration prospective trials of DBS vs optimal medical management would provide tremendous clinical guidance. A large multicenter, randomized, double masked trial examining the long-term effects of DBS of the GPi and the STN compared to optimal medical management is currently underway and is anticipated to provide a stronger level of evidence for the effects of DBS vs optimal medical management. Research to determine cost-benefit analysis over the longer term is necessary. In addition, research to document regional disparity in access is needed.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative

methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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