Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease

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

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ABSTRACT

Objective: Nonmotor symptoms (sleep dysfunction, sensory symptoms, autonomic dysfunction, mood disorders, and cognitive abnormalities) in Parkinson disease (PD) are a major cause of morbidity, yet are often underrecognized. This evidence-based practice parameter evaluates treatment options for the nonmotor symptoms of PD. Articles pertaining to cognitive and mood dysfunction in PD, as well as treatment of sialorrhea with botulinum toxin, were previously reviewed as part of American Academy of Neurology practice parameters and were not included here.

Methods: A literature search of MEDLINE, EMBASE, and Science Citation Index was performed to identify clinical trials in patients with nonmotor symptoms of PD published between 1966 and August 2008. Articles were classified according to a 4-tiered level of evidence scheme and recommendations were based on the level of evidence.

Results and Recommendations: Sildenafil citrate (50 mg) may be considered to treat erectile dysfunction in patients with Parkinson disease (PD) (Level C). Macrogol (polyethylene glycol) may be considered to treat constipation in patients with PD (Level C). The use of levodopa/carbidopa probably decreases the frequency of spontaneous nighttime leg movements, and should be considered to treat periodic limb movements of sleep in patients with PD (Level B). There is insufficient evidence to support or refute specific treatments for urinary incontinence, orthostatic hypotension, and anxiety (Level U). Future research should include concerted and interdisciplinary efforts toward finding treatments for nonmotor symptoms of PD. *Neurology*® 2010;74:924–931

GLOSSARY

AAN = American Academy of Neurology; **DBS** = deep brain stimulation; **ED** = erectile dysfunction; **EDS** = excessive daytime somnolence; **ESS** = Epworth Sleepiness Score; **FDA** = Food and Drug Administration; **FSS** = Fatigue Severity Scale; **MFI** = Multidimensional Fatigue Inventory; **OH** = orthostatic hypotension; **PD** = Parkinson disease; **PLMS** = periodic limb movements of sleep; **PSG** = polysomnography; **QSS** = Quality Standards Subcommittee; **RBD** = REM sleep behavior disorder; **RLS** = restless legs syndrome; **STN** = subthalamic nucleus; **VAS** = visual analog scale.

The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) develops scientifically sound, clinically relevant practice parameters to aid in the practice of neurology. This article evaluates treatment options for nonmotor symptoms of Parkinson disease (PD).

While PD is considered a disorder characterized by motor symptoms, nonmotor symptoms are an integral part of this syndrome. These symptoms can be as troublesome as motor symptoms and impact activities of daily living, though they are often underrecognized by

health care professionals.^{1,2} The nonmotor symptoms reviewed for this guideline were autonomic dysfunction (gastrointestinal disorders, orthostatic hypotension, sexual dysfunction, urinary incontinence), sleep disorders (restless legs syndrome, periodic limb movements of sleep, excessive daytime somnolence, insomnia, REM sleep behavior disorder), fatigue, and anxiety. Articles pertaining to cognitive and mood dysfunction in PD, as well as treatment of sialorrhea with botulinum toxin, were reviewed as part of previous AAN practice parameters^{3,4} and were not included here.

Supplemental data at
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Appendices e-1–e-4, tables e-1 and e-2, and references e1 and e2 are available on the *Neurology*® Web site at www.neurology.org.

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Table	Search terms used
General terms	Nonmotor symptoms, human
Treatment-related terms	Treatment, therapy, drug, medication, trial, surgery, deep brain stimulation, cognitive-behavioral therapy, care
Sleep	Sleep, night, sleepiness, sleep apnea, sleep disordered breathing, parasomnia, REM sleep behavior disorder, sleepwalking, sleep attack, sleep disorders, insomnia, excessive daytime sleepiness, sudden onset of sleep, restless legs syndrome, periodic limb movements of sleep, vivid dreaming, fatigue
Autonomic	Autonomic, orthostatic hypotension, orthostasis, constipation, incomplete bowel emptying, fecal incontinence, nausea, vomiting, heat intolerance, urinary, urination, urinary frequency, urinary incontinence, urinary urgency, nocturia, sweating, hypersalivation, drooling, seborrhea, sexual dysfunction, hypersexuality, erectile dysfunction, impotence
Psychological	Anxiety, obsessive, gambling, hallucinations, delusion, motivation, apathy, concentration
Sensory	Smell, olfaction, taste, saliva, cramp, paresthesia, vision, diplopia
Miscellaneous	Weight loss, anorexia, leg swelling, leg edema

DESCRIPTION OF THE ANALYTIC PROCESS

In April 2005, the QSS of the AAN convened an expert panel of investigators from the United States and Europe who have published extensively in the field of nonmotor symptoms in PD. The panel was selected to represent a broad range of relevant expertise and opinion. In November 2006, a literature search was performed (in all languages) using the search terms shown in the table.

Therapies reviewed included pharmaceuticals as well as other therapies such as the continuous positive airway pressure machine in patients with sleep abnormalities, dietary modifications, homeopathic treatments, surgery, and interventional therapies such as electroconvulsive therapy.

Three databases (MEDLINE, EMBASE, and Science Citation Index) were searched from 1966 to November 2006 (with manual searches until August 2008), resulting in 3,369 citations. Each abstract was reviewed by at least 2 members of the panel for relevance for further review. Articles that evaluated treatment of a nonmotor symptom in patients with PD were considered relevant. This resulted in a list of 523 articles, each of which was reviewed by at least 2 members of the panel for relevance. Any disagreements were arbitrated by a third reviewer. After detailed review of all 523 articles, the panel decided 46 articles contributed relevant, assessable data. Articles were excluded if they did not relate to PD or treatment of nonmotor PD symptoms or if they related to treatment of cognitive or mood disorders in PD or

treatment of sialorrhea with botulinum toxin. The articles were classified for quality of evidence based on the AAN therapeutic classification scheme (appendix e-3 on the *Neurology*[®] Web site at www.neurology.org) and recommendations were based on class of evidence (appendix e-4).

ANALYSIS OF EVIDENCE Autonomic symptoms.

What treatments are effective for sexual dysfunction in PD?

Sexual dysfunction is common in both men and women with PD and is a complex problem resulting from diverse etiologies including motor dysfunction, medication side effects, mood disorders, and dysautonomia. Dysautonomia manifests as erectile dysfunction (ED) but also as reduced genital sensitivity and lubrication and difficulties reaching orgasm.⁵ Controlled clinical trials were available only for ED in PD. One Class II study evaluated the efficacy of sildenafil citrate (Viagra[®]) in treating ED in 12 patients with PD.⁶ Sildenafil was initiated at 50 mg, with dose adjustments depending on efficacy and tolerability. The primary outcome measure was the International Index of Erectile Function Questionnaire. Criteria for study entry included a definite neurologic diagnosis and a standing systolic blood pressure of 90–180 mm Hg and diastolic blood pressure of 50–110 mm Hg. Sildenafil citrate enabled men to achieve and maintain an erection with an improved sex life compared to placebo, with minimal changes in blood pressure. Self-ratings were significantly higher in the treatment group than the placebo group for obtaining an erection (3.71 vs 1.56) and for maintaining an erection (3.79 vs 1.44).

Conclusions. Sildenafil citrate (50 mg) is possibly efficacious in the treatment of ED in PD (1 Class II study).

Clinical context. A complete medical evaluation should determine whether other treatable causes of ED may be present, including other medical conditions or side effects of medications. The United States Food and Drug Administration (FDA) has approved sildenafil citrate as a medication to treat impotence.

What treatments are effective for orthostatic hypotension in PD?

The American Autonomic Society defines orthostatic hypotension (OH) as a symptomatic drop of 20 mm Hg in systolic or 10 mm Hg in diastolic blood pressure.⁷ Patients may experience lightheadedness or syncope, or nonspecific complaints including fatigue, unsteadiness, headache, neck tightness, and cognitive slowing. There have been few placebo-controlled trials of treatment for OH in PD. In a comparative study of 17 patients, domperidone and fludrocortisone improved the Clinical Global Impression of Change scale and the Composite Autonomic Symptom Scale scores, with domperidone

showing greater improvement⁸ (Class III). Domperidone, a peripheral D2 receptor antagonist, was hypothesized to treat OH because presynaptic dopamine receptors on sympathetic nerve endings also modulate noradrenaline release. Indomethacin is a nonsteroidal anti-inflammatory drug that is less commonly used to treat OH.⁷ However, one small study found that it significantly improved OH after oral administration (Class III) and intravenous (Class IV) infusion.⁹ Additionally, a double-blind dose-response study of midodrine for the treatment of neurogenic OH included a patient with PD,¹⁰ and a prospective open-label trial of pyridostigmine for treatment of OH included 3 patients with PD (out of 15 total patients in the study),¹¹ but data for the patients with PD were not reported separately.

Conclusions. Data are insufficient to make a recommendation on the use of indomethacin, fludrocortisones, pyridostigmine, or domperidone in treating OH in PD.

Clinical context. Randomized controlled trials of mineralocorticoids, alpha-sympathomimetics, and pyridostigmine in patients with PD are lacking. However, their pharmacologic action is consistent with improvement in OH. The only medications that are currently FDA-approved to treat OH are midodrine and L-threo-dihydroxyphenylserine (L-threo-DOPS; Droxidopa), an orally active synthetic precursor of norepinephrine.

What treatments are effective for urinary incontinence in PD? Urinary incontinence in PD is usually associated with detrusor hyperreflexia caused by basal ganglia dysfunction.¹² One Class III study found that apomorphine, a dopamine agonist used to treat 10 patients with PD with urinary symptoms, resulted in improved voiding efficiency and increased mean and maximum flow rates.¹³ Two Class IV studies found that deep brain stimulation (DBS) of the subthalamic nucleus (STN) improved bladder capacity and volume.^{14,15}

Conclusions. Data for the treatment of urinary incontinence with apomorphine or DBS are insufficient.

Clinical context. Although randomized controlled trials of anticholinergics in patients with PD are lacking, their pharmacologic action and widespread clinical use are consistent with benefit in urinary incontinence. Anticholinergics have been shown to cause confusion in patients with PD.

What treatments are effective for gastrointestinal symptoms in PD? Constipation is a commonly encountered symptom of autonomic nervous system dysfunction in PD. One Class II¹⁶ and 4 Class III¹⁷⁻²⁰ studies evaluated the efficacy of pharmacologic agents to treat constipation. Isosmotic macrogol (polyethylene glycol

3350) solution was found to improve bowel movement frequency ($p < 0.002$) and stool consistency ($p < 0.006$) (Class II).¹⁶ In the United States, polyethylene glycol is contained in a product called Miralax[®]. A Class III study evaluated the effects of 100 U of botulinum toxin in 10 patients with PD with chronic constipation.²¹ One month after treatment, anal tone during straining was reduced by 58% in the group compared to baseline ($p = 0.00001$). There was no change in resting anal tone or maximum voluntary contraction. Controlled trials evaluating treatment of other gastrointestinal symptoms including fecal incontinence, nausea, vomiting, weight loss, and anorexia are lacking.

Conclusions. Isosmotic macrogol (polyethylene glycol) possibly improves constipation in PD (1 Class II study). Data are insufficient regarding the use of botulinum toxin for constipation in PD.

Clinical context. Although randomized controlled trials of treatments for constipation in patients with PD are lacking, their pharmacologic action and widespread clinical use are consistent with benefit in constipation. Additionally, nonpharmacologic treatments such as increased water and dietary fiber intake have shown clinical benefit in relieving constipation. Drugs used to treat many conditions, including PD, can cause constipation.

What treatments are effective for other autonomic symptoms in PD? Controlled trials evaluating treatment for other autonomic symptoms, including heat intolerance, urinary frequency, urinary urgency, nocturia, sweating, hypersalivation, seborrhea, hypersexuality, and leg edema, are lacking. The use of botulinum toxin as a treatment for sialorrhea was reviewed as part of a previous AAN practice parameter,⁴ which concluded that botulinum toxin should be considered for drooling (Level B).

Sleep dysfunction. **What treatments are effective for excessive daytime somnolence in PD?** The etiology of excessive daytime somnolence (EDS) in PD may be the disease process, medications, or other sleep disorders. EDS may be related to dopaminergic medications and is more common with dopamine agonists than levodopa.^{22,23} Three Class I studies assessed the therapeutic efficacy of modafinil, a medication that is FDA-approved to treat narcolepsy, in the treatment of EDS in patients with PD.²⁴⁻²⁶ Two Class I studies found that modafinil improved EDS on a subjective level using the Epworth Sleepiness Score (ESS),^{25,26} while a third study seemed to demonstrate some subjective improvements using the ESS (2.7-point improvement [14%] in modafinil group compared to 1.5-point improvement [9.4%] in placebo group) that were nonsignificant.²⁴ In 2 Class I studies, there was no objective improvement in EDS as measured by the maintenance of wakefulness test or Multiple

Sleep Latency Test,^{24,26} although one study may have been underpowered.²⁴

Conclusions. For patients with PD and EDS, modafinil is effective in improving patients' perception of wakefulness (2 Class I studies), but is ineffective in objectively improving EDS as measured by objective tests (2 Class I studies).

What treatments are effective for insomnia in PD? Patients with PD frequently complain of an inability to fall asleep and numerous nighttime awakenings. The etiology of insomnia in PD is multifactorial, including mood disturbances, persistent tremor, nighttime re-emergence of PD symptoms, nocturia, and reversal of sleep patterns. There are few controlled trials that have evaluated the use of conventional sleeping aids as treatment for insomnia in PD. Two Class I studies evaluated the effect of levodopa/carbidopa on sleep quality in PD.^{27,28} One study found that levodopa/carbidopa administered at bedtime improved sleep quality from 67% to 93% using a visual analog scale (VAS).²⁷ The other Class I study found that levodopa/carbidopa slow release tablets did not improve the number of hours slept, number of awakenings, sleep latency, or general sleep satisfaction.²⁸ However, there was a significant improvement in mean nocturnal akinesia score in the levodopa-treated group.

Melatonin, a hormone produced by the pineal gland, is involved in regulating the circadian cycle.²⁹ One Class I study that measured nocturnal sleep by actigraphy, sleep diaries, and the ESS found that melatonin had a small benefit in treating insomnia in doses of 5 mg and 50 mg.³⁰ Total sleep time improved by 10 minutes (from 5 hours 13 minutes to 5 hours 23 minutes; 3%) with the 50-mg dose of melatonin, and the general sleep disturbance scale showed improvements in sleep quantity with the 5-mg dose. Another Class I study found that melatonin 3 mg improved sleep quality by subjective, but not objective, measures (i.e., polysomnography [PSG]).³¹

Conclusions. Levodopa/carbidopa improved sleep-associated motor symptoms that may contribute to insomnia, but data demonstrating an improvement in objective sleep parameters or sleep satisfaction are insufficient. Melatonin is established as effective in improving patients' perception of sleep quality (2 Class I studies) but data are conflicting regarding objective improvement in sleep quality as measured by PSG.

Is surgical treatment of PD with DBS of the STN effective treatment for insomnia? DBS is used to treat the symptoms of PD. Three Class III studies using PSG found an improvement in sleep quality following DBS of the STN.³²⁻³⁴ In one study, total sleep time increased from a mean of 281 minutes before DBS to a mean of 360 minutes after DBS (with DBS on), an

improvement of 28%.³² Other studies showed a significant decrease in the arousal index from 18.0 to 11.2 (38%),³³ and total sleep efficiency increased by a mean of 36%.³⁴

Conclusions. DBS STN therapy possibly improves sleep quality in patients with advanced PD (Class III studies). However, none of the studies performed DBS STN to treat insomnia as a primary symptom.

Clinical context. DBS STN is not currently used to treat sleep disorders.

What treatments are effective for restless legs syndrome and periodic limb movements of sleep in PD? Restless legs syndrome (RLS) occurs in up to 20% of patients with PD.³⁵ While the dopamine agonists ropinirole and pramipexole are FDA-approved to treat RLS in the general population, there are no controlled trials in patients with PD with RLS. One Class III open-label study of 15 patients with PD with periodic limb movements of sleep (PLMS) who were treated with cabergoline found that it increased the number of awakenings and stage shifts, but reduced PLMS in sleep ($p < 0.05$).³⁶ A Class I study found that levodopa/carbidopa administered at bedtime decreased the frequency of spontaneous movements in bed from 43/night to 28–33/night. Nighttime movements were measured by a system involving a load transducer placed under each bed leg to monitor the frequency of movements and distance moved.²⁷

Conclusions. Levodopa/carbidopa probably decreases the frequency of spontaneous nighttime leg movements (1 Class I study). Data regarding the use of non-ergot dopamine agonists to treat RLS and PLMS specifically in patients with PD are insufficient.

Clinical context. Data on the use of dopamine agonists to treat RLS and PLMS specifically in patients with PD are lacking. The dopamine agonists ropinirole and pramipexole are the only FDA-approved agents for the treatment of moderate to severe primary RLS.

What treatments are effective for REM sleep behavior disorder in PD? REM sleep behavior disorder (RBD) is a type of parasomnia and is characterized by patients acting out dramatic or violent dreams during the REM sleep stage.

Conclusions. Data regarding the treatment of RBD in PD are insufficient.

Clinical context. The antiepileptic drug clonazepam and melatonin are often used to treat RBD in the general population.

Fatigue. What treatments are effective for fatigue in PD? Fatigue is commonly experienced by patients with PD. The etiology of fatigue in PD is unclear and may be multifactorial. One Class II randomized, double-blind, placebo-controlled trial evaluated methylphenidate for the treatment of fatigue in patients with PD.³⁷ Thirty-six patients were randomized to

receive either methylphenidate (10 mg 3 times per day; $n = 17$) or placebo ($n = 19$) for 6 weeks. The primary outcome measures were the change from baseline on 2 separate self-report fatigue questionnaires (Fatigue Severity Scale [FSS] and the Multidimensional Fatigue Inventory [MFI]). There were reductions in the mean FSS score and MFI score in the treatment arm ($p < 0.04$).

Conclusions. Methylphenidate is possibly useful in treating fatigue in patients with PD (1 Class II study).

Clinical context. Methylphenidate has the potential for abuse.³⁸ Although there is no current evidence to suggest such a risk in PD, patients with PD do have a risk for dopamine dysregulation syndrome and impulse control disorders that share many clinical and functional imaging features with addiction.

Regarding sleep disorders, there are currently no controlled studies on treatment for sleep apnea, sleep-disordered breathing, parasomnia, and sleepwalking.

Psychological symptoms. What treatments are effective for anxiety in PD? Anxiety occurs frequently in PD, often coexistent with depression.³⁹ One study compared the effects of levodopa immediate release and levodopa controlled release on anxiety in patients with PD.⁴⁰ Fourteen patients without a diagnosed anxiety disorder participated in this study. Treatments were administered in a double-blind, randomized, crossover fashion after withholding PD medications overnight. Assessments included the State Trait Anxiety Inventory and a VAS for anxiety and were conducted before treatment and 0.5, 1, 2, 2.5, 3.5, 5, and 6 hours after levodopa administration. VAS scores showed a trend toward reduced anxiety but this result was not significant. Patients with wearing-off had a reduction in VAS anxiety scores 3.5 hours after taking the immediate release formulation compared to stable patients (stable 5.2 ± 0.8 , fluctuating 3.6 ± 1.5 , $p = 0.02$); similar effects were not seen with the controlled release formulation (Class III).

Conclusions. Data regarding the treatment of anxiety in PD are insufficient.

Clinical context. Although randomized controlled trials of antianxiety agents in patients with PD are lacking, their pharmacologic action and widespread clinical use are consistent with benefit in anxiety. Antianxiety medications have been associated with ataxia, falls, and cognitive dysfunction.

Controlled studies of treatment for other psychological symptoms, including obsessive behaviors, gambling, delusions, decreased motivation, apathy, and concentration difficulties, are lacking.

RECOMMENDATIONS

1. Erectile dysfunction
 - Sildenafil citrate may be considered in patients with PD with erectile dysfunction (Level C).
2. Orthostatic hypotension
 - There is insufficient evidence to support or refute treatments of OH in PD (Level U).
3. Urinary incontinence
 - There is insufficient evidence to support or refute treatments of urinary incontinence in PD (Level U).
4. Constipation
 - Isosmotic macrogol (polyethylene glycol) may be considered to treat constipation in PD (Level C).
 - There is insufficient evidence to support or refute the use of botulinum toxin to treat constipation in PD (Level U).
5. Excessive daytime somnolence
 - Modafinil should be considered for patients to improve their subjective perception of EDS (Level A). There is insufficient evidence to support or refute a safety benefit in patients with PD with EDS who engage in activities where sleepiness poses a potential danger (e.g., driving) (Level U). It should be noted that patients who are treated with modafinil may experience an improvement in sleep perception without an actual improvement in objective sleep measurements.
6. Insomnia
 - There is insufficient evidence to support or refute the benefit of levodopa on objective sleep parameters that are not affected by motor status (Level U).
 - There is insufficient evidence to support or refute the treatment of poor sleep quality with melatonin (Level U).
7. Periodic limb movements of sleep
 - Levodopa/carbidopa should be considered to treat PLMS (Level B).
 - There is insufficient evidence to support or refute the treatment of RLS and PLMS with non-ergot dopamine agonists (Level U).
8. Fatigue
 - Methylphenidate may be considered in patients with fatigue (Level C).
9. REM sleep behavior disorder
 - There is insufficient evidence to support or refute the treatment of RBD (Level U).
10. Anxiety
 - There is insufficient evidence to support or refute the treatment of anxiety in PD with levodopa (Level U).

RECOMMENDATIONS FOR FUTURE RESEARCH

Although common, nonmotor symptoms of PD are underdiagnosed. There is a paucity of research concerning treatment of nonmotor symptoms in PD.

A concerted and multidisciplinary effort needs to be made toward finding treatments for nonmotor symptoms in PD. The NMS Quest study^{e1} established a valid and reliable questionnaire to identify nonmotor symptoms in PD. Additionally, a revised version of the Unified Parkinson's Disease Rating Scale will include an expanded section to assess nonmotor symptoms.^{e2} These tools should assist in screening and early identification of nonmotor symptoms in PD.

There are few dedicated controlled trials of drugs to treat nonmotor symptoms in PD. Such trials are urgently required. These symptoms include the following.

1. Sleep disorders (including sleepiness, sleep apnea, sleep-disordered breathing, parasomnia, RBD, sleepwalking, sleep attacks, insomnia, EDS, sudden onset of sleep, RLS, PLMS, vivid dreaming, and fatigue)
2. Autonomic symptoms (including OH, orthostasis, constipation, incomplete bowel emptying, fecal incontinence, nausea, vomiting, heat intolerance, urinary frequency, urinary incontinence, urinary urgency, nocturia, sweating, hypersalivation, drooling, seborrhea, sexual dysfunction in men and women, hypersexuality, erectile dysfunction, and impotence)
3. Psychological symptoms (including anxiety, obsessive behaviors, delusions, decreased motivation, apathy, and decreased concentration)
4. Sensory dysfunction (including smell, olfaction, taste, saliva, paresthesias, and visual disturbances)
5. Other nonmotor symptoms (including weight loss, anorexia, and leg edema)

DISCLOSURE

Dr. Zesiewicz has received funding for travel from and served on speakers' bureaus for Boehringer Ingelheim and Teva Pharmaceutical Industries Ltd.; and receives research support from Boehringer Ingelheim, Novartis, GlaxoSmithKline, UCLA-RAND, Teva Neuroscience, Pfizer Inc, Allergan, Inc., the National Ataxia Foundation, Friedreich's Ataxia Research Association, and from the Bill Allison Ataxia Research Center. Ms. Sullivan reports no disclosures. Dr. Arnulf has served on scientific advisory boards for UCB and BioProject Pharma; has received funding for travel from UCB and for educational activities not funded by industry; received speaker honoraria from UCB and AstraZeneca; and has received research support UCB and BioProject Pharma. Dr. Chaudhuri serves on scientific advisory boards for Solvay Pharmaceuticals, Inc., Boehringer Ingelheim, GlaxoSmithKline, Merck Serono, Teva Pharmaceutical Industries Ltd.; serves on the editorial board of *Parkinson's Disease and Related Disorders*; receives research support from UCB, SCHWARZ PHARMA, Boehringer Ingelheim, Britannia Pharmaceuticals, and Solvay Pharmaceuticals, Inc.; and estimates that 10% of his clinical effort is administering botulinum toxin for dystonia. Dr. Morgan serves on a scientific advisory board for

Boehringer Ingelheim; serves on speakers' bureaus for Boehringer Ingelheim, GlaxoSmithKline, Teva Pharmaceutical Industries Ltd., Novartis, and SCHWARZ PHARMA; and receives research support from Boehringer Ingelheim, GlaxoSmithKline, UCB, Teva Pharmaceutical Industries Ltd., Novartis, ACADIA Pharmaceuticals, Santhera Pharmaceuticals, the NIH (NET-PD LS-1 [sub-investigator]), and from the National Parkinson Foundation. Dr. Gronseth serves as an editorial advisory board member of *Neurology Now*; serves on a speakers' bureau for Boehringer Ingelheim; and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. Dr. Miyasaki has served on a scientific advisory board for Teva Pharmaceutical Industries Ltd.; has received honoraria for educational activities not funded by industry; serves on the editorial board of *Movement Disorders*; has received speaker honoraria from Biovail Corporation; serves/has served as a consultant to Ortho-McNeil-Janssen Pharmaceuticals, Inc., Merz Pharmaceuticals, LLC, Schering-Plough Corp., the NIH (Independent Medical Monitor), Ontario Drug Benefits, and Common Drug Review, Canada; and receives research support from Teva Pharmaceutical Industries Ltd., Boehringer Ingelheim, Solvay Pharmaceuticals, Inc., Solstice Neurosciences, Inc., Impax Laboratories, Neurogen, Medivation, Inc., the National Parkinson Foundation, the Parkinson Society Canada, the Michael J Fox Foundation, and the Huntington Study Group. Dr. Iverson reports no disclosures. Dr. Weiner has served on scientific advisory boards for Santhera Pharmaceuticals, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Teva Pharmaceutical Industries Ltd.; serves as Editor of *Current Treatment Options in Neurology* and on the editorial board of *Parkinsonism and Related Disorders*; receives royalties from the publication of *Parkinson's Disease: A Complete Guide for Patients and Families* (The Johns Hopkins University Press, 2001), *Parkinson's Disease: Diagnosis and Clinical Management* (Demos Medical Publishing, Inc., 2002), and *Neurology for the Non-Neurologist 5th ed.* (Lippincott Williams & Wilkins, 2004); and has received research support from Santhera Pharmaceuticals, Boehringer Ingelheim, and Teva Pharmaceutical Industries Ltd.

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. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology*[®] peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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