

The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease

Klaus Seppi, MD,^{1*} Daniel Weintraub, MD,² Miguel Coelho, MD,³ Santiago Perez-Lloret, MD, PhD,⁴ Susan H. Fox, MRCP (UK), PhD,⁵ Regina Katzenschlager, MD,⁶ Eva-Maria Hametner, MD,¹ Werner Poewe, MD,¹ Olivier Rascol, MD, PhD,⁴ Christopher G. Goetz, MD,⁷ and Cristina Sampaio, MD, PhD^{8*}

¹Department of Neurology, Medical University Innsbruck, Innsbruck, Austria

²Department of Psychiatry, University of Pennsylvania School of Medicine; Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA

³Neurological Clinical Research Unit, Instituto de Medicina Molecular, Hospital Santa Maria, Lisbon, Portugal

⁴Department of Clinical Pharmacology, Toulouse University Hospital, Toulouse, France

⁵Movement Disorder Clinic, Toronto Western Hospital, Toronto, Ontario, Canada

⁶Department of Neurology, Danube Hospital/SMZ-Ost, Vienna, Austria

⁷Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA

⁸Instituto de Medicina Molecular, University of Lisbon, Lisbon, Portugal

ABSTRACT: The Movement Disorder Society (MDS) Task Force on Evidence-Based Medicine (EBM) Review of Treatments for Parkinson's Disease (PD) was first published in 2002 and was updated in 2005 to cover clinical trial data up to January 2004 with the focus on motor symptoms of PD. In this revised version the MDS task force decided it was necessary to extend the review to non-motor symptoms. The objective of this work was to update previous EBM reviews on treatments for PD with a focus on non-motor symptoms. Level-I (randomized controlled trial, RCT) reports of pharmacological and nonpharmacological interventions for the non-motor symptoms of PD, published as full articles in English between January 2002 and December 2010 were reviewed. Criteria for inclusion and ranking followed the original program outline and adhered to EBM methodology. For efficacy conclusions, treatments were designated: *efficacious*, *likely efficacious*, *unlikely efficacious*, *non-efficacious*, or *insufficient evidence*. Safety data were catalogued and reviewed. Based on the combined efficacy and safety assessment, Implications for clinical practice were determined using the following designations: *clinically useful*, *possibly useful*, *investigational*, *unlikely useful*, and *not useful*. Fifty-four new studies qualified for efficacy review while several other studies covered safety issues. Updated and new

efficacy conclusions were made for all indications. The treatments that are efficacious for the management of the different non-motor symptoms are as follows: pramipexole for the treatment of depressive symptoms, clozapine for the treatment of psychosis, rivastigmine for the treatment of dementia, and botulinum toxin A (BTX-A) and BTX-B as well as glycopyrrolate for the treatment of sialorrhea. The practical implications for these treatments, except for glycopyrrolate, are that they are clinically useful. Since there is insufficient evidence of glycopyrrolate for the treatment of sialorrhea exceeding 1 week, the practice implication is that it is possibly useful. The treatments that are likely efficacious for the management of the different non-motor symptoms are as follows: the tricyclic antidepressants nortriptyline and desipramine for the treatment of depression or depressive symptoms and macrogol for the treatment of constipation. The practice implications for these treatments are possibly useful. For most of the other interventions there is insufficient evidence to make adequate conclusions on their efficacy. This includes the tricyclic antidepressant amitriptyline, all selective serotonin reuptake inhibitors (SSRIs) reviewed (paroxetine, citalopram, sertraline, and fluoxetine), the newer antidepressants atomoxetine and nefazodone, pergolide, Ω -3 fatty acids as well as repetitive transcranial magnetic stimulation.

*Correspondence to: Cristina Sampaio, Instituto de Medicina Molecular, University of Lisbon, Lisbon, Portugal; crissampaio@mac.com; Klaus Seppi Department of Neurology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria, klaus.seppi@uki.at.

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nial magnetic stimulation (rTMS) for the treatment of depression or depressive symptoms; methylphenidate and modafinil for the treatment of fatigue; amantadine for the treatment of pathological gambling; donepezil, galantamine, and memantine for the treatment of dementia; quetiapine for the treatment of psychosis; fludrocortisone and domperidone for the treatment of orthostatic hypotension; sildenafil for the treatment of erectile dysfunction, ipratropium bromide spray for the treatment of sialorrhea; levodopa/carbidopa controlled release (CR), pergolide, eszopiclone, melatonin 3 to 5 mg and melatonin 50 mg for the treatment of insomnia and modafinil for the treatment of excessive daytime sleepiness. Due to safety issues the practice implication is that pergolide and nefazodone are not useful for the above-mentioned indications. Due to safety issues, olanzapine remains not useful for the treatment of psychosis. As none of the studies exceeded a duration of 6 months, the recommendations given are for the short-term management of the different

non-motor symptoms. There were no RCTs that met inclusion criteria for the treatment of anxiety disorders, apathy, medication-related impulse control disorders and related behaviors other than pathological gambling, rapid eye movement (REM) sleep behavior disorder (RBD), sweating, or urinary dysfunction. Therefore, there is insufficient evidence for the treatment of these indications. This EBM review of interventions for the non-motor symptoms of PD updates the field, but, because several RCTs are ongoing, a continual updating process is needed. Several interventions and indications still lack good quality evidence, and these gaps offer an opportunity for ongoing research. © 2011 *Movement Disorder Society*

Key Words: Parkinson's disease; evidence-based medicine; dopamine agonists; tricyclic antidepressants; selective serotonin reuptake inhibitors (SSRIs); omega-3 fatty-acids; transcranial magnetic stimulation

Although Parkinson's disease (PD) is generally considered a paradigmatic movement disorder, a majority, if not all PD patients also suffer from non-motor symptoms adding to the overall burden of parkinsonian morbidity.^{1,2} Non-motor symptoms in PD are numerous and include mood and affect disorders, cognitive dysfunction and dementia, psychosis, autonomic dysfunction, and disorders of sleep-wake cycle regulation. They become increasingly prevalent and obvious over the course of the illness and are a major determinant of quality of life, progression of overall disability, and of nursing home placement of PD patients.³ In their various combinations, non-motor symptoms may become the chief therapeutic challenge in advanced stages of PD. Despite the high prevalence and associated disability of non-motor symptoms in PD, many of the non-motor symptoms may not have effective treatment options. One mechanism of assisting clinicians in decision-making is the use of evidence-based medicine (EBM), whose principles allow clinically meaningful conclusions to be drawn from clinical trials, and therefore the comparison of results from these different trials is simplified. By using the current evidence in the medical literature, EBM helps to provide the best possible care to patients.⁴

The *Movement Disorder Society* (MDS) has already performed 2 EBM reviews of treatments for PD.^{5,6} In 2002,⁵ the MDS published a detailed EBM analysis of pharmacological, surgical, and psychosocial interventions for the treatment of PD, including non-motor elements of PD such as depression, psychosis, and dysautonomia. In 2005, this review was updated with a focus on the pharmacological and surgical interventions of motor aspects of PD.⁶ Since 2002, the MDS

has sponsored educational events for clinicians in order to broaden the applicability of these guidelines in daily practice. This current report updates the previous reviews and incorporates new data on (1) efficacy, (2) safety, and (3) implications for clinical practice of treatments for non-motor symptoms of PD published from January 2002 to December 2010. A separate article will focus on updates in treatments of motor aspects of PD (from January 2004 for pharmacological and surgical, and from 2001 for nonpharmacological realms).

The treatments identified for inclusion in this review were based on consensus among the authors, and for each type of intervention the evidence was reviewed regarding aspects of the symptomatic management of the following domains of non-motor symptoms in PD:

- Depression, mood disorders, anxiety disorders, apathy, and fatigue
- Cognitive dysfunction and dementia
- Psychosis
- Medication-related impulse controls disorders and other compulsive behaviors
- Autonomic dysfunction:
 - Orthostatic hypotension
 - Sexual dysfunction
 - Gastrointestinal dysfunction
 - Sialorrhea
 - Sweating
- Disorders of sleep and wakefulness:
 - RBD
 - Sleep fragmentation and insomnia
- Daytime Sleepiness and sudden onset of sleep.

TABLE 1. Definitions for specific recommendations⁵

Efficacy conclusions	Definition	Required evidence
Efficacious	Evidence shows that intervention has a positive effect on studied outcomes	Supported by data from at least 1 high-quality (score \geq 75%) RCT without conflicting level-I data
Likely efficacious	Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes	Supported by data from any Level-I trial without conflicting level-I data
Unlikely efficacious	Evidence suggests that the intervention does not have a positive effect on studied outcomes	Supported by data from any Level-I trial without conflicting level-I data
Non-efficacious	Evidence shows that the intervention does not have a positive side effect on studied outcomes	Supported by data from at least 1 high-quality (score \geq 75%) RCT without conflicting level-I data.
Insufficient evidence	There is not enough evidence either for or against efficacy of the intervention in treatment of Parkinson's disease	All the circumstances not covered by the previous statements
Safety		
	Acceptable risk without specialized monitoring	
	Acceptable risk with specialized monitoring	
	Unacceptable risk	
	Insufficient evidence to make conclusions on the safety of the intervention	
Implications for clinical practice		
Clinically useful	For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit	
Possibly useful	For a given situation, evidence available suggests, but insufficient to conclude that the intervention provides clinical benefit	
Investigational	Available evidence is insufficient to support the use of the intervention in clinical practice, further study is warranted	
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit	
Unlikely useful	Evidence suggests that the intervention does not have a positive effect on studied outcomes	

RCT, randomized controlled trial.

There were no randomized clinical trials (RCTs) that met inclusion criteria for the treatment of anxiety disorders, apathy, medication-related impulse dyscontrol and abnormal repetitive behaviors other than pathological gambling, RBD, sweating, or urinary dysfunction.

Materials and Methods

The search strategy, inclusion criteria and evaluation methods followed those previously reported.^{5,6} A literature search was undertaken for articles published between January 2002 and December 2010, using electronic databases including Medline, the Cochrane Library central database, and systematic checking of reference lists published in review articles and other clinical reports. Drugs to treat anxiety disorders, apathy, fatigue, medication-related impulse dyscontrol, and abnormal repetitive behaviors, sexual dysfunction, sialorrhea, sweating, as well as disorders of sleep and wakefulness were not reviewed in the original review. Therefore, a literature search for these indications was performed for articles published before January 2002. The following inclusion criteria were adhered to:

- Randomized controlled trials in idiopathic PD that measured non-motor symptoms as the primary endpoint.
- Interventions included pharmacological, surgical and nonpharmacological therapies that were commercially available in at least 1 country.
- In most cases, papers were only selected for review when there was:
 - an established rating scale or well described measurement of endpoints;
 - a minimum of 20 subjects that were treated for a minimum duration of 4 weeks;
 - a report in full-paper format in English.

A quality assessment for each article was calculated using predetermined criteria (see Table 1) described in the original review.⁵ In cases where the above listed inclusion criteria were not fulfilled, special exceptions were made when there was a justification for inclusion. The reasons for inclusion of such studies are given in Table 2. For each intervention we provide a description of the new clinical trials followed by a summary with conclusions. These conclusions are summarized in Tables 3 to 9. Each table covers efficacy, safety, and implications for clinical practice as defined in Table 1 for each of the above indications.

TABLE 2. Reasons for inclusion of studies not meeting inclusion criteria

Study	Reason for not fulfilling inclusion criteria	Reason for inclusion in the review
Leentjens et al. (2003) ¹¹	n < 20	Limited number of placebo-controlled studies available for the treatment of depression in PD
Avila et al. (2003) ¹³	n < 20	Limited number of controlled studies available for the treatment of depression in PD
Lou et al. (2010) ³³	n < 20	Limited number of placebo-controlled studies using modafinil for the treatment of fatigue in PD available
Fernandez et al. (2009) ⁶³	n < 20	The only positive placebo-controlled study using quetiapine for the treatment of psychosis in PD
Tyne et al. (2010) ³⁴	n < 20	Limited number of placebo-controlled studies using modafinil for the treatment of fatigue in PD available
Thomas et al. (2010) ³⁹	n < 20	Limited number of placebo-controlled studies using amantadine for the treatment of pathological gambling in PD available; crossover study – power higher than in parallel group studies
Aarsland et al. (2002) ⁴²	n < 20	Limited number of placebo-controlled studies using donepezil for the treatment of dementia in PD available; crossover study – power higher than in parallel group studies
Leroi et al. (2004) ⁴⁴	n < 20	Limited number of placebo-controlled studies using donepezil for the treatment of dementia in PD available
Schoffer et al. (2007) ⁶⁷	n < 20	Limited number of studies available for the treatment of OH in PD
Hussain et al. (2001) ⁶⁹	n < 20; PD and MSA patients included	Limited number of studies available for the treatment of erectile dysfunction in PD; analysis given separately for MSA and PD patients
Thomsen et al. (2007) ⁷⁹	n < 20; study duration 2 weeks	Limited number of studies using anticholinergics available for the treatment of sialorrhea in PD; for endpoint sialorrhea 2-week study duration sufficient
Arbouw et al. (2010) ⁸⁰	Study duration 1 week	Limited number of studies using anticholinergics available for the treatment of sialorrhea in PD; for endpoint sialorrhea 1-week study duration sufficient
Ondo et al. (2004) ⁸⁴	n < 20	Limited number of placebo-controlled studies using BTX-B for the treatment of sialorrhea in PD available
Stocchi et al. (1998) ⁸⁸	Study duration 2 weeks	Limited number of studies using levodopa for the treatment of insomnia available
Adler et al. (2003) ¹⁰¹	Study duration 3 weeks	Limited number of studies using modafinil for the treatment of EDS available
Högl et al. (2002) ⁹⁹	n < 20	Limited number of placebo-controlled studies using modafinil for the treatment of EDS in PD available; crossover study – power higher than in parallel group studies

PD, Parkinson's disease; OH, orthostatic hypotension; MSA, multiple system atrophy; BTX-B, botulinum toxin B; EDS, excessive daytime somnolence.

Studies that failed to meet the criteria but were deemed important for inclusion have been reviewed with reasons for inclusion given. Changes from the 2002 review listed are indicated by a gray background with italicized text, and conclusions that have not changed are listed with a white background.

Results

Drugs to Treat Depression Including Depressive Symptoms in PD

Thirteen new studies were published for the treatment of depression in PD with 11 out of them fulfilling the inclusion criteria for review. For this indication an exception was made to include all randomized controlled trials regardless of patient numbers (see Table 2). The clinical trials reviewed for the treatment of depression used varying inclusion criteria to define depression. Some studies required the presence

of a major depressive episode as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV),⁷⁻¹² which is traditional for depression treatment studies and will result in a sample of patients with depressive symptoms of moderate–severe severity. Other studies enrolled patients either with depressive syndromes of lesser severity (eg, minor depressive episode or dysthymia)¹³⁻¹⁷ or clinically-significant depressive symptoms on the basis of a depression rating scale score.^{18,19}

Dopamine Agonists

In the previous review, dopamine agonists were not examined for the indication of depression in PD.⁵ The role of dopaminergic deficiency in PD depression is illustrated by the common clinical occurrence of *off*-period related depressive symptoms in fluctuating PD.²⁰ This is further demonstrated in a study by Maricle et al.²¹ who have shown anti-anxiolytic and mood brightening short-term effects of levodopa (L-

dopa) infusions in a double-blind, single-dose placebo-controlled study of 8 patients with fluctuating PD. There have also been claims of antidepressant efficacy of the dopamine agonist bromocriptine in a small open-label study.²²

Pramipexole (Three New Studies,^{8,16,18} Conclusion: Efficacious). Barone et al. (2010)¹⁸ conducted a 12-week, randomized, double-blind, placebo-controlled (1:1 ratio), parallel-group trial of pramipexole (0.125–1.0 mg, 3 times per day) in patients with mild-to-moderate PD (Hoehn & Yahr [H&Y] stages 1–3) for the treatment of clinically relevant depressive symptoms. At study entry, motor symptoms had to be under satisfactory control as judged by the local investigator and were treated with L-dopa, amantadine, anticholinergic drugs, catechol-O-methyl transferase (COMT) inhibitors, or monoamine oxidase B (MAO-B) inhibitors whose dosing had to be stable for at least 4 weeks before baseline and had to have remained unchanged during the study. Patients were required to have clinically relevant depressive symptoms, as documented by baseline scores of at least 5 on the 15-item geriatric depression scale (GDS-15; score range 0–15, with higher scores suggesting increasing severity of depressive symptoms) and of at least 2 on part 1, item 3 (depression) of the *Unified Parkinson's Disease Rating Scale* (UPDRS-I). Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) were allowed if the dose was stable for at least 6 weeks before baseline and remained unchanged during the study. Exclusion criteria were presence of motor fluctuations, a Mini-Mental State Examination (MMSE) score < 24, the current use of dopamine agonists, current psychotherapy, and severe depression, defined by the presence of suicidal ideation. Pramipexole-treated patients received a mean daily dose of 2.18 mg (standard deviation [SD] 0.83), and the placebo group received a placebo dose equivalent of 2.51 mg (SD 1.66). The primary efficacy endpoint was the change between baseline and week 12 in total score on the Beck Depression Inventory (BDI) version 1A. All treated patients who had at least 1 postbaseline efficacy assessment were included in the primary analysis (full analysis set [FAS]). Secondary efficacy outcomes included the BDI responder rate (the proportion of patients with at least a 50% reduction in BDI score from baseline) and changes from baseline on the GDS-15; UPDRS-II and -III; Clinical Global Impression-Improvement (CGI-I) scale categories; the Parkinson's disease questionnaire (PDQ-39); European Quality of Life Scale (EUROQOL [EQ]-5D); Snaith-Hamilton pleasure scale (SHAPS), and the 0–10 visual analogue scale for pain. The per-protocol (PP) set included all patients in the FAS who had no important protocol violation (defined as any protocol violation that could

potentially have an effect on efficacy). To differentiate between direct treatment effects on depressive symptoms and effects that were mediated indirectly through alleviation of motor symptoms, a prespecified path analysis with regression models to assess the relation between BDI and UPDRS-III changes was performed. Safety analysis was performed for all patients who received at least 1 dose of the study drug. Of 323 enrolled patients, 296 were randomly assigned to pramipexole or placebo, 287 were included in the primary analysis (139 in the pramipexole group and 148 in the placebo group). BDI scores decreased by an adjusted mean 5.9 (SE 0.5) points in the pramipexole group and 4.0 (0.5) points in the placebo group (difference 1.9; 95% confidence interval [CI], 0.5–3.4; $P = .01$). Thirty-eight of 139 patients in the pramipexole group and 27 of 147 in the placebo group were BDI clinical responders. This corresponded to an odds ratio (OR) of 1.8 (95% CI, 1.0–3.1; $P = .05$). Pramipexole provided significant benefits over placebo with respect to the following other secondary efficacy variables: CGI-I; GDS-15; EUROQOL and UPDRS-II and -III. Forty-six of 139 patients in the pramipexole group were rated as either “much” or “very much improved” on the CGI-I compared with 32 of 148 patients in the placebo group (OR 1.8; 95% CI, 1.2–2.8; $P = .006$). The UPDRS motor score decreased by an adjusted mean of 4.4 (0.6) points in the pramipexole group and 2.2 (0.5) points in the placebo group (difference 2.2; 95% CI, 0.7–3.7; $P = .003$). The PP analyses were consistent with the intention-to-treat (ITT) analyses. Path analysis showed the direct effect of pramipexole on depressive symptoms accounted for 80% of total treatment effect ($P = .04$) and 20% was caused by its effect on motor function. Adverse events (AEs) were reported in 105 of 144 patients in the pramipexole group and 101 of 152 in the placebo group. AEs in the pramipexole group were consistent with the known safety profile of the drug with no pramipexole recipient reporting any AE that suggested development of an impulse control disorder or behaviors related to impulse control disorders. (Quality score, 87%.)

Barone et al. (2006)⁸ conducted a 14-week randomized comparison study of the dopamine agonist pramipexole and the SSRI sertraline for the treatment of a major depressive episode as defined by the DSM-IV and a 17-item Hamilton Depression Rating Scale (HDRS-17) score ≥ 16 . Sixty-seven patients were randomized to flexible doses (1.5 to 4.5 mg every day [qd]) of pramipexole ($n = 33$) or fixed dose (50 mg qd) sertraline ($n = 34$). At study entry patients were required to stabilize from a motor standpoint and were treated with L-dopa. Exclusion criteria were presence of motor fluctuations, current use of dopamine agonists, antipsychotic use, and cardiovascular disease

or symptomatic orthostatic hypotension. The primary outcome measure was the change from baseline in HDRS-17 score. Secondary measures were changes from baseline to endpoint in UPDRS-II and -III, the Zung self-rating depression scale total score and the Medical Outcome Survey Short Form-36 Quality of Life scale (SF-36) total score. Efficacy was assessed by ITT analyses. Overall, 88% of subjects completed the study, 8 subjects withdrew (7 subjects on sertraline, 5 due to AEs, and 1 on pramipexole). At the end of the study the mean daily doses of pramipexole and sertraline in the ITT population were 3.24 ± 1.3 mg and 48.1 ± 5.9 mg, respectively. Overall, HDRS scores declined significantly over the course of treatment ($P < .001$), with no differences between pramipexole (-10.76 ± 5.74) and sertraline (-9.03 ± 7.28) treatment ($P = .005$). The response ($\geq 50\%$ decrease in HDRS score from baseline) rate was similar in the pramipexole- and the sertraline-treated groups (69.7% [$n = 23$] vs 48.5% [$n = 16$], respectively, $P = .08$), but the remission (final HDRS score ≤ 8) rate was higher in the pramipexole-treated group (60.6% [$n = 20$] vs 27.3% [$n = 9$], $P = .006$). Quality of life improved similarly in the 2 groups over the course of treatment. The UPDRS-III score improved over the course of the study in the pramipexole group (5.7 ± 8.5 ; $P < .05$), but not in the sertraline group (0.9 ± 7.2), and the between-group difference for change was significant ($P = .02$). AEs were reported in 9% (dyskinesia, nausea, abdominal pain, and hypothyroidism) of pramipexole- and 24% (vertigo, nausea, anxiety, and abdominal pain) of sertraline-treated patients. (Quality score, 76%.)

Rektorová et al. (2003)¹⁶ conducted an 8-month, randomized, open-label (with blinded rater), parallel-group study in 41 subjects with International Classification of Diseases (ICD-10) diagnoses of mild or moderate depression and fluctuations with or without dyskinesias. Patients were randomized to treatment with pramipexole ($n = 22$) or pergolide ($n = 19$) as add-on therapy to L-dopa. Both medications were flexibly dosed at 1.5 to 4.5 mg/day, resulting in a mean daily dosage of 2.7 ± 0.5 mg for pramipexole and 3.0 ± 0.3 mg for pergolide at study end. Exclusion criteria included significant medical comorbidity, antipsychotic treatment, MMSE ≤ 24 , severe depression, and presence of psychosis or delirium. The primary outcome measure was change from baseline in the Montgomery Asberg Depression Rating Scale (MADRS). Data from study completers ($n = 34$) show a significant ($P < .05$) decrease in MADRS score with pramipexole treatment (15.11–9.28 points), but not with pergolide treatment (11.25–10.06 points). Response ($\geq 50\%$ decrease in MADRS score from baseline) rates were 44% in the pramipexole group and 18.7% in the pergolide group. L-Dopa dosage decreased by 22% (558 ± 275 mg to 458 ± 254 mg) in the pramipexole group and 28% ($709 \pm$

301 mg to 491 ± 218 mg) in the pergolide group over the course of the study. UPDRS motor scores decreased significantly (and to a similar extent) in both groups. Five subjects discontinued study participation (pramipexole, 3; pergolide, 2). The most common AEs in both groups were sleep disturbances, worsening dyskinesias, nausea, orthostatic hypotension, and hallucinations, and between-group differences in AEs were noted only for sleep disturbances (pramipexole 4, pergolide 10). (Quality score, 58%).

Efficacy conclusions. Based on these 3 studies, pramipexole can be rated as efficacious for the treatment of depressive symptoms in PD.

Pergolide (One New Study,¹⁶ Conclusion: Insufficient Evidence). Rektorová et al. (2003)¹⁶ (see above under Pramipexole). (Quality score, 58%.)

Efficacy conclusion. Based on this study, which did not include a placebo arm, there is *insufficient evidence* for pergolide to be rated for the treatment of depression in PD.

Safety Conclusions Related to Dopamine Agonists: See Article on the “Treatments for the Motor Symptoms of PD”. The safety of the different dopamine agonists is evaluated in the EBM review for the treatments of motor symptoms of PD. Although the use of pergolide has an acceptable risk with specialized monitoring—namely, periodic monitoring for the development of valvular disease or fibrosis for the treatment of motor symptoms of PD—the use of pramipexole has an acceptable risk without specialized monitoring.

Tricyclic Antidepressants

In the original 2002 review,⁵ only 2 RCTs were identified for the treatment of depression in PD. One of these two RCTs was of nortriptyline, a tricyclic antidepressant (TCA), which was considered *likely efficacious* for the treatment of depression in PD. Meanwhile, 3 new studies^{7,10,15} were published using TCAs, 1 of which was not placebo-controlled. Another study, comparing amitriptyline and fluoxetine, without using a placebo arm, for the treatment of severely depressed patients found that patients randomized to amitriptyline significantly improved, while those treated with fluoxetine did not.²³ This study was published in Spanish and was therefore not included in this review. As this study did not contain a placebo arm, the efficacy conclusion would not have been changed.

Nortriptyline (One New Study,¹⁵ Conclusion: Likely Efficacious). Menza et al. (2009)¹⁵ conducted a double-blind, randomized, placebo-controlled comparison study of nortriptyline (a TCA) and paroxetine controlled release (CR) (an SSRI) for the treatment of depression in PD. Fifty-two subjects with a DSM-IV

diagnosis of major depressive episode or dysthymia were randomized to receive paroxetine ($n = 18$), nortriptyline ($n = 17$), or placebo ($n = 17$) for 8 weeks. Dosing of active medications was flexible (up to 37.5 mg paroxetine qd and up to 75 mg nortriptyline qd). The mean dosage of active medication was 28.4 mg for paroxetine CR and 48.5 mg for nortriptyline, with the latter dosage being lower than usually given. Exclusion criteria were an MMSE score < 26 , being off $> 50\%$ of the day, or a DSM-IV Axis I diagnosis other than a depressive or anxiety disorder. The primary outcome measures were change from baseline in the HDRS-17 score, and the percentage of responders (defined as $\geq 50\%$ reduction in HDRS-17 score). An ITT approach was applied for analyses. Sixty-five percent (65%) of patients completed the study, with no between-group differences in discontinuation rates. Nortriptyline was superior to placebo regarding change in HDRS-17 score ($P = .002$, effect size 1.20), while paroxetine was not ($P = .165$, effect size 0.51). Response rates favored nortriptyline (nortriptyline 53%, paroxetine 11%, placebo 24%; $P = .024$), and nortriptyline was superior to paroxetine in the planned contrasts of response rates ($P = .034$). Nortriptyline, but not paroxetine, was also superior to placebo on sleep, anxiety, and social functioning outcomes. Both medications were well tolerated, with no differences in study discontinuation rates and cognitive outcomes. Paroxetine CR, but not nortriptyline, was associated with a higher average number of side effects than placebo ($P = .03$), including fatigue and orthostatic hypotension. (Quality score, 82%.)

Efficacy conclusion. Due to the small sample size of this study,¹⁵ nortriptyline remains likely efficacious for the treatment of depression in PD.

Desipramine (One New Study,¹⁰ Conclusion: Likely Efficacious). Devos et al. (2008)¹⁰ conducted a randomized, double-blind, placebo-controlled study of desipramine (a TCA) and citalopram (an SSRI) for the treatment of major depressive disorder (DSM-IV and MADRS ≥ 20). Forty-eight PD patients were randomized to receive desipramine 75 mg qd ($n = 17$), citalopram 20 mg qd ($n = 15$), or placebo ($n = 16$) for 30 days. Exclusion criteria were age ≥ 80 years, duration of PD ≤ 2 years, MMSE score < 27 or Mattis Dementia Rating Scale score < 130 , presence of psychosis, and other psychotropic medications. Dopamine replacement therapies were kept constant throughout the study. The primary outcome measure was change from baseline in MADRS score. The study completion rate was 94%. Both citalopram ($P = .03$) and desipramine ($P = .002$) showed significant improvements in overall MADRS score compared to placebo (effect sizes not given in the original publication). There was no significant worsening in cognitive or motor symptoms with time, but AEs were twice as common under

desipramine compared to the other 2 groups. The most common AEs in the desipramine group were dry mouth, constipation, and hyperhidrosis. (Quality score, 74%.)

Efficacy conclusion. Based on this study, desipramine can be rated *likely efficacious* for the treatment of depression in PD.

Amitriptyline (One New Study,⁷ Conclusion: Insufficient Evidence). Antonini et al. (2006)⁷ compared the effects of low-dose (50 mg qd) sertraline (an SSRI) and low-dose (25 mg qd) amitriptyline (a TCA) on depression and quality of life in 31 PD patients with a DSM-IV diagnosis of major depressive episode in a 12-week, single-blind (blinded assessment of study outcomes), randomized parallel-group study. Patients were randomized to receive either sertraline ($n = 16$) or amitriptyline ($n = 15$); no changes in dopamine replacement therapy were made during the course of the study. Patients with severe motor fluctuations, a history of psychosis or antipsychotic treatment, a diagnosis of dementia or a MMSE score < 24 , and treatment-resistant depression were excluded. The primary outcome measure was response (defined as a $\geq 50\%$ reduction in the HDRS-17 score). Study completion rates were 75% for sertraline and 73% for amitriptyline. AEs causing discontinuation were nausea, confusion, and hypotension in the sertraline group and confusion, visual hallucinations, sleepiness, headache, and tachycardia in the amitriptyline group. The ITT analysis showed a significant reduction in HDRS-17 scores for both arms (sertraline $P < .005$ and amitriptyline $P < .005$). The responder rate was 63% (83.3% for completers) for sertraline and 53% (72.7% for completers) for amitriptyline. Remission rates (defined as an HDRS-17 scale score ≤ 7) were 38% (50% for completers) for all sertraline subjects and 33% (45.4% for completers) of all amitriptyline subjects. Sertraline, but not amitriptyline (values not given in the original publication) was associated with a significant improvement in quality of life as measured by the PDQ-39 scale. No change in UPDRS-III score or MMSE score was found in either group. (Quality score, 60%.)

Efficacy conclusion. Based on this study, which did not include a placebo arm, there is *insufficient evidence* for amitriptyline to be rated for the treatment of depression in PD, although patients randomized to amitriptyline significantly improved compared to baseline.

Safety Conclusions Related to Tricyclic Antidepressants (Conclusions: Acceptable Risk Without Specialized Monitoring). There were no new safety concerns identified in the above reviewed studies, where TCAs were used at moderate doses. One placebo-controlled study comparing desipramine and citalopram for the

treatment of depression in PD reported that AEs were twice as common with desipramine compared to citalopram and placebo with typical antimuscarinic AEs including dry mouth, constipation, and hyperhidrosis being the most common in the desipramine group. In general, TCAs should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, or increased intraocular pressure, as well as patients with cardiovascular disorders. Concomitant treatment of PD patients with TCAs can contribute to psychosis, sedation, and daytime sleepiness, as well as to cognitive dysfunction or delirium when used in patients with PD dementia.

SSRIs

SSRIs are the most commonly used class of drugs to treat depression in PD, and are considered the first-line option for 63% of patients by the North American Parkinson Study Group (PSG) investigators.²⁴ The efficacy of SSRIs in PD-associated depression has been suggested by numerous open-label studies covering a variety of agents (fluoxetine, sertraline, paroxetine).^{5,25} While in the original 2002 review⁵ no RCT using SSRIs to treat depression in PD was considered, 8 new studies using SSRIs have been published since then, 2 of these were not placebo-controlled.

Citalopram (Two New Studies,^{10,12} Conclusion: Insufficient Evidence). Wermuth et al. (1998)¹² conducted a 6-week, randomized, placebo-controlled study of citalopram for the treatment of DSM-III-R major depressive episodes in 37 PD (H&Y stages 1–3) patients with a HDRS score ≥ 13 . Patients were randomized to citalopram ($n = 18$) or placebo ($n = 19$). Exclusion criteria were dementia, other significant psychiatric or medical diseases, and current antidepressant use. The primary outcome measure was change in HDRS score from baseline. Subjects < 65 years received 20 mg/day whereas those 65 years or older received 10 mg/day. The study completion rate was 81%. Overall, there was a significant decrease over time in HDRS score (16.16 ± 3.08 to 11.65 ± 4.89 in the placebo group vs 16.61 ± 3.50 to 11.69 ± 4.50 in the citalopram group), but no significant citalopram treatment effect could be demonstrated using either ITT analysis or completers only. Treatment was well tolerated, with no change over time or between-group difference in UPDRS-III score or Udalvalg for Kliniske Undersøgelser (UKU) side effect scale. (Quality score, 63%.)

Devos et al. (2008)¹⁰ (see above under Tricyclic Depressants).

Efficacy conclusion. Based on these 2 small-sized studies with divergent efficacy results, there is *insufficient evidence* for citalopram to be rated for the treatment of depression in PD.

Sertraline (Three New Studies,^{7,8,11} Conclusion: Insufficient Evidence). Leentjens et al. (2003)¹¹ conducted a

10-week, randomized, placebo-controlled study of sertraline for the treatment of major depressive episodes (DSM-IV) in 12 PD patients. Patients were randomized to sertraline ($n = 6$) or placebo ($n = 6$). The sertraline group started with a dose of 25 mg, which was increased to 50 mg after 1 week. If there was no response within 6 weeks of randomization, the dose was again doubled, to 100 mg. The primary outcome measure was the score on the MADRS: number of responders in the sertraline group and the placebo group with response being defined as at least a 50% reduction of the pretreatment MADRS score and magnitude of response by comparing the changes in MADRS scores during treatment in both groups. Three out of 6 patients from the sertraline group (50%), and 4 of 6 from the placebo group (67%) responded, which was not significant. There was a significant treatment effect in both the sertraline and the placebo groups. However, there was no significant difference in effect between the 2 groups. (Quality score, 40%.)

Barone et al. (2006)⁸ (see above under Pramipexole).

Antonini et al. (2006)⁷ (see above under Tricyclic Depressants).

Efficacy conclusion. Although results appear to be positive in 2 of the studies,^{7,8} lack of a placebo arm in these studies prevents any conclusion on efficacy, thus there is *insufficient evidence* for efficacy.

Paroxetine (One New Study,¹⁵ Conclusion: Insufficient Evidence). Menza et al. (2009)¹⁵ (see above under Tricyclic Depressants).

Efficacy conclusion. Although results appear to be negative, low sample size prevents change in conclusions, which remain *insufficient evidence* for efficacy.

Fluoxetine (Two New Studies,^{13,14} Conclusion: Insufficient Evidence). Fregni et al. (2004)¹⁴ conducted an 8-week, randomized, double-blind, sham stimulation and placebo-controlled study of repetitive transcranial magnetic stimulation (rTMS) versus fluoxetine for the treatment of major or minor depression in PD. Forty-two patients with PD and major depression (DSM-IV), were randomized to rTMS and placebo ($n = 21$) or sham rTMS + fluoxetine ($n = 21$). Exclusion criteria included recent antidepressant use, history of seizures or head trauma, dementia, and psychotic symptoms. Focal rTMS was administered to the left dorsolateral prefrontal cortex with 40 trains of 5 seconds each, using 110% intensity of motor threshold and 15 Hz frequency. Treatments were administered for 10 days during the initial 2-week period of the study. The fluoxetine dose was 20 mg/day for the entire 8-week study period. The primary outcome measures were change from baseline in HDRS and BDI scores. All patients completed the study; only 1 patient was excluded due to an unrelated intestinal infection. The

authors focused on the week 2 outcomes, and reported a significant decrease in depressive symptomatology in both treatment groups, with no between-group differences. Specifically, in the rTMS group the HDRS score decreased by 38% and the BDI score by 32% at week 2; the respective numbers were 41% and 33% in the fluoxetine group. After 2 weeks in each group, 9 patients (43%) were classified as treatment responders (50% reduction in HDRS scores). ITT analysis showed 9 of 22 (41%) and 9 of 21 (43%) treatment responders in the rTMS group and in the fluoxetine group. There was no effect for either treatment on UPDRS motor scores over time. AEs were more common in the fluoxetine + sham rTMS group than the rTMS + placebo group ($P = .03$), but information about specific AEs was not included. (Quality score, 74%.)

Avila et al. (2003)¹³ conducted a 90-day, single-blind (blinded assessment of study outcomes), randomized, parallel-group study to compare the effects of nefazodone (a serotonin antagonist and reuptake inhibitor [SARI]; initial dose 50 mg/day, which was increased to 200–500 mg/day; mean dosage 200 mg/day, range 100–300 mg/day) and fluoxetine (an SSRI; initial dose of 10 mg/day, which was increased to 20–50 mg/day; mean dosage 25 mg/day, range 20–40 mg/day) on depression and motor symptoms in 16 PD patients with a DSM-IV diagnosis of a depressive disorder (either major depression or dysthymic disorder). Patients were randomized to receive either nefazodone ($n = 9$) or fluoxetine ($n = 7$); no changes in dopamine replacement therapy were made during the course of the study. Patients with motor fluctuations, a diagnosis of clinically relevant cognitive dysfunction and a treatment with selegiline were excluded. An exact primary endpoint was not defined. Outcome measures included the BDI, the CGI-S, the UPDRS-II and -III, total UPDRS (II + III), Abnormal Involuntary Movement Scale (AIMS), the H&Y, the Schwab-England Activities of Daily Living Scale, and the UKU. ITT and PP analyses were applied with similar results. Antidepressant treatment was effective in all the patients studied. The BDI scores significantly improved from baseline to the final visit at 90 days in both the nefazodone (BDI: from 23.7 ± 6.9 to 15.2 ± 7.0 ; CGI-S: from 3.7 ± 0.7 to 2.9 ± 0.9 ; both $P < .001$) and the fluoxetine (25.4 ± 6.5 to 15.0 ± 6.5 ; CGI-S: from 4.0 ± 0.7 to 3.0 ± 0.9 ; both $P < .001$) groups, with no significant differences between the 2 treatment groups. Patients on nefazodone showed a significant improvement over time in the total UPDRS ($P = .004$) and in the UPDRS-III ($P = .003$) with none of these scores changing over time in the fluoxetine group. During the first month of treatment, 3 patients discontinued nefazodone treatment due to AEs (increase in tremor, $n = 2$; diarrhea, $n = 1$). A wide variety of minor AEs events were observed, with the most common comprising asthenia, anxiety, orthostatic dizziness, and constipation. (Quality score, 60%.)

Efficacy conclusion. Based on these 2 studies, which did not contain a placebo arm, there is *insufficient evidence* for fluoxetine to be rated for the treatment of depression in PD.

Safety Conclusions Related to SSRIs (Conclusions: Acceptable Risk Without Specialized Monitoring). There were no safety concerns identified in the above reviewed studies. SSRIs, when studied in psychiatric populations, have been found to exhibit an improved safety profile over TCAs with lower incidences of anticholinergic side effects or cardiac arrhythmias. Indeed, 1 placebo-controlled study comparing desipramine and citalopram for the treatment of depression in PD reported that AEs were twice as common in the desipramine compared to the citalopram and placebo groups. Although not reported in the above reviewed studies, SSRIs may, however, worsen PD tremor in some 4% to 5% of patients²⁶ and occasionally parkinsonism.²⁷ Furthermore, there are concerns about the induction of the serotonin syndrome when used in conjunction with the MAO-B inhibitors selegiline and rasagiline. This somewhat loosely defined condition involves hyperpyrexia, tremor, agitation, and other mental status changes and has been found to occur in severe form in 0.24% of PD cases exposed to SSRIs in the presence of the MAO-B inhibitor selegiline in 1 large survey.²⁸ Hyponatremia may be associated with SSRI use, especially in elderly people with low body weight and concomitant use of diuretics, thought to be secondary to the development of the syndrome of inappropriate antidiuretic hormone (SIADH), with the incidence varying from 0.5% to 32%.²⁹

Newer Antidepressants

So far there are very limited data to actually support the efficacy or safety of newer antidepressant agents. Two new studies were published, 1 on a selective norepinephrine reuptake inhibitor (NRI)¹⁹ and another with a SARI¹³; the latter study was not placebo-controlled.

Atomoxetine (One New Study,¹⁹ Conclusion: Insufficient Evidence). Weintraub et al. (2010)¹⁹ conducted an 8-week, randomized, placebo-controlled study of atomoxetine (an NRI) for the treatment of clinically significant depressive symptoms in 55 subjects with PD and moderate depression as defined by a score of ≥ 22 on the Inventory of Depressive Symptomatology-Clinician (IDS-C; 30-items, scores 0–84, increasing scores indicating greater depression severity). Patients were randomized to receive atomoxetine ($n = 28$; target dosage 80 mg/day) or placebo ($n = 27$). Exclusion criteria included deep brain stimulation within the previous 6 months, current use of MAO inhibitors and an MMSE < 15 . The 2 primary measures of

depression treatment response included a >50% decrease in IDS-C score from baseline and a CGI-I score of 1 or 2. Secondary outcomes included changes in the MMSE to assess global cognition, the Epworth sleepiness scale (ESS) to assess daytime sleepiness, State Anxiety Inventory (STAI) to assess anxiety, the Apathy Scale (AS) to assess apathy, and the UPDRS-III to assess motor function. Statistical analysis was performed using ITT modeling procedures. Possible AEs were assessed using the Treatment Emergent Symptoms Scale. Completion rates for the atomoxetine and placebo patients were 79% and 78%, respectively. Of the study completers, 97.7% (42/43) were taking 80 mg/day of atomoxetine or a placebo equivalent at the final visit. There were no significant between-group differences in the priori-defined depression response rates. Atomoxetine and placebo groups did not differ in response rates on the IDS-C at 8 weeks (22.7% vs 9.5% for atomoxetine and placebo; OR 2.79; 95% CI, 0.48 to 16.33; $P = .25$) as well as on the CGI-C (45.5% and 33.3% for atomoxetine and placebo; OR 1.67; 95% CI, 0.48 to 5.74; $P = .42$). Using a more liberal response criterion of >40% decrease in IDS-C score from baseline, there was a trend for atomoxetine-treated patients to have a superior response (31.8% vs 9.5%; OR 4.43; 95% CI, 0.80 to 24.54; $P = .08$). Patients receiving atomoxetine experienced significantly greater improvement in global cognition with a mean group difference in MMSE change from baseline of 1.31 (standard error [SE] 0.41, $P = .003$) and in daytime sleepiness with a mean group difference in ESS change from baseline of -2.90 (SE 0.83, $P = .001$). There was a trend for greater reduction in anxiety with a mean group difference of STAI change from baseline of -4.69 (SE 2.62, $P = .08$). There were no between-group differences in UPDRS motor scores throughout the course of the study ($P = .87$). Atomoxetine was well tolerated. Constipation (25.9%) was the most common AE in atomoxetine-treated patients and more common than in placebo-treated patients ($P = .05$). (Quality score, 88%.)

Efficacy conclusion. Although results appear to be negative, low sample size means that there is *insufficient evidence* to conclude on efficacy.

Safety conclusion related to atomoxetine, a selective norepinephrine reuptake inhibitor (conclusion: acceptable risk without specialized monitoring). There were no safety concerns identified in the above reviewed study on atomoxetine in PD-associated depression.

Nefazodone (One New Study,¹³ Conclusion: Insufficient Evidence). Avila et al. (2003)¹³ (see above under SSRIs)

Efficacy conclusion. Based on this study, which did not contain a placebo arm, there is insufficient evi-

dence for nefazodone to be rated for the treatment of depression in PD.

Safety conclusion related to nefazodone, a serotonin antagonist and reuptake inhibitor (conclusion: unacceptable risk). There were no safety concerns identified in the above reviewed study on nefazodone in PD-associated depression. Its sale however was discontinued in 2003 in several countries due to the rare incidence of hepatotoxicity, which could lead to the need of a liver transplant, or even death. The incidence of severe liver damage is approximately 1 in every 250,000 to 300,000 patient-years. Periodic serum transaminase testing has not been proven to prevent serious hepatic injury but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery, and patients should be advised to be alert for signs and symptoms of liver dysfunction (such as jaundice, anorexia, gastrointestinal complaints, malaise).³⁰ As there are other antidepressants available, the safety conclusion is *unacceptable risk* of life-threatening hepatotoxicity.

Alternative Therapies

Omega-3 Fatty-Acids (One New Study,⁹ Conclusion: Insufficient Evidence). Da Silva et al. (2008)⁹ conducted a randomized, double-blind, placebo-controlled 12-week study of omega-3 fatty-acids for the treatment of a major depressive episode (DSM-IV) in PD. Thirty-one subjects were randomized to receive omega-3 (each capsule containing 180 mg eicosapentaenoic acid [EPA] and 120 mg docosahexaenoic [DHA] and tocopherol; $n = 14$ completers) or placebo ($n = 15$ completers). Randomization was stratified on the basis of current antidepressant use, creating four treatment blocks. Exclusion criteria included H&Y stage ≥ 3 , cognitive impairment or dementia, antidepressant duration of ≤ 1 year (if applicable), and substance abuse. The primary outcome measures were changes from baseline on the MADRS, BDI, and CGI scales. Two patients dropped out of the study, 1 due to collateral effects of supplementation (no further details are given in the original publication) and 1 due to a general worsening in health status. These patients were excluded from the efficacy analysis. When examining study completers, omega-3 supplementation was superior to placebo in reducing depression severity based on the MADRS ($P = .01$) and the CGI ($P = .02$) with no significant difference in BDI score ($P = .26$). Response ($\geq 50\%$ decrease in MADRS score from baseline) rates were 42% in the omega-3 group and 6% in the placebo group ($P = .08$). There was no mention of AEs. (Quality score, 64%.)

Efficacy conclusion. Based on this small-sized, low-quality study, there is *insufficient evidence* for omega-3 fatty acids to be rated for the treatment of depression in PD.

Safety conclusion related to omega-3 fatty acids (conclusion: acceptable risk without specialized monitoring). There were no safety concerns identified in the above reviewed study on omega-3 fatty-acids in PD-associated depression.

Nonpharmacological Interventions

Nonpharmacological interventions for the treatment of depression in PD comprise electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and psychotherapy. The latter was not reviewed in the original 2002 EBM review. No new RCTs using ECT have been published since the original review. Two new RCTs using rTMS for depression in PD fulfill this review's inclusion criteria.^{14,17} In addition, one RCT³¹ using psychodrama to evaluate whether an improvement in quality of life would decrease the symptoms of anxiety and depression was published. The study showed significant positive changes in the psychotherapeutic intervention group for depression, anxiety, and quality of life in comparison to the control group. Because inclusion criteria did not specify if patients had depressive symptoms or if they had anxiety, this study was not included for review.

rTMS (Two New Studies,^{14,17} Conclusion: Insufficient Evidence). Fregni et al. (2004)¹⁴ (see above under Fluoxetine).

Pal et al. (2010)¹⁷ conducted a double-blind, sham stimulation RCT of rTMS for the treatment of depression in PD. Twenty-two patients with PD and mild to moderate depression (DSM-IV criteria) were randomized to rTMS (n = 12) or sham rTMS (n = 10). Exclusion criteria included antidepressant use within 2 months of the study beginning, history of seizures or dementia, and presence of any implanted cardiac pacemaker or deep brain stimulator. Focal rTMS was administered to the left dorsolateral prefrontal cortex with 12 trains of 10 seconds each, using 90% intensity of motor threshold and 5 Hz frequency. Treatments were administered for 10 days. Outcome measures were evaluated at baseline as well as 1 day (short-term effects) and 30 days (long-term effects) after the treatment session by an investigator blinded to the treatment. All of the enrolled patients finished the study protocol. No side effects occurred in the treated group except for a mild transient headache (n = 2). This study had no predefined primary endpoint and no correction for multiple testing. Efficacy variables included the MMSE, BDI, and MADRS, treatment responders on the MADRS (ie, at least 2 points improve-

ment on MADRS 30 days after the rTMS treatment), the Stroop and Trail-making tests, the UPDRS including the H&Y, and the Schwab and England scale, a timed up and go (TUG) test, the visual analogue scale (VAS) for quality of life, as well as the ESS. In the actively treated group only there was a significant (for all $P < .05$) improvement on the depression rating scales at days 1 and 30. In the actively treated group the BDI score decreased from 9.0 ± 4.5 to 5.0 ± 4.0 at day 1 and to 5.0 ± 4.5 at day 30, and the MADRS score decreased from 11.5 ± 13.5 to 10.0 ± 6.5 at day 1 and to 8.5 ± 3.5 at day 30; the respective numbers were from 9.5 ± 6.0 to 8.0 ± 7.0 at day 1 and to 8.5 ± 6.0 at day 30 as well as from 12.0 ± 14.0 to 11.5 ± 7.0 at day 1 and to 11.0 ± 5.0 at day 30 in the sham-treated group. Between-group differences and comparisons were not given. The number of treatment responders in the actively treated group was significantly higher (P value not given, n = 9, 75%) than in the sham group (n = 2, 20%). (Quality score, 78%.)

Efficacy conclusion. Based on these 2 studies (the study by Fregni et al.¹⁴ [2004] did not contain a placebo plus sham rTMS arm; the study by Pal et al.¹⁷ [2010] had no predefined primary endpoint, no correction for multiple testing and did not analyze between-group differences), there is *insufficient evidence* for rTMS to be rated for the treatment of depression in PD.

Safety conclusion related to transcranial magnetic stimulation (conclusion: acceptable risk without specialized monitoring). There were no new safety concerns identified in the above reviewed study on rTMS in PD-associated depression, and therefore rTMS is still considered to have an acceptable risk without specialized monitoring).

Treatment of Depression Including Depressive Symptoms in PD—Summary and Practice Implications

The practice implications for the treatment of depression in PD are summarized in Table 3. Several of the drugs for the treatment of depression in PD, including the TCAs desipramine and amitriptyline, the SSRIs citalopram, sertraline, and fluoxetine, the newer antidepressants atomoxetine and nefazodone, and the dopamine agonists pramipexole and pergolide, as well as Ω -3 fatty acids, were not previously reviewed. All but 2 studies (8 months in the study by Rektorová et al. (2003)¹⁶ and 6 months in the study by Sproesser et al. 2010)³¹ did not exceed the study durations of 3 months. Therefore, all recommendations given here are for the short-term treatment of depression in PD. Furthermore, varying inclusion criteria have been used to define depression across the different studies. Additional research is needed to further delineate and validate depression subtypes in PD.

TABLE 3. Conclusions on drugs to treat depression including depressive symptoms^a in PD

	Efficacy	Safety	Practice implications
Dopamine agonists			
Pramipexole	<i>Efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Clinically useful</i>
Pergolide	<i>Insufficient evidence</i>	<i>Acceptable risk with specialized monitoring</i>	<i>Not useful</i>
TCA			
Nortriptyline	<i>Likely efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Possibly useful</i>
Desipramine	<i>Likely efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Possibly useful</i>
Amitriptyline	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational^b</i>
SSRIs			
Citalopram	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational^b</i>
Sertraline	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational^b</i>
Paroxetine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational^b</i>
Fluoxetine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational^b</i>
MAO-Inhibitors			
Moclobemide	Insufficient evidence	Insufficient evidence ^c	Investigational ^d
Selegiline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Newer antidepressants			
Atomoxetine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Nefazodone	<i>Insufficient evidence</i>	<i>Unacceptable risk</i>	<i>Not useful</i>
Alternative therapies			
Ω-3 fatty acids	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Nonpharmacological interventions			
rTMS	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
ECT	Insufficient evidence	Insufficient evidence	Investigational

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.

^aThe clinical trials reviewed for the treatment of depression used varying inclusion criteria to define depression.

^bWhile the EBM review in 2002 (Goetz et al.⁵) referred to evidence for antidepressant efficacy in non-PD major depression as a criterion for the practical implications for clinical use also in PD, the current recommendations are based solely on evidence available from RCTs performed in PD depression.

^cCombined treatment with either TCAs or SSRIs carries an unacceptable risk.

^dCombined treatment with either TCAs or SSRIs is unacceptable.

PD, Parkinson's disease; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy; EBM, evidence-based medicine; RCT, randomized controlled trial; MAO-I, MAO-inhibitors.

Although such subtypes might differentially respond to treatment, the recommendations given here do not distinguish between the varying inclusion criteria used. While the EBM review in 2002⁵ referred to evidence for the efficacy of antidepressants in treating non-PD major depression as a criterion for the practical implications for their clinical use in PD, the current recommendations are based solely on evidence available from RCTs performed in patients with PD depression.

Desipramine and nortriptyline are *likely efficacious* for the treatment of depression in PD. There is *insufficient evidence* of amitriptyline for the treatment of depression in PD. Safety conclusions are that TCAs have an *acceptable risk* without specialized monitoring. Based on the available evidence, the practice implications are that treatment of depression with desipramine and nortriptyline is *possibly useful* and treatment with amitriptyline is *investigational*.

There is *insufficient evidence* for all the SSRIs reviewed (paroxetine, citalopram, sertraline, and fluoxetine) for the treatment of depression in PD. Safety conclusions are that all SSRIs reviewed have an *acceptable risk without specialized monitoring*, and the practice implications are that they are *investigational* for the treatment of depression in PD.

There is insufficient evidence of the newer antidepressants atomoxetine and nefazodone for the treatment of depression in PD. Atomoxetine is considered to have an *acceptable risk without specialized monitoring*, while nefazodone has an *unacceptable risk*. The practice implications are that atomoxetine is *investigational* and that nefazodone is *not useful* for the treatment of depression in PD.

Pramipexole is *efficacious* for the treatment of depressive symptoms in PD. There is *insufficient evidence* regarding pergolide. Pramipexole is considered to have an *acceptable risk without specialized monitoring*, while pergolide has an *acceptable risk with specialized monitoring*. Based on the available evidence, the practice implications are that treatment of depressive symptoms with pramipexole is considered *clinically useful* and that due to safety reasons, treatment of depression with pergolide is considered *not useful* for chronic use.

There is *insufficient evidence* of Ω-3 fatty acids for the treatment of depression in PD. They are considered to have an *acceptable risk without specialized monitoring*. Practice implications are that they are *investigational* in this indication.

There is *insufficient evidence* of rTMS for the treatment of depression in PD. Safety conclusions are that rTMS has an acceptable risk without specialized monitoring. There is no change in the practice implications that rTMS is investigational for the treatment of depression in PD.

Drugs to Treat Fatigue in PD

Drugs to treat fatigue in PD were not included in the previous review. Three studies^{32–34} were published for the treatment of fatigue in PD with 1 of them fulfilling the inclusion criteria for review. For this indication an exception was made to include all randomized controlled trials regardless of patient numbers (see Table 2).

Methylphenidate (One New Study,³² Conclusion: Insufficient Evidence). Mendonça et al. (2007)³² examined the effects of methylphenidate (30 mg qd) for the treatment of fatigue in PD in a double-blind, placebo-controlled parallel-group RCT. Thirty-six patients with idiopathic PD, on stable antiparkinsonian medications, and with a score ≥ 27 on the Fatigue Severity Scale (FSS; scores 0–54, higher scores indicate greater fatigue) were randomized to receive either methylphenidate 10 mg 3 times per day (tid) ($n = 17$) or matching placebo ($n = 19$) for 6 weeks. Exclusion criteria included psychoactive drugs that might interfere with stimulant functioning, active depression on clinical interview, active substance abuse, and objective weakness or fatigability on physical exam. Primary outcome measures were change from baseline on 2 separate self-report fatigue questionnaires: the FSS and the Multidimensional Fatigue Inventory (MFI; scores 0–80, higher scores indicate greater fatigue). Secondary outcomes included change in UPDRS motor score and change in the 5 subscores of the MFI. ITT analysis was applied. Eighty-two percent (82%) of methylphenidate-treated patients and 84% of placebo-treated patients completed the study on randomized treatment. Both FSS (mean change, 6.5 points; 95% CI, 0.5–12.4; effect size, 0.79) and MFI (mean change, 8.4 points; 95% CI, 0.7–16.0; effect size, 0.63) scores were reduced significantly in the treatment arm over the course of the study ($P < .04$), and the placebo group did not experience a significant decline (FSS: mean change, 1.9, 95% CI, –3.4 to 7.2; MFI: mean change, 48.5, 95% CI, –4.1 to 10.5) over the course of treatment; however, statistical analysis for the 2 primary outcome measures was not corrected for multiple comparisons and no direct comparison of methylphenidate and placebo treatment was made. Examining MFI subscores (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue), the methylphenidate group experienced a significant reduction only in general fatigue with treatment ($P < .001$). There were no changes in UPDRS

motor scores over the course of the study in either group. Side effects and the frequency of occurrence were similar between the 2 treatment arms. (Quality score, 74%.)

Efficacy Conclusion. Although results appear to be positive, the quality score of 74% and methodological concerns (the study had no correction for multiple testing and did not analyze between-group differences) mean that there is *insufficient evidence* for efficacy.

Safety Conclusion Related to Methylphenidate (Conclusion: Insufficient Evidence). There were no safety concerns identified in the above reviewed study on methylphenidate for the treatment of fatigue in PD. Methylphenidate, however, has the potential for abuse³⁵ and concerns have been raised that long-term therapy might cause drug dependence, psychotic symptoms and behavioral sensitization, similar to other stimulants.³⁶ The fact that methylphenidate is a controlled substance in most countries, and that there are a lack of safety data, especially over the long-term, concerning methylphenidate's cardiovascular effects—including increase of blood pressure or elevated heart rate in elderly populations,³⁷ mean that there is *insufficient evidence* to make conclusions on its safety.

Modafinil (Two New Studies,^{33,34} Conclusion: Insufficient Evidence). There were 2 randomized placebo-controlled trials using modafinil to treat fatigue in PD. Although neither study fulfills inclusion criteria (inadequate patient numbers), they were included in this review as they were the only trials available that studied modafinil for this indication.

Lou et al. (2009)³³ conducted a randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy of modafinil for the treatment of fatigue in PD. Nineteen patients with PD and an MFI Score ≥ 48 were randomized to receive modafinil 100 mg 2 times per day (bid) ($n = 9$) or placebo ($n = 10$) for 8 weeks. Patients with other neurological or medical disorders that might cause excessive fatigue were excluded. None of the patients who participated in the study had motor fluctuations. Three subjects randomized to receive active treatment dropped out due to AEs. These subjects were not included in the analysis. An exact primary outcome measure was not given, but overall outcome measures included MFI for subjective fatigue and finger tapping and intermittent force generation for physical fatigability. The ESS and the Center of Epidemiological Study-Depression scales were also used. After 2 months, the modafinil group showed a higher tapping frequency ($P < .05$), shorter dwell time ($P < .05$), and less fatigability in finger tapping and tended to have lower ESS scores than the placebo group. However, there was no significant difference between groups over time for any dimension of the MFI. (Quality score, 50%.)

Tyne et al. (2010)³⁴ conducted a 9-week double-blind, placebo-controlled, parallel-group RCT of modafinil in patients with PD for the treatment of fatigue. Thirteen patients with PD, on stable antiparkinsonian medications, with a score > 4 on the Fatigue Severity Index (FSI; scores 0–54, higher scores indicate greater fatigue) were randomized to either modafinil (titrated up to 400 mg/day) (n = 6) or matching placebo (n = 7). Modafinil was up-titrated over 4 weeks to a maximum of 400 mg/day with increments of 100 mg/week given once daily. A 5-week maintenance phase followed before reassessment. Exclusion criteria included psychoactive drugs that might interfere with stimulant functioning, and active depression as assessed by the Hospital Anxiety and Depression ScaleM (HADS). Primary outcome measures were change from baseline to end of maintenance phase on the FSI, which includes the FSS as a shorter form. Further outcome measures included the CGI, the UPDRS, and the ESS. Statistical analysis was performed on all patients included. No statistically significant differences in the change in FSI (modafinil: median at baseline 5.6 and at end of maintenance 5.4; placebo: median at baseline 5.1 and at end of maintenance 4.7; $P = 1.0$) and FSS (modafinil: median at baseline 6.1 and at end of maintenance 5.7; placebo: median at baseline 5.4 and at end of maintenance 5.1; $P = .312$) between the 2 groups were found. A moderate or marked improvement in fatigue, as measured with the CGI fatigue, was reported in 67% of patients in the active group compared to the 29% in the placebo arm ($P = .29$). There was a small significant change in the ESS from baseline to week 9 ($P < .05$) in the modafinil group. No significant change was seen in any safety measure. (Quality score, 58%.)

Efficacy Conclusion. Based on these 2 studies, there is *insufficient evidence* for modafinil to be rated for the treatment of fatigue in PD.

Safety Conclusion Related to Modafinil (Conclusion: *Insufficient Evidence*). There were no new safety concerns identified in the above reviewed studies on modafinil for the treatment of fatigue in PD. Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in adults and children in worldwide postmarketing experience. Estimates of the incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.³⁸ Psychiatric AEs have been reported in patients treated with modafinil with many, but not all, patients having had a prior psychiatric history; postmarketing AEs associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation, and aggression, some resulting in hospitalization.³⁸

TABLE 4. Conclusions on drugs to treat fatigue in PD

	Efficacy	Safety	Practice implications
Methylphenidate	<i>Insufficient evidence</i>	<i>Insufficient evidence</i>	<i>Investigational</i>
Modafinil	<i>Insufficient evidence</i>	<i>Insufficient evidence</i>	<i>Investigational</i>

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds. PD, Parkinson's disease.

The lack of safety data, especially over the long term, concerning modafinil's cardiovascular effects—including increase of blood pressure or elevated heart rate in elderly populations,³⁷ mean that there is *insufficient evidence* to make conclusions on its safety.

Treatment of Fatigue in PD—Summary and Practice Implications

The practice implications for the treatment of fatigue in PD are summarized in Table 4. Treatment of fatigue in PD was not previously reviewed. None of the studies exceeded 8 weeks. Therefore, all recommendations given here are for the short-term treatment of fatigue in PD.

There is *insufficient evidence* for both the efficacy and safety of methylphenidate and modafinil for the treatment of fatigue in PD. Based on the available evidence, the practice implications are that treatment of fatigue with both methylphenidate and modafinil is *investigational* for the treatment of fatigue in PD.

Drugs to Treat Medication-Related Impulse Dyscontrol and Abnormal Repetitive Behaviors in PD

Drugs to treat medication-related impulse dyscontrol and abnormal repetitive behaviors in PD were not included in the previous review. One study³⁹ was published for the treatment of pathological gambling in PD. For this indication an exception was made to include all randomized controlled trials regardless of patient numbers (see Table 2).

Amantadine (One New Study,³⁹ Conclusion: *Insufficient Evidence*). Thomas et al. (2010)³⁹ conducted a 17-week, double-blind randomized placebo-controlled crossover study to investigate the effect of amantadine 200 mg daily (100 mg bid) on pathological gambling in PD. Seventeen PD patients with severe pathological gambling—that did not decrease when dopamine agonist treatment was reduced or stopped, or when behavioral strategies were used—were included in this study. Pathological gambling was identified according to DSM-IV and South Oaks Gambling Scale (SOGS) criteria. Patients affected by manic episodes or bipolar disorders as well as patients on antipsychotics or

anticholinergic agents were excluded. Pathological gambling was quantified by blinded raters with the Gambling-Symptom Assessment Scale (G-SAS) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Daily diaries assessed the time spent gambling as well as gambling cost per day. The study consisted of a 4-week placebo run-in period followed by 2 sequential 4-week treatment periods, with a washout period of 1 week in-between and a consecutive 4-week open-label follow-up period. For statistical analysis, an intention to treat model was applied. Five patients dropped out due to side effects (confusion, orthostatic hypotension, insomnia, and visual hallucinations). In these patients the worst score attained on the G-SAS and Y-BOCS during the run-in phase was considered as the score at the end of the study. No carryover effect was observed. The existence of a period effect was not tested. G-SAS and Y-BOCS scores during amantadine treatment were reduced by 80% compared to baseline, whereas no change occurred during placebo treatment. In the amantadine arm the G-SAS score decreased significantly from 31.2 ± 0.7 to 5.6 ± 0.8 ($P < .001$), and the Y-BOCS score decreased significantly from 28.5 ± 0.6 to 4.5 ± 0.7 ($P < .001$); the respective numbers were from 31.3 ± 0.7 to 29.5 ± 0.7 ($P =$ not significant [NS]) as well as from 28.8 ± 0.6 to 27.9 ± 0.6 ($P =$ NS) in the placebo arm. Differences between treatment arms in the crossover study were statistically significant. (G-SAS: $P < .001$; Y-BOCS: $P < .001$). (Quality score, 72%.)

Efficacy Conclusion. Based on this small-sized, low-quality study, there is *insufficient evidence* for amantadine to be rated for the treatment of pathological gambling in PD.

Safety Conclusion Related to Amantadine (Conclusion: Acceptable Risk Without Specialized Monitoring). No new safety issues were reported. The safety of the amantadine is evaluated in the EBM review for the treatments of motor symptoms of PD. There are case reports of reversible corneal edema in PD patients on amantadine.⁴⁰ To date, routine ophthalmological monitoring is not currently recommended for patients using amantadine but clinicians need to be vigilant to patients reporting sudden visual changes. One study has demonstrated that amantadine use in PD is associated with impulse control disorders in general, and with compulsive gambling, buying, and sexual behavior in particular.⁴¹

Treatment of Medication-Related Impulse Dyscontrol and Abnormal Repetitive Behaviors (Pathological Gambling) in PD - Summary and Practice Implications

The practice implications for the treatment of pathological gambling in PD are summarized in Table 5. Treatment of pathological gambling in PD was not

TABLE 5. Conclusions on drugs to treat pathological gambling in PD

	Efficacy	Safety	Practice implications
Amantadine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds. PD, Parkinson's disease.

previously reviewed. The study did not exceed 4 weeks. Therefore, all recommendations given here are for the short-term treatment of pathological gambling in PD.

There is *insufficient evidence* for the efficacy of amantadine for the treatment of pathological gambling in PD. Safety conclusions are that the amantadine has an *acceptable risk without specialized monitoring*. Based on the available evidence, the practice implications are that treatment of pathological gambling with amantadine is *investigational* for the treatment of fatigue in PD.

Drugs to Treat Dementia

At the time of the first EMB review in 2002, no RCT had been published for the treatment of dementia in PD. More recently, efficacy and safety of the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine as well as of memantine, a low-affinity antagonist to glutamate NMDA receptors, have been evaluated in 8 RCTs. Six fulfilled this review's inclusion criteria, but all studies are discussed (see Table 2) because so little overall information exists on the treatment of cognitive impairment in PD.

Acetylcholinesterase Inhibitors

Donepezil (Three New Studies,⁴²⁻⁴⁴ Conclusion: Insufficient Evidence). Two crossover^{42,43} RCTs and 1 parallel-group placebo-controlled RCT⁴⁴ have examined donepezil in patients with PD and dementia. All of them included small numbers of patients ranging from 14 to 22.

Aarsland et al. (2002)⁴² assessed the efficacy of donepezil in a double-blind, placebo controlled, crossover setting with 2 sequential treatment periods lasting 10 weeks each without any washout period between the treatment periods. Study drug doses started at 5 mg/day and, if tolerated, increased to 10 mg/day after 6 weeks. Fourteen patients with PD, who developed dementia (DSM-IV criteria) at least 1 year after the onset of motor symptoms and who had an MMSE score of 16 to 26, were included in the trial. In the first treatment period, 8 patients were allocated to the donepezil group and 6 to the placebo group. Primary outcome variables included the MMSE, the clinician

interview based impression of change (CIBIC+), and the motor section of the UPDRS (UPDRS-III). Further outcome variables included the Neuropsychiatric Inventory (NPI) and a battery of neuropsychological tests. Carryover or residual effects were not observed. Patients were included in the efficacy analysis if they had both a baseline score and at least 1 score after baseline (last observation carried forward [LOCF]). Two patients (14%, both on donepezil) withdrew from the study because of AE (dizziness, nausea, and diarrhea) before the evaluation at week 6 of the first study period. The remaining 12 completed the study and were included in the final analyses. After 10 weeks of treatment, patients on donepezil had MMSE change scores from baseline (increase by 2.1 ± 2.7 points, mean \pm SD) compared with those on placebo (increase by 0.3 ± 3.2 points; $P = .013$). At 10 weeks of treatment, the mean (\pm SD) CIBIC+ score was 3.3 ± 0.9 on donepezil and 4.1 ± 0.8 on placebo ($P = .034$) and in the responder analysis, 42% of the patients on donepezil and 17% on placebo were rated as improved (ie, a CIBIC+ score ≤ 3). This analysis handled missing data on the CIBIC+ (3 patients) as no change for the primary analysis. After 10 weeks of treatment, patients on donepezil had lower CIBIC+ and higher MMSE scores (compared to baseline) than those on placebo, indicating improvement under donepezil treatment. However, 3 patients had missing data on the CIBIC+ (2 at week 6 and 1 at week 16). These data points were coded as no change for the primary analysis. At 10 weeks of treatment, the mean (\pm SD) MMSE score was increased by 2.1 ± 2.7 points on donepezil and 0.3 ± 3.2 points on placebo ($P = .013$), and the mean (\pm SD) CIBIC+ score was 3.3 ± 0.9 on donepezil and 4.1 ± 0.8 on placebo ($P = .034$). Indeed, after 10 weeks of treatment, 5 (42%) patients on donepezil and 2 (17%) on placebo were rated as improved (ie, a CIBIC+ score ≤ 3). Reanalysis of the data without recoding the missing CIBIC+ data points, thereby excluding data from the 3 cases from the analysis, resulted in a P value of .79 for the comparison of the CIBIC+ between donepezil and placebo. Analysis of the UPDRS-III scores from both groups did not reveal any significant change of motor function in either group. Furthermore, no significant treatment effects were observed with regard to any of the NPI items. The number of patients reporting an AE was 10 out of 14 (71%) for donepezil and 9 out of 12 (75%) for placebo. There were 2 dropouts in the donepezil group due to the occurrence of peripheral cholinergic AEs (dizziness, nausea, and diarrhea). (Quality score, 82%.)

Ravina et al. (2005)⁴³ conducted a double-blind, placebo-controlled, crossover trial to assess donepezil in 22 patients with PD and dementia. There were 2 sequential 10-week treatment periods, with a washout period of 6 weeks between. Patients with PD were included if they fulfilled the DSM-IV criteria for dementia, if they developed cognitive decline at least 2

years after the onset of motor symptoms and if they had an MMSE ranging from 17 to 26. Donepezil was started at 5 mg/day and increased, if tolerated, to 10 mg/day after 4 weeks. The primary outcome measure was the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog); secondary outcome measures included the MMSE and the MDRS. Further efficacy variables were the Clinical Global Impression of Change (CGI-C), the Brief Psychiatric Rating Scale (BPRS), and the UPDRS. Missing data were imputed using the LOCF. There were no significant carryover effects between treatment periods. A nonsignificant improvement on the ADAS-Cog of 1.9 points (SE 1.4) was reported with donepezil compared to placebo. On donepezil the mean (\pm SD) scores on the ADAS-Cog were 22.5 (6.9) compared to 24.4 (± 9.4) on placebo ($P = .18$). Furthermore, there were no treatment effects on the MDRS and its subscores. On the other hand, MMSE scores were significantly higher (ie, improved) on donepezil compared with placebo ($P = .004$). This difference was 2.0 (SE 0.61) points. On donepezil the mean (\pm SD) scores on the MMSE at follow-up were 24.5 (3.2) compared to 22.5 (4.7) on placebo. Donepezil significantly improved CGI scores by (0.37 points); no treatment effect as recorded on the BPRS, total UPDRS, or on the UPDRS-III. In the first period, 2 subjects on donepezil (worsening psychosis and worsening arrhythmia) and 1 on placebo (worsening psychosis) withdrew from the study. In the second period, 2 patients discontinued the use of donepezil and 1 patient discontinued the use of placebo. The number of patients reporting an AE was 52% (11/21) for donepezil and 45% (9/20) for placebo. Worsening psychosis and agitation were the most common AEs occurring in 5 patients in each treatment arm. (Quality score, 70%.)

Leroi et al. (2004)⁴⁴ randomized 7 patients to receive donepezil (2.5–10 mg/day, mean 6.4 mg/day) and 9 patients to receive placebo in an 18-week double-blind, placebo-controlled, parallel-group RCT. Patients with PD were included if they fulfilled the DSM-IV criteria for dementia and if they had an MMSE ≥ 10 . The primary efficacy outcomes included several neuropsychological battery tests that assessed global cognitive status as well as memory, attention, psychomotor speed, and visuospatial and executive functions; secondary efficacy outcomes included psychiatric symptoms and activities of daily living rating scales. The UPDRS was used to assess motor function. Apart from a slight but significant improvement in the dementia rating scale (DRS) memory subscale after 18 weeks, no statistically significant difference in any of the other outcome variables was found between the 2 treatment groups. Ten of the 16 patients (62.5%) completed the trial. A total of 6 patients withdrew from the trial due to AEs, 5 (71.4%) from the donepezil group (these included relapse of a preexisting mood

disorder, acute diplopia, light-headedness, constipation, nausea and vomiting, hypersalivation, rhinorrhea, urinary frequency, and worsening of motor symptoms [gait impairment, increased number of falls, increased tremor]—and 1 (11.1%) from the placebo group due to diarrhea, disorientation, and visual hallucinations. Even though worsening of motor symptoms was reported as an AE in the donepezil group, no significant group differences on the UPDRS could be detected. (Quality score, 63%.)

Efficacy conclusion. Based on these 3 studies with small sample sizes and conflicting results, there is *insufficient evidence* for donepezil to be rated for the treatment of dementia in PD. Indeed, 2 studies^{42,43} seem to be positive. However, 1 of these studies was positive for 1 of the 2 primary endpoints only⁴² and the other study⁴³ failed to have positive results for the primary endpoint.

Rivastigmine (One New Study,⁴⁵ Conclusion: Efficacious). Emre et al. (2004)⁴⁵ in a multicenter, parallel-group, double-blind placebo-controlled trial sought to determine the efficacy of rivastigmine in treating dementia in 541 patients with PD and dementia. Inclusion criteria were mild to moderate dementia (DSM-IV), due to PD with MMSE between 10 and 24; cognitive decline occurring at least 2 years after onset of PD motor symptoms. Patients were randomized in a 2:1 ratio to receive either rivastigmine (n = 362) or placebo (n = 172). Study drug doses were increased by 3 mg/day at intervals of at least 4 weeks during a 16-week dose-escalation period with the highest well-tolerated dose for each patient being maintained for the rest of the study. The mean dose of rivastigmine was 8.6 mg/day at the end of the dose-escalation phase, which remained stable throughout the maintenance phase. More than one-half of the patients (n = 201, 55.5%) were receiving 9 to 12 mg/day of rivastigmine. Primary efficacy variables included the scores for the cognitive subscale of the ADAS-cog and the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC). Secondary outcomes comprised the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), the 10-item NPI, the MMSE, the Cognitive Drug Research (CDR) Computerized Assessment System, the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test, and the 10-point Clock Drawing Test. The UPDRS-III was used to assess motor function. Statistical analysis was performed on ITT and PP with consistent results of the different analyses. The paper presents the data of all randomized patients who received at least one dose of study medication and who were assessed for 1 of the primary efficacy variables at baseline and at least once after baseline. A total of 131 patients discontinued the study prematurely, mostly due to AEs (27.3% in the treatment group, 17.1% in the placebo group). After 24

weeks of treatment, the rivastigmine group showed a mean (\pm SD) improvement of 2.1 (\pm 8.2) points (corresponding to a 8.8% improvement) on the ADAS-cog as compared to the baseline score (23.8 \pm 10.2), whereas the placebo group showed a worsening of 0.7 (\pm 7.5) points (corresponding to a 2.9% deterioration) from baseline (24.3 \pm 10.5), yielding an absolute difference of 11.7%. The mean (\pm SD) scores for the ADCS-CGIC at week 24 were 3.8 (\pm 1.4) in the rivastigmine group and 4.3 (\pm 1.5) in the placebo group. Comparing outcomes in the seven possible response categories of the ADCS-CGIC (marked, moderate, or minimal improvement; no change; or marked, moderate, or minimal worsening) revealed that significantly more patients had a favorable outcome in the rivastigmine group than in the placebo group ($P = .007$). Indeed, clinically meaningful improvement (ie, “moderate” or “marked” improvement) was observed in 19.8% in the rivastigmine arm compared to 14.5% in the placebo arm ($P = .007$). Furthermore, clinically meaningful worsening (ie, “moderate” or “marked” worsening) was observed in 13% in the rivastigmine group and 23.1% in the placebo group ($P = .007$). Moreover, rivastigmine provided significant benefits over placebo with respect to all secondary efficacy variables. Frequent AEs leading to withdrawal from the study were nausea and vomiting, and occurred more frequently in the treatment group. Even though parkinsonian symptoms (27.3% in the rivastigmine arm vs 15.6% in the placebo arm, $P = .002$) especially tremor (10.2% in the rivastigmine arm vs 3.9% in the placebo arm, $P = .01$) were more frequently complained about in the treatment group, statistical analysis did not reveal any significant difference on the UPDRS including the tremor-related items between both groups. Tremor was severe enough to cause withdrawal from the study of 1.7% of patients in the rivastigmine group and none of the patients in the placebo group ($P = .19$). Significantly more patients on rivastigmine (n = 303, 83.7%) reported an AE compared to placebo (n = 127, 70.9%; $P < .001$). The following AEs occurred more significantly in the rivastigmine than the placebo group: nausea (rivastigmine: n = 105, 29.0% vs placebo: n = 20, 11.2%; $P < .001$), vomiting (rivastigmine: n = 60, 16.6% vs placebo: n = 3, 1.7%; $P < .001$), tremor (rivastigmine: n = 37, 10.2% vs placebo: n = 7, 3.9%; $P = .01$) and dizziness (rivastigmine: n = 21, 5.8% vs placebo: n = 2, 1.1%; $P = .01$). (Quality score, 93%.)

Efficacy conclusion. Based on this study, rivastigmine can be rated as *efficacious* for the treatment of dementia in PD.

Galantamine (One New Study,⁴⁶ Conclusion: Insufficient Evidence). Litvinenko et al. (2008)⁴⁶ conducted a 24-week, open-label, parallel-group RCT, to study the

effects of galantamine treatment in 41 patients with PD and dementia. Patients were allocated to either the galantamine treatment group ($n = 21$) or continued taking the preexisting therapy (control group; $n = 20$). Patients with PD were included if they fulfilled the ICD-10 criteria for dementia, if they developed cognitive decline at least 2 years after the onset of motor symptoms, and if they had a MMSE < 25 . Galantamine was started at a dose of 4 mg twice a day during the first 4 weeks and was subsequently increased to 8 mg twice a day. Primary outcome variables were not specified. Outcome variables included the MMSE, the ADAS-Cog, the Frontal Assessment Battery (FAB), the Clock Drawing Test, the NPI, the Disability Assessment for Dementia (DAD), an assessment of distress of the relatives, and the UPDRS-III. Two patients in the control group dropped out because they were not able to accomplish the neuropsychological test battery. Galantamine provided significant benefits over placebo on all measures of severity of cognitive impairment (MMSE, $P < .005$; ADAS-cog, $P < .005$; FAB, $P < .01$; the Clock Drawing Test, $P < .005$), to the NPI ($P < .01$), to the DAD ($P < 0.01$), and to the assessment of distress of the relatives ($P < .01$). There was no significant treatment effect on motor function as assessed by the UPDRS-III. Side effects were seen in 7 patients (30%) treated with galantamine including increased drooling ($n = 5$), increased orthostatic hypotension ($n = 2$), increased tremor ($n = 2$), nausea ($n = 2$), and urinary frequency ($n = 1$). (Quality score, 50%.)

Efficacy conclusion. Based on this open-label low-quality study, there is *insufficient evidence* for galantamine to be rated for the treatment of dementia in PD.

Safety Conclusions Related to Acetylcholinesterase Inhibitors (Conclusion: Acceptable Risk Without Specialized Monitoring). There were no safety concerns identified in the above reviewed study on acetylcholinesterase-inhibitors for the treatment of dementia in PD. The small RCTs⁴²⁻⁴⁴ using donepezil for dementia in PD were consistent in showing good tolerability of donepezil without worsening of UPDRS motor scores. Nausea and vomiting were the most common side effects observed with rivastigmine, affecting between 17% and 29% of patients.⁴⁵ Although there were no statistically significant differences in UPDRS motor scores between rivastigmine and placebo-treated patients, more patients on rivastigmine reported tremor as an AE.⁴⁵ Worsening of tremor occurred in some patients treated with galantamine.⁴⁶ Standard medical monitoring for cholinergic effects can include blood pressure or electrocardiograph (ECG) monitoring. Therefore acetylcholinesterase inhibitors are considered to pose an acceptable risk without specialized monitoring.

NMDA Receptor Antagonists

Memantine (Three New Studies,⁴⁷⁻⁴⁹ Conclusion: Insufficient Evidence). A recent meta-analysis of RCTs by the Cochrane Dementia and Cognitive Improvement Group found that the N-methyl D-aspartate (NMDA) receptor antagonist memantine had a small beneficial effect at 6 months on cognition, behavior and the ability to perform daily activities in patients with moderate to severe Alzheimer's disease. This was based on 3 RCTs; however, in mild to moderate Alzheimer's disease another 3 RCTs⁵⁰ reported only a marginal beneficial effect at 6 months on cognition, but no effect on behavior or the ability to perform activities of daily living. Three parallel-group, randomized placebo-controlled trials have been conducted using memantine for the treatment of dementia in PD,⁴⁷⁻⁴⁹ 2 of these were performed in patients with both PD dementia as well as dementia with Lewy bodies.^{48,49}

Leroi et al. (2009)⁴⁷ conducted a 22-week placebo-controlled, parallel-group RCT on memantine for the treatment of dementia in PD, with a discontinuation of study drug at week 16. For inclusion into the trial, patients had to have Parkinson's dementia (DSM-IV) and an MMSE score of 10 to 27. Cognitive decline had to occur at least 1 year after onset of PD motor symptoms. Cholinesterase inhibitors were allowed if they were stable for at least 6 months prior to the study and if there was no improvement in cognition or behavior for at least 4 weeks prior to study entry; this was the case of 4 patients in each treatment group. Patients were randomized to either placebo ($n = 14$) or memantine ($n = 11$) at a fixed dose of 20 mg/day. The primary outcome was defined as improvement on the DRS. Secondary outcome variables included the MMSE, NPI, and CIBIC+. There were no significant benefits over placebo with respect to the DRS, MMSE, NPI, and NPI subscores at week 16 between patients on memantine and placebo. After 16 weeks of treatment, the difference in mean DRS scores between baseline and end of drug treatment between the two treatment arms was 0.1 (95% CI, -19.3 to 19.6) (mean baseline scores \pm SD: memantine 94.1 ± 38.5 vs placebo 88.4 ± 31.7). Improvement in global functioning, as measured by mean CIBIC+ scores, was greater under memantine (60%) compared to placebo (43%) ($P = .07$). At week 22, which was 6 weeks after discontinuation of the study drug, there was more deterioration, as measured on the CIBIC+, under memantine (70%) than placebo (29%; $P = .04$; mean CIBIC+ \pm SD score: 5.4 ± 1.2 vs 4.4 ± 0.5 , respectively). However, no significant changes between treatment groups were found on the other outcome variables. There were no significant effects on motor function as assessed with the

UPDRS-III in either group. The rate of AEs was similar between the 2 treatment groups. (Quality score, 82%.)

Aarsland et al. (2009)⁴⁸ performed a 24-week trial in 72 patients with either PD dementia or dementia with Lewy bodies (DLB). Patients were randomly assigned to receive either memantine ($n = 34$) or placebo ($n = 38$). Inclusion criteria were patients with DLB according to the revised consensus operational criteria for DLB, or for PD patients they had to have developed dementia (DSM-IV) at least 1 year after the onset of motor symptoms. Dementia had to be mild to moderate (MMSE ≥ 12). The primary outcome measure was the CGI-C of all patients included in the trial, although a preliminary descriptive subgroup analysis is also given in the paper. Statistical analysis was performed on the ITT population. Secondary outcome measures included the MMSE, a quick test of cognitive speed (AQT), the NPI, the disability assessment for dementia (DAD), and a modified UPDRS motor subscale. A total of 56 patients completed the study (78%; 27 on memantine and 29 on placebo). At week 24 the patients receiving memantine (3.5 ± 1.5) had better CGI-C scores than those on placebo (4.2 ± 1.2) (mean difference 0.7; 95% CI, 0.04–1.39; $P = .03$). The preliminary descriptive subgroup analysis revealed that the mean CGI-C score in the PD dementia group was 4.3 for placebo versus 2.9 for memantine with a mean difference 1.4 between the treatment groups (95% CI, 0.6–2.2). As there were no differences in the mean CGI-C between the memantine and placebo treatments in patients with DLB, the authors of the study concluded that there was a more pronounced global response in patients with PD dementia. A moderate or substantial clinical improvement was found in 8 (27%) patients on memantine versus no patients on placebo. On the other hand, moderate worsening was noted in 5 (17%) patients on memantine versus 6 (18%) on placebo. With the exception of improved speed on attentional tasks in the memantine group using the AQT (mean difference 12.4, 95% CI, 6.0–30.9; $P = .004$), there were no significant differences between memantine and placebo in secondary outcome measures. Thirty-five patients (47%; 20 on placebo and 15 on memantine) reported AEs during the study; 16 patients (21%; 9 on placebo and 7 on memantine) dropped out due to AEs with 11 (7 on placebo and 4 on memantine) of them due to worsening of the disease. (Quality score, 93%.)

Emre et al. (2010)⁴⁹ examined the effects of memantine (20 mg/day) for the treatment of DLB in a randomized, double-blind, placebo-controlled study. For inclusion in the trial, patients had to meet the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD, and have subsequently developed dementia (DSM-IV) at least 1 year after the onset of motor symptoms, or to have met the revised

consensus criteria for DLB. Dementia had to be mild to moderate (MMSE score 10–24) and severity of motor symptoms had to be H&Y ≤ 3 in the *on* state. Study drug doses were titrated in 5-mg increments over 4 weeks up to 20 mg once daily in the morning. This study had no predefined primary endpoint and no correction for multiple testing. Efficacy variables included the ADCS-CGIC scale, the ADCS-activities of daily living, 23-item (ADCS-ADL23) scale (scores range from 0 to 78, with a higher score indicating better performance), the Zarit burden interview to assess the physical, psychological, and social consequences of caregiver burden, the NPI; 16 different cognition tests to assess 5 cognitive domains including attention, executive function, language, memory, and visuospatial function, and the UPDRS. While safety analyses were performed for the all patients treated set (APTS; ie, all patients who took at least 1 dose of memantine or placebo), efficacy analyses were performed on the full-analysis set (FAS; ie, all patients in the APTS who had at least 1 valid postbaseline assessment on any of the efficacy scales). A total of 199 patients with DLB ($n = 78$) or PD dementia ($n = 121$) were randomly assigned to receive memantine or placebo. The FAS consisted of 93 patients given memantine (33 with DLB, and 60 with PDD) and 97 given placebo (41 with DLB, and 56 with PD dementia). Although at week 12, the ADCS-CGIC mean score showed significantly greater improvement in patients who were given memantine than in those given placebo, both in the total population (3.4 vs 3.8, treatment difference -0.4 , [95% CI, -0.7 to -0.1]; $P = .014$) and in patients with PD dementia (3.4 vs 3.7, treatment difference -0.5 [95% CI, -0.9 to -0.1]; $P = .023$), the difference was not significant at week 24 either for the total study population (3.5 with memantine vs 3.8 with placebo, treatment difference -0.3 [95% CI, -0.7 to 0.1]; $P = .120$) or for the patients with PD dementia (3.6 with memantine vs 3.8 with placebo, treatment difference -0.1 [95% CI, -0.6 to 0.3]; $P = .576$). However, at week 24, patients with DLB who received memantine showed greater improvement according to ADCS-CGIC than those who received placebo (mean change from baseline 3.3 vs 3.9, respectively, difference -0.6 [95% CI, -1.2 to -0.1]). NPI scores improved more significantly in the memantine group than in the placebo group (-4.3 vs 1.7, respectively, difference -5.9 [95% CI, -11.6 to -0.2]; $P = .041$) in patients with DLB, but not in those with PD dementia (-1.6 vs. -0.1 , respectively, difference -1.4 [95% CI, -5.9 to 3.0]; $P = .522$) or in the total patient population (-2.6 vs 0.4, respectively, difference -2.9 [95% CI, -6.3 to 0.5]; $P = .092$). In most of the cognitive test scores, ADCS-ADL23, and Zarit caregiver burden scores, there were no significant differences between the 2 treatment groups in any of the study populations. UPDRS-III scores did not differ in any group of patients at any time point. The incidence of AEs and number of discontinuations due to AEs were similar in the 2 groups. The most common AEs were falls (8% in each

TABLE 6. Conclusions on drugs to treat dementia in PD

	Efficacy	Safety	Practice implications
Acetylcholinesterase inhibitors			
Donepezil	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Rivastigmine	<i>Efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Clinically useful</i>
Galantamine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
NMDA Receptor Antagonists			
Memantine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds. PD, Parkinson's disease.

treatment arm) and somnolence (memantine: 5%; placebo: 3%). The proportion of AEs leading to withdrawal was similar in the 2 treatment groups: 11 patients (5 DLB, 6 PD dementia) treated with memantine and 12 (7 DLB, 5 PD dementia) treated with placebo withdrew from the study. (Quality score, 77%.)

Efficacy Conclusion. Due to the conflicting data from these 3 studies, there is *insufficient evidence* for memantine to be rated for the treatment of dementia in PD.

Safety Conclusion Related To Memantine (Conclusions: Acceptable Risk Without Specialized Monitoring). There were no safety concerns identified in the above reviewed study on memantine for the treatment of dementia in PD. A recent meta-analysis by the Cochrane Dementia and Cognitive Improvement Group found that memantine was well tolerated in patients with Alzheimer's disease and vascular dementia.⁵⁰ Therefore memantine is considered to have an *acceptable risk without a need for specialized monitoring*.

Treatment of Dementia in PD—Summary and Practice Implications

The practice implications for the treatment dementia in PD are summarized in Table 6. Drugs for the treatment of dementia in PD, including the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, as well as the NMDA receptor antagonist memantine were not previously reviewed. None of the studies exceeded 24 weeks. Therefore, all recommendations given here are for the short-term treatment of dementia in PD.

Rivastigmine is *efficacious* for the treatment of dementia in PD. There is *insufficient evidence* for donepezil and galantamine for the treatment of dementia in PD. Safety conclusions are that the acetylcholinesterase inhibitors donepezil, rivastigmine and galantamine have an *acceptable risk without specialized monitoring*. The practice implications are that rivastigmine is *clinically useful* for the treatment of dementia in PD, while the practice implications for donepezil and galantamine are that they are both *investigational* for the treatment of dementia in PD.

There is *insufficient evidence* of memantine for the treatment of dementia in PD. Safety conclusions are that memantine has an *acceptable risk without specialized monitoring*. The practice implications are that it is *investigational* for the treatment of dementia in PD.

Drugs to Treat Psychosis in PD

In the original 2002 MDS review, clozapine was the only antipsychotic agent with consistent evidence from RCTs to be rated for efficacy, and as far as safety was concerned, it was considered to have an acceptable risk but specialized monitoring is necessary due to the association of the drug with the rare (0.38%) but serious and potentially life-threatening occurrence of agranulocytosis. In the meantime, 9 new studies on 10 RCTs have been published for the treatment of psychosis in PD. Furthermore, 2 open-label extensions of 2 RCTs comparing clozapine and placebo for the treatment of psychosis in PD are now available.

Atypical Antipsychotics

Clozapine (Three New Studies,^{51–53} Conclusion: Efficacious). There are two 12-week open-label extensions of two 4-week, multicenter, placebo-controlled, double-blind, RCTs. The two 4-week, multicenter, placebo-controlled, double-blind, RCTs were considered in the original review. Furthermore, among new RCTs examining the treatment of psychosis in patients with PD, there are 2 new studies, which were both performed with quetiapine as the comparator drug and were both rater-blinded.

Factor et al. (2001)⁵¹ and the Parkinson's Study Group conducted a 12-week, prospective, open-label extension of the 4-week, multicenter, placebo-controlled, double-blind Psychosis and Clozapine in the Treatment of Parkinsonism (PSYCLOPS) trial, that sought to examine the chronic safety and efficacy of clozapine in the treatment of drug-induced psychosis in all 53 PD patients who completed the double-blind study. There was 1 further withdrawal from clozapine due to a low white blood cell (WBC) count below 3,000/m³, which returned to normal after discontinuation of therapy. However, there was an unexpectedly high death rate in this open-label extension phase, with the death

of 6 patients as a result of the nature of the advanced disease and not of clozapine as stated by the authors.

Pollak et al. (2004)⁵² conducted a 4-week, randomized, double-blind, parallel-group comparison of clozapine and placebo, followed by a 12-week clozapine open phase. This was then followed by a 1-month washout period. Fifty-five patients who completed the double-blind study continued on the open-label extension phase. At the end of this open period, 25 patients had completely recovered from delusions and hallucinations and of these, 19 experienced a relapse within 1 month of the clozapine washout period.

Morgante et al. (2004)⁵³ conducted a 12-week randomized, rater-blinded trial to compare the efficacy of quetiapine and clozapine in 20 PD patients who had had drug-induced psychosis (not otherwise specified) for at least 4 weeks before study entry. In addition, patients needed to have a baseline score of ≥ 3 on the items hallucinations or unusual thought content (or delusions) of the BPRS. Daily dosages ranged from 25 to 200 mg (mean 91 mg/day) in the quetiapine arm and from 12.5 to 50 mg (mean 26 mg/day) in the clozapine arm. Outcome measures included the BPRS and the CGI-S to assess the severity of psychosis, the UPDRS-III to assess motor impairment and the AIMS to assess dyskinesias. Sample size calculations were based on the BPRS, suggesting that the primary outcome variable was the BPRS. Among the 45 patients originally included in the trial, there were 5 dropouts, 3 from the clozapine arm (dizziness in week 1, severe hypotension at week 2, over sedation at week 3) and 2 from the quetiapine arm (over sedation at week 1, confusional state at week 2). Data analysis was performed on the completers of the trial (PP analysis). Psychosis scores improved significantly in both groups as recorded on both the BPRS and the CGI-S ($P < .001$). The mean (SD) scores on the BPRS improved from 37.1 (6.1) to 28.7 (4.2) in the quetiapine group versus 37.4 (5.4) to 26.7 (3.6) in the clozapine group; the mean (\pm SD) scores on the CGI-S improved from 3.6 (0.7) to 2.1 (0.6) on quetiapine and from 3.8 (0.8) to 1.9 (0.6) under clozapine. However, UPDRS-III scores remained stable in both groups, although motor worsening was reported in 3 patients on quetiapine. The AIMS improved significantly in both groups ($P < .05$), from 7.8 (2) to 6 (1.3) in the quetiapine group and from 7.2 (2.1) to 5.4 (1.3) in the clozapine group. No significant differences were found in the psychosis and motor scores between the two groups. (Quality score, 67%.)

Merims et al. (2006)⁵⁴ conducted a 22-week parallel-group, comparison RCT on quetiapine ($n = 13$, dosage: 25–150 mg/day, mean 91 mg/day) and clozapine ($n = 14$, dosage: 6.25–50 mg/day, mean 13 mg/day). Inclusion criteria were PD patients who had experienced recent-onset, significant psychotic symptoms (not otherwise specified), which required antipsychotic treatment. The initial dose was 6.25 mg for

clozapine and 25 mg for quetiapine, given once daily at bedtime. Dose adjustments were gradually increased every 2 weeks during the first 10 weeks (maximal daily dose of 50 mg for clozapine and 150 mg for quetiapine) until psychosis was considered to be satisfactorily under control. Primary endpoints were selected items (ie, hallucinations, delusions) from the NPI-20 and the CGI-C questionnaires with assessments being done by a blinded neuropsychologist. Furthermore, satisfactory control of symptoms was defined as disappearance of hallucinations or at least marked reduction of hallucinations based on the clinical impression of the treating physician and the caregiver. During the first month of treatment both treatment groups showed a significant improvement of about 1 point over time as assessed by the CGI-C ($P < .001$), with no significant difference between the groups. On the CGI-C, both drugs were equally effective with 11 patients from each arm reaching satisfactory control of psychotic symptoms. There was a more significant reduction in delusions (NPI) on clozapine compared to quetiapine. Compared to baseline, clozapine but not quetiapine, significantly improved the frequency scores of the categories “hallucinations” and “delusions” of the NPI. There was no significant change in the severity scores of the categories “hallucinations” and “delusions” of the NPI over time in either group. Overall, only 7 of the 14 patients randomized to receive clozapine and 9 of the 13 randomized to receive quetiapine completed the study. Five patients withdrew from the study because of severe paranoid delusions (clozapine, $n = 3$; quetiapine, $n = 2$); 4 more patients on clozapine withdrew due to either a decrease in the leukocytes count ($n = 3$, with 1 patient having had significant leucopenia and neutropenia), which was reversible after stopping clozapine in all 3 cases; or due to difficulties in doing the weekly blood count ($n = 1$). For quetiapine, 2 patients withdrew due to sleepiness as a limiting factor of dose escalation and a further 4 withdrew due to lack of efficacy. The authors did not observe any worsening in parkinsonian symptoms as measured by the UPDRS in either of the treatment arms. (Quality score, 65%.)

Efficacy Conclusion. These 2 new RCTs support the previous designation of clozapine as being efficacious for the treatment of psychosis in PD.

Safety Conclusion Related to Clozapine (Conclusion: Acceptable Risk with Specialized Monitoring). Consistently reported side effects, even with the low clozapine doses, included sedation, increased drooling, and occasionally orthostatic hypotension or “dizziness”. Due to the association of clozapine with the rare (0.38%)⁵⁵ but serious and potentially life-threatening occurrence of agranulocytosis, safety conclusions remain unchanged from the 2002 review, that is, clozapine has an *acceptable risk with specialized monitoring*.

Olanzapine (Two New Studies^{56,57} on Three RCTs, Conclusion: Unlikely Efficacious). Breier et al. (2002)⁵⁶ conducted 2 placebo-controlled, double-blind, parallel-group RCTs (N = 160, 1 in the United States [n = 83] and the other in Europe [n = 77]) to examine the efficacy of low-dose olanzapine (initiated at 2.5 mg/day, with 2.5-mg/day increases allowed every 3–4 days, maximum dose: 15 mg/day) for the treatment of drug-induced psychosis in patients with PD. Both studies were reported in 1 publication. Patients were randomized 1:1 in the U.S. study, and 2:1 in the European study to receive olanzapine or placebo. Inclusion criteria were PD patients with drug-induced psychosis (DSM-IV) experiencing hallucinations, delusions, or both in the 2-week period before study entry. Furthermore, all patients were required to have an individual hallucinations/delusions item score of ≥ 2 on the NPI. The positive symptom cluster subscore of the BPRS was the primary outcome measure of antipsychotic efficacy in the 2 studies. Secondary outcome measures of antipsychotic efficacy included the BPRS total and negative symptom cluster scores, the CGI-S score for psychosis, and the NPI total score and individual item subscores. The UPDRS total score, the UPDRS-II, III, and IV scores, the UPDRS tremor subscore, and the CGI-S for motor symptoms, were used to assess motor function during the study. The authors did not state if the analysis of the outcome measures was done on the ITT or PP population. The mean (\pm SD) daily doses of olanzapine in the United States and European studies were 4.2 mg \pm 2.6 and 4.1 mg \pm 2.0, respectively. The authors report a significant improvement in both the olanzapine and placebo groups in several psychosis rating scores (BPRS total, positive cluster, and BPRS hallucinations item scores, NPI total and NPI hallucinations item scores, and CGI-S psychosis scores in both the U.S. and European studies as well as the NPI delusions item scores in the European study). No significant treatment-group differences in any psychosis ratings were found in either study. Although no significant treatment-group differences regarding psychosis measures were observed, motor function worsened significantly in patients on olanzapine compared to placebo in both trials with significant treatment-group differences on the UPDRS total, UPDRS-II, and UPDRS-III scores in both trials. In the U.S. study, patients in the olanzapine group showed significantly higher reported incidences of 3 Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART): extrapyramidal syndrome (olanzapine, 24.4%; placebo, 2.4%; $P = .003$), hallucinations (olanzapine, 24.4%; placebo, 4.8%; $P = .013$), and increased salivation (olanzapine, 22.0%; placebo, 4.8%; $P = .026$), while in the European study, olanzapine treatment was not associated with any significantly higher incidence of any AE compared to placebo. (Quality score, 63%.)

Ondo et al. (2002)⁵⁷ in a smaller double-blind, placebo-controlled, parallel-group RCT, 30 patients

underwent 9 weeks of treatment with olanzapine (2.5–10 mg/day; mean dosage 4.6 mg/day) or placebo (2:1 ratio). The inclusion criteria were PD patients with drug-induced hallucinations clinically problematic enough to justify intervention. Outcome measures included the UPDRS item 2 (thought disorder), a 9-point structured interview for hallucinations assessing the content and severity of the hallucinations (maximal score 27) and global assessments (from “much better” to “much worse”) to assess psychosis severity, and the UPDRS with the UPDRS-II assessing motor function through the average *on* and *off* scores. Further outcome measures included a battery of neuropsychological tests. Due to lack of efficacy, there was 1 dropout in each group; a further patient on olanzapine dropped out before taking any study medication. These 3 patients were not included in the statistical analysis. This study also failed to detect significant differences between olanzapine and placebo in any of the psychosis measures. Again, there was significant worsening of UPDRS motor scores in the olanzapine arm; motor decline was mainly seen through the worsening of gait and bradykinesia subscores. On the other hand, there was no change in the UPDRS ADL scores. The neuropsychological battery showed no significant differences between olanzapine and placebo in measures of cognition (executive function, language, and memory) or mood on any test. AEs occurred in 18 patients on olanzapine including worsening movement (n = 6), worse posture (n = 3), dysarthria (n = 2), edema (n = 2), drooling (n = 2), weight gain, dry mouth, nausea, insomnia, sedation, perspiration, and agitation. AEs occurred in 12 patients on placebo including insomnia, sedation, leg cramps, lightheadedness, weakness, and tremor. (Quality score, 68%.)

Efficacy Conclusion. Based on these 2 new studies on 3 RCTs, olanzapine can be rated *unlikely efficacious* for the treatment of psychosis in PD.

Safety Conclusion Related to Olanzapine (Conclusion: Unacceptable Risk). Safety conclusions remain unchanged from the 2002 review and the use of olanzapine has an unacceptable risk of motor deterioration. Furthermore, atypical and conventional antipsychotics are associated with a similarly increased risk for all-cause mortality and cerebrovascular events in elderly patients with dementia.^{58,59} Olanzapine therefore has an unacceptable risk for the treatment of psychosis in PD.

Quetiapine (Six New Studies,^{53,54,60–63} Conclusion: Insufficient Evidence). Six studies^{53,54,60–63} using quetiapine for the treatment of psychosis in PD were published since the original MDS review in 2002. Two of the studies were clozapine-controlled randomized trials, which were rater-blinded only and 4 of the studies

were double-blinded placebo-controlled randomized trials.

Ondo et al. (2005)⁶⁰ conducted a double-blind, placebo-controlled, parallel-group study of quetiapine for hallucinations in PD. Thirty-one patients with drug-induced, subjectively-problematic, visual hallucinations were randomized in a 2:1 ratio to 12 weeks of treatment with quetiapine ($n = 21$, up to 200 mg/day, mean dosage 170 mg/day) or placebo ($n = 10$). The primary efficacy endpoints were the Baylor PD Hallucination Questionnaire and the UPDRS. Further outcome measures were the Goetz Dyskinesia Rating Scale to assess motor function and a battery of neuropsychological tests. Among the 31 patients originally included in the trial, there were 6 dropouts, 4 in the quetiapine arm (serious unrelated illness, $n = 2$; lack of effect and poor compliance, $n = 1$ each) and 2 in the placebo group (serious unrelated illness both resulting in deaths). However, the authors stated that there were 26 completers in the study, thus resulting in a discrepancy in the number of dropouts (6/31) and completers ($n = 26$). Dropouts were not included in the statistical analysis when data were not available. However, it is not clear how many of the patients were considered for the final statistical analysis, but it seems to have been 17 patients on quetiapine and 8 patients on placebo. Compared to placebo, none of the hallucination, psychosis, or motor impairment assessments nor other outcome variables changed significantly on quetiapine, although the authors stated that the Baylor PD Hallucination Questionnaire showed a trend toward improvement compared to placebo not reaching statistical significance ($P = .19$). A total of 8 of 17 patients (quetiapine [47.1%] compared to 2 out of 8 treated with placebo [25.0%]) believed they were meaningfully better. According to the authors, there were no dropouts caused by quetiapine-related AEs. The most common AE was sedation in both arms (quetiapine $n = 9$, 43% vs placebo $n = 4$, 40%). Subjective worsening of PD was reported by 4 patients on quetiapine (19%). One further AE was reported by 10 different subjects in each arm. Post hoc, the authors performed a power calculation which revealed that the study was underpowered with a power of 22% considering an effect size of 35%. (Quality score, 68%.)

Rabey et al. (2007)⁶¹ conducted a double-blind, placebo-controlled, parallel-group, 12-week trial investigating a total of 58 PD patients (quetiapine $n = 30$; placebo $n = 28$), of whom 29 (treatment allocation not stated) were demented. Demented and nondemented patients were randomized separately in consecutive order, according to their group pertinence. One patient dropped out before randomization. Psychosis was defined as the presence of severe visual or auditory hallucinations and/or delusions, which signifi-

cantly affected the patient's quality of life. Primary outcome measures included the BPRS and the CGI-S to assess effects of the study drug on psychosis. Secondary outcome measures included the UPDRS-III to assess effects on motor function, the MMSE to assess effects of the study drug on cognitive function, the ESS to assess effects on daytime somnolence, and the HDRS to assess effects on mood (in the nondemented patients). Statistical analysis was performed on the ITT population, including all the patients who completed the 12 weeks of treatment and also the last observation visit of patients who dropped out before study completion (LOCF). Quetiapine was started at 12.5 mg/day and increased under a flexible dosing regimen (duration 4 days to 4 weeks) until it caused either symptomatic effects or AEs. The mean quetiapine dose was 119.2 ± 56.4 mg/day. This study was characterized by a high dropout rate of 45% ($n = 26$) primarily due to lack of efficacy, which was the reason for interruption of the trial in 10 of 15 patients in the quetiapine arm and 9 of 11 patients in the placebo arm. Further reasons for dropout were noncompliance in 1 patient in each arm, side effects (quetiapine, somnolence: $n = 2$; not further specified: $n = 1$), and somatic problems (quetiapine, $n = 1$ not further specified). One patient in the placebo arm died following a hip fracture. Compared to placebo neither the primary outcome variables (BPRS including subitems of the BPRS concerning hallucinations and delusions and the CGI-S) nor any of the secondary outcome variables, changed significantly on quetiapine on ITT analysis. This was also true when considering only the demented or the nondemented patients. Based on the CGI-S, improvement (ie, CGIS-items "mildly improved", "much improved" or "very much improved") of psychosis was observed in 9 of 29 patients on quetiapine (31%) compared to 13 of 27 patients (48%) on placebo. The mean (\pm SD) scores on the BPRS changed from 34.2 (5.0) at baseline to 34.0 (6.7) at week 12 for quetiapine, versus 36.0 (8.8) to 31.9 (8.2) for placebo; the mean (\pm SD) scores on the UPDRS-III changed from 37.0 (9.6) to 39.2 (9.8) for quetiapine and from 39.5 (13.1) to 37.6 (14.7) for placebo. (Quality score, 74%.)

Shotbolt et al. (2009)⁶² conducted a placebo-controlled, parallel-group RCT of quetiapine ($n = 11$) in 24 subjects with a BPRS ≥ 3 . Exclusion criteria included current treatment with cholinesterase inhibitors, antipsychotic medication within the previous 2 weeks, and DLB. The mean quetiapine dose was 72.7 ± 26.1 mg/day. A total of 13 patients completed the 6 weeks of the study (quetiapine $n = 4$; placebo $n = 9$) and 8 completed the 12-week double-blind phase (4 from each group). The primary outcome measure was time to dropout due to a lack of improvement of psychosis. Secondary outcome measures included

standard rating scales for PD and psychiatric symptoms. Due to the high dropout rate, secondary outcome measures (Baylor PD hallucination, scale, UPDRS, NPI, and BPRS) were only analyzed at 6 weeks. The results showed no significant difference in time to dropout between patients receiving quetiapine or placebo ($P = .68$). ITT analysis was used to examine secondary outcome measures after 6 weeks and no significant changes were found for any of these endpoints in either group. Three patients on quetiapine and 3 patients in the placebo group dropped out due to drowsiness, and 1 patient on placebo dropped out due to confusion. (Quality score, 65%.)

Fernandez et al. (2009)⁶³ conducted a double-blind, placebo-controlled, parallel-group, 1-month polysomnographic study of quetiapine for the treatment of visual hallucinations, using changes in REM architecture, as demonstrated via polysomnography (PSG), as the primary endpoint. This study was designed to determine whether the mechanism of quetiapine's effects on visual hallucinations in PD was due to its effect on REM sleep architecture. Sixteen patients with PD experiencing consistent and persistent, predominantly nocturnal visual hallucinations under stable doses of PD medications, were randomized to receive quetiapine or placebo. Quetiapine (or matching placebo) was initiated at 25 mg at bedtime and was then gradually increased to 150 mg/day or until a complete resolution of nocturnal hallucinations was achieved. The mean study drug dose was 58.3 mg/day (range, 25–100 mg/day). Exclusion criteria included previous unresponsiveness to antipsychotic drugs, threatening psychosis or delusions, significant cognitive impairment, treatment with clonazepam or other sleeping agents, and known central sleep disorders. All patients randomized underwent pre- and posttreatment PSG over 2 consecutive nights. The primary outcome measure was length of REM stage as assessed by PSG. Secondary outcome measures included the BPRS, the CGI-S, and the UPDRS motor part in the *on* state. Data analysis was performed by an ITT approach and statistical significance was set at .05, without correcting for multiple testing. Of the 16 patients ($n = 8$ quetiapine, $n = 8$ placebo) randomized, 11 patients completed the study ($n = 4$ quetiapine, $n = 7$ placebo). There was no significant difference in the change in REM duration pre- versus posttreatment in either arm. The length of REM stage increased in the active treatment arm (quetiapine arm: 40.1 minutes vs 53.7 minutes, change: 7.0 ± 41.8 minutes; placebo: 74.6 minutes vs 46.3 minutes, change: -31.4 ± 35.8 minutes; $P = .19$). Compared to baseline, patients on quetiapine improved on the CGI-S more than those on placebo (2.8 ± 0.8 vs 3.9 ± 1.0 ; $P = .03$). There was

also a significant improvement in item no. 12 (hallucination) on the BPRS in the quetiapine treated patients (-1.3 ± 1.1 vs -0.04 ± 0.8 ; $P = .02$). However the change in total BPRS from pre- to posttreatment was not significant between the 2 treatment arms (1.0 ± 7.0 vs -0.3 ± 7.6 ; $P = .78$). AEs that were more common in the active treatment group included drowsiness (3 vs 1) and loss of balance/increase in parkinsonism (3 vs 0), although none of the patients dropped out due to worsening of parkinsonism and although there was a nonsignificant improvement of the UPDRS in the quetiapine arm. (Quality score, 68%.)

Morgante et al. (2004)⁵³ (see above under Clozapine).

Merims et al. (2006)⁵⁴ (see above under Clozapine) conducted a 22-week randomized study to compare the efficacy of quetiapine (dosage: 25–150 mg/day, mean 91 mg/day) and clozapine (dosage: 6.25–50 mg/day, mean 13 mg/day) in 17 PD patients with recent-onset, significant psychotic symptoms requiring antipsychotic treatment. During the first month of treatment both treatment groups showed a significant improvement of about 1 point over time as assessed by the CGI-C ($P < .001$), with no significant difference between the groups. On the CGI-C, both drugs were equally effective, with 11 patients from each arm reaching satisfactory control of psychotic symptoms. There was a more significant reduction in delusions (NPI) on clozapine compared to quetiapine. Compared to baseline, clozapine, but not quetiapine, significantly improved the frequency scores of the categories “hallucinations” and “delusions” of the NPI. There was no significant change in the severity scores of the categories “hallucinations” and “delusions” of the NPI over time in either group. Overall, only 7 of the 14 patients randomized to receive clozapine and 9 of the 13 randomized to receive quetiapine completed the study. Withdrawals were due to severe paranoid delusions (clozapine, $n = 3$; quetiapine, $n = 2$); a decrease in the leukocyte count (clozapine $n = 3$, with 1 patient having had significant leucopenia and neutropenia), which was reversible, sleepiness (quetiapine, $n = 2$), and lack of efficacy (quetiapine, $n = 4$). The authors did not observe any worsening in parkinsonian symptoms as measured by the UPDRS in either of the treatment arms. (Quality score, 65%.)

Efficacy Conclusion. Because of conflicting data on the efficacy of quetiapine and several methodological concerns of the studies (small sample size, low quality rating), there is insufficient evidence for quetiapine for the treatment of psychosis in PD.

Safety Conclusion Related to Quetiapine (Conclusion: Acceptable Risk Without Specialized Monitoring). There were no new safety concerns identified in the above

TABLE 7. Conclusions on drugs to treat psychosis in PD

	Efficacy	Safety	Practice implications
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Olanzapine	<i>Unlikely efficacious</i>	<i>Unacceptable risk</i>	<i>Not useful</i>
Quetiapine	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds. PD, Parkinson's disease.

viewed study on quetiapine for the treatment of psychosis in PD. Consistently reported side effects of quetiapine include sedation and hypotension. However, there is a recent case report where low-dose (12.5 mg) quetiapine exposure in a psychotic PD patient was associated with rhabdomyolysis.⁶⁴ In open-label trials some motor worsening was reported at one point during prolonged treatment in up to one-third of patients.⁶⁵ In 1 double-blind, placebo-controlled study, loss of balance/increase in parkinsonism was reported in 3 out of 8 patients treated with quetiapine; although none of the patients dropped out due to worsening of parkinsonism, there was also a nonsignificant improvement of the UPDRS in the quetiapine-treated patients.⁶³ One study compared efficacy and safety of quetiapine between parkinsonian patients with and without dementia and found demented patients to have a higher propensity for worsening of motor symptoms.⁶⁶ Furthermore, atypical and conventional antipsychotics are associated with a similarly increased risk for all-cause mortality and cerebrovascular events in elderly patients with dementia.⁵⁸

Treatment of Psychosis in PD—Summary and Practice Implications

The practice implications for the treatment of psychosis in PD are summarized in Table 7. None of the studies exceeded a duration of 22 weeks. Therefore, all recommendations given here are for the short-term treatment of psychosis in PD.

The studies reviewed do not permit changes from the prior EBM review in the practice implications for the atypical antipsychotics clozapine and quetiapine. Clozapine is *efficacious* for the treatment of psychosis in PD. Safety conclusions remain unchanged from the prior EBM review that clozapine has an *acceptable risk with specialized monitoring*, that is, regular blood count monitoring. Based on the available evidence, the practice implications are that clozapine is clinically useful in this indication.

There is *insufficient evidence* to conclude on the efficacy of quetiapine for the treatment of psychosis in PD, and the safety conclusion is that it has an acceptable risk without specialized monitoring. The practice implications are that quetiapine is investigational for the treatment of psychosis in PD.

Olanzapine is *unlikely efficacious* for the treatment of psychosis in PD and the safety conclusion is that it has an unacceptable risk of motor deterioration. The practice implications are that it is *not useful* for the treatment of psychosis in PD.

Drugs to Treat Autonomic Dysfunction in PD: Drugs to Treat Orthostatic Hypotension in PD

At the time of the original EBM review in 2002, insufficient data were available to assess the efficacy of drugs to treat orthostatic hypotension (OH) in PD, including midodrine, fludrocortisone, dihydroergotamine, etilefrine hydrochloride, indomethacine, yohimbine, L-threo-3,4-dihydroxyphenylserine. Since then only 1 study⁶⁷ has been published. In the pragmatic treatment of OH, it is usually worthwhile to try a variety of nonpharmacological measures (such as sleeping in a head-up position, fragmentation of meals, physical counter maneuvers such as squatting, bending over forward, or leg crossing with tension of the thigh, bottom, and calf muscles [party position] at the onset of presyncopal symptoms, avoidance of low-sodium and carbohydrate rich meals, increased water [2–2.5 L/day] and salt intake [>8 g or 150 mmol/day], and wearing support stockings) before initiating adjunct treatment with antihypertensive agents.⁶⁸

Fludrocortisone/Domperidone (One New Study,⁶⁷ Conclusion: Insufficient Evidence). Schoffer et al. (2007)⁶⁷ conducted a 2-phase study that sought to assess the efficacy and safety of both nonpharmacological and pharmacological interventions for OH in PD. The first phase of the study was an open-label assessment of nonpharmacological measures, while in the second phase the efficacy and safety of fludrocortisone and domperidone were compared in a randomized double-blind crossover design. This second phase was included and analyzed for this review. Although the study was on the treatment of OH in PD, not all patients had OH at baseline of the randomized controlled phase of the trial. Patients were randomly assigned to 1 of 2 possible treatment sequences, starting with 1 of the drugs (fludrocortisone or domperidone) and were then switched to the other, allowing a 1-week washout period. Tilt test and Composite Autonomic Symptom Scale (COMPASS-OD)

were evaluated at baseline and at the end of each 3-week period. CGI focusing on orthostatism was assessed at the end of each drug-treatment period. Analysis was done PP on the concluders of the study (13/17). COMPASS-OD scores were 9 ± 3 at baseline after nonpharmacological therapy and improved to 6 ± 3 on fludrocortisone ($P < .02$) and to 7 ± 2 on domperidone ($P < .04$). The average CGI score improved by 0.6 ± 1.2 after fludrocortisone, and by 0.9 ± 1.2 after domperidone (no statistical comparisons were available). Furthermore, there was a trend toward reduced blood pressure on tilt table testing. There was a similar frequency of AEs between the 2 arms. (Quality score, 48%.)

Efficacy conclusions. Based on this study with methodological concerns, there is *insufficient evidence* for both fludrocortisone and domperidone to be rated for the treatment of OH in PD.

Safety conclusions relating to fludrocortisone and domperidone (conclusions: insufficient evidence). There were no new safety concerns identified in the above reviewed study on fludrocortisone and domperidone to be rated for the treatment of OH in PD. Therefore, the safety conclusion is still that there is insufficient evidence.

Treatment of Orthostatic Hypotension in PD – Summary and Practice Implications

The practice implications for the treatment of OH in PD are summarized in Table 8. There is *insufficient evidence* concerning midodrine, fludrocortisone, dihydroergotamine, etilefrine hydrochloride, indomethacine, yohimbine and L-threo-3,4-dihydroxyphenylserine for the treatment of OH in PD. There is *insufficient evidence* to make conclusions on the safety of these drugs in PD patients. The practice implications are that these drugs are *investigational* for the treatment of OH in PD.

Drugs to Treat Autonomic Dysfunction in PD: Drugs to Treat Sexual Dysfunction in PD

At the time of the first EMB review in 2002, no RCT had been published for the treatment of sexual dysfunction in PD. More recently, efficacy and safety of the phosphodiesterase type 5 (PDE-5) inhibitor sildenafil has been evaluated in 2 RCTs for the treatment of erectile dysfunction in PD.^{69,70} However, 1 of the 2 RCTs⁷⁰ was retracted by the publishers and is therefore not considered in this EBM review. Other disorders of sexual dysfunction are not covered in this review.

Sildenafil (One New Studies,⁶⁹ Conclusion: Insufficient Evidence). Hussain et al. (2001)⁶⁹ conducted the only randomized, double-blind, crossover study available to assess the efficacy and safety of sildenafil for the treatment of erectile dysfunction in PD and multi-

ple system atrophy (MSA). This study consisted of 2 sequential treatment periods lasting 10 weeks each, without any washout period. A total of 24 patients (12 with a diagnosis of PD and 12 with MSA) were included in the study. All patients had to have a well documented medical history of erectile dysfunction and were excluded if they had no stable sexual partner, penile deformity, other sexual or psychological disorders, a known history of alcohol or drug dependence, or secondary causes of erectile dysfunction. Only results from PD patients ($n = 12$) were reviewed. Outcome measures were the International Index of Erectile Function (IIEF) as well as quality of life questionnaires. Primary endpoints were the responses to IIEF questions 3 and 4 (ie, the ability to achieve and maintain an erection, respectively) and the quality of life questionnaires. Subjects were treated for 10 weeks with a flexible dosing regimen of sildenafil (25–100 mg on an “as needed” basis 1 hr before initiation of sexual intercourse). Patients were randomized to receive first sildenafil and then placebo or the other way around, with no washout period between. Out of the 12 PD men recruited, only 10 completed the study (1 patient withdrew consent due to a lack of efficacy and the other was diagnosed with lung cancer). Eight patients were titrated up to 100 mg. Although no treatment effect estimates were given, significant improvements in the ability to achieve and maintain an erection after sildenafil but not after placebo were noticed. Between-group comparisons in the study were not given for the PD group. For the whole study population there were significant improvements in the ability to achieve and maintain an erection after sildenafil compared to placebo. Although the overall quality of life score was unchanged by sildenafil, there was a marked improvement in sex life domain. Nine of 10 patients reported a good response to sildenafil citrate, 1 patient reported lack of efficacy. One patient reported headache and flushing after sildenafil. (Quality score, 67%.)

Efficacy conclusion. Based on this small-sized, low-quality study, there is *insufficient evidence* for sildenafil to be rated for the treatment of erectile dysfunction in PD.

Safety conclusion related to sildenafil (conclusion: insufficient evidence). No new safety issues were reported in this small-sized trial. Sildenafil was well tolerated in the aforementioned study, transient AEs included headache, flushing, and dyspepsia. As PD patients with cardiovascular disease were excluded from the trial, the safety of sildenafil in PD patients with cardiovascular disease is not established. Autonomic function is common in PD and consequences of sildenafil treatment in this population have not been widely explored. Cautious use is advised in parkinsonian patients with OH. PDE-5 inhibitors including sildenafil are contraindicated in patients on nitrate medications for coronary heart disease.⁷¹

TABLE 8. Conclusions on drugs to treat autonomic dysfunction in PD

	Efficacy	Safety	Practice implications
Orthostatic hypotension			
Fludrocortisone	Insufficient evidence	Insufficient evidence	Investigational
Domperidone	Insufficient evidence	Insufficient evidence	Investigational
Midodrin	Insufficient evidence	Insufficient evidence	Investigational
Dihydroergotamine	Insufficient evidence	Insufficient evidence	Investigational
Etilefrine hydrochloride	Insufficient evidence	Insufficient evidence	Investigational
Indomethacine	Insufficient evidence	Insufficient evidence	Investigational
Yohimbine	Insufficient evidence	Insufficient evidence	Investigational
L-threo-3,4-dihydroxyphenylserine	Insufficient evidence	Insufficient evidence	Investigational
Sexual dysfunction			
Sildenafil	<i>Insufficient evidence</i>	<i>Insufficient evidence</i>	<i>Investigational</i>
Gastrointestinal motility problems (Constipation)			
Macrogol	<i>Likely efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Possibly useful</i>
Gastrointestinal motility problems (Anorexia, nausea and vomiting associated with levodopa and/or dopamine agonist treatment)			
Domperidone	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Metoclopramide	Insufficient evidence	Unacceptable risk	Not useful
Sialorrhea			
Ipratropium bromide spray	<i>Insufficient evidence</i>	<i>Insufficient evidence</i>	<i>Investigational</i>
Glycopyrrolate	<i>Efficacious^a</i>	<i>Insufficient evidence</i>	<i>Possibly useful</i>
Botulinum toxin B	<i>Efficacious</i>	<i>Acceptable risk with specialized monitoring</i>	<i>Clinically useful</i>
Botulinum toxin A	<i>Efficacious</i>	<i>Acceptable risk with specialized monitoring</i>	<i>Clinically useful</i>
Urinary frequency, urgency, and/or urge incontinence			
Oxybutynin	Insufficient evidence	Insufficient evidence	Investigational
Tolteradine	Insufficient evidence	Insufficient evidence	Investigational
Flavoxate	Insufficient evidence	Insufficient evidence	Investigational
Propiverine	Insufficient evidence	Insufficient evidence	Investigational
Prazosin	Insufficient evidence	Insufficient evidence	Investigational
Desmopressin	Insufficient evidence	Insufficient evidence	Investigational

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.

^aAlthough efficacious for the very short term, the study provides insufficient evidence for the treatment of sialorrhea in PD exceeding 1 week. PD, Parkinson's disease.

Treatment of Erectile Dysfunction in PD – Summary and Practice Implications

The practice implications for the treatment of erectile dysfunction in PD are summarized in Table 8. There is *insufficient evidence* concerning the use and safety of sildenafil for the treatment of erectile dysfunction in PD. The practice implications are that sildenafil is *investigational* for the treatment of erectile dysfunction in PD.

Drugs to Treat Autonomic Dysfunction in PD: Drugs to Treat Gastrointestinal Motility Problems in PD

At the time of the original EBM review in 2002, domperidone was rated likely efficacious in reducing anorexia, nausea, and vomiting associated with L-dopa and/or dopamine agonist treatment, while there were insufficient efficacy data for metoclopramide in this indication. Because of an aggravation of motor symptoms in PD, the latter has been considered to pose an unacceptable risk in this patient population. Since the original 2002 MDS review, 2 new RCTs were published for the treatment of constipation in PD, 1 using

macrogol, a polyethylene glycol electrolyte solution working on an osmotic basis, and another using the prokinetic agent tegaserod. The latter randomized, double-blind, placebo-controlled study that assessed the efficacy of tegaserod for the of constipation in PD has not been included in this review as the study only included 15 patients and use of tegaserod is restricted (geographically and by indication).⁷²

Macrogol (One New Study,⁷³ Conclusion: Likely Efficacious). Zangaglia et al. (2007)⁷³ examined the efficacy of an isosmotic macrogol electrolyte solution for the treatment of constipation in PD in an 8-week, double-blind, randomized, placebo-controlled parallel-group study. To be included PD patients had to fulfill Rome-II criteria for constipation. Use of drugs affecting gastrointestinal motility was not allowed. Secondary causes of constipation were excluded. Patients received 7.3 g of macrogol plus electrolytes, which had to be dissolved in 250 mL of water each day, or matching placebo. Stool frequency, straining, stool consistency, and use of a rectal laxative as a rescue therapy were evaluated before and after 4 and 8 weeks of treatment. A patient was considered to have responded to

treatment if he/she had complete relief or a marked improvement of the predominant symptom and at least 1 associated symptom or sign, from those aforementioned. Fifty-seven patients were included in this study. No apparent differences in the demographics and PD characteristics between the 2 groups were noted. Ten patients were excluded from the efficacy analysis at week 4 and another 4 at the 8-week analysis due to noncompliance or failure to return for the evaluations. The responder rate was higher in the macrogol group compared with placebo (80% vs 30%, $P < .001$). A higher rate of withdrawals was seen in the macrogol group compared to placebo. AEs were not reported. (Quality score, 74%.)

Efficacy conclusion. Based on this study, macrogol can be rated *likely efficacious* for the treatment of constipation in PD.

Safety conclusion related to macrogol (acceptable risk without specialized monitoring). There were no safety concerns identified in the above reviewed study on macrogol for the treatment of constipation in PD. Although there is weak evidence on safety for macrogol in PD patients with constipation, it can be used with an *acceptable risk without specialized monitoring* due to its low toxicity which has been demonstrated in other patient populations.⁷⁴

Treatment of Gastrointestinal Motility Problems in PD—Summary and Practice Implications

The practice implications for the treatment of gastrointestinal motility problems in PD are summarized in Table 8. The study included lasted 8 weeks. Therefore, the recommendations given here are for the short-term treatment of constipation in PD.

Macrogol is *likely efficacious* for the treatment of constipation in PD. Safety conclusions are that macrogol has an *acceptable risk without specialized monitoring*. The practice implications are that it is *possibly useful* in this indication.

Drugs to Treat Autonomic Dysfunktion in PD: Drugs to Treat Sialorrhea in PD

Drugs to treat sialorrhea in PD were not included in the last review. Two RCTs using muscarinic receptor antagonists for parasympathetic tone suppression at the salivary gland have been published. Moreover, several studies using botulinum toxin A (BTX-A) or B (BTX-B) have been performed. Two double-blind, controlled studies using BTX-A for the treatment of sialorrhea in PD did not include a placebo arm. One of these studies compared the efficacy of intraparotid injections of BTX-A with and without ultrasound guidance,⁷⁵ the other compared the effect of injecting BTX-A into the parotid or submandibular glands.⁷⁶ These 2 studies were not included in this review as

they did not fulfill inclusion criteria (study population <20 patients in both studies) in the absence of a placebo arm, while a third, high-quality study did meet inclusion criteria using BTX-A for the treatment of sialorrhea in PD.⁷⁷ In addition, another parallel-group, double-blind placebo-controlled trial⁷⁸ using BTX-B for the treatment of sialorrhea in PD was not included in the review, as it was performed in a mixed population of 4 patients with neuroleptic-induced parkinsonism and four patients with PD.

Ipratropium Bromide Spray (One New Study,⁷⁹ Conclusion: Insufficient Evidence). Thomsen et al. (2007)⁷⁹ conducted a 5-week (including washout), double-blind, crossover RCT to assess the efficacy and safety of up to 168 µg ipratropium bromide applied sublingually by means of a metered spray. PD patients with bothersome drooling (>1 on UPDRS-II item 6) were included. Patients under acetylcholinesterase, cholinergic, anticholinergic agents, or botulinum toxin and those with hallucinations, urinary retention, or glaucoma were excluded. Patients were randomized to receive either ipratropium or placebo for 2 weeks and then, following a 1-week washout period, switched to the other treatment for a further 2 weeks. The primary outcome measure was an objective measure of saliva production, which was performed by inserting cotton rolls into the mouth of the patients and calculating the rolls' weight difference before and after insertion. In order to assess drug effect at its peak, a measurement 1 hr after each treatment with 2 doses of the study drug was performed. Secondary outcomes included UPDRS-II item 6 and a daily self-evaluation of drooling severity by a validated subjective scale before and 1 hr after treatment. Bromide ipratropium or matching placebo was administered using a sublingual spray. Subjects were instructed to self-administer 1 or 2 doses (each dose had 21 µg of ipratropium bromide) as needed, separated by at least 4 hr and not exceeding 4 times per week (ie, maximum dose 168 µg). Seventeen patients were included in the study, from which only 15 patients completed all study evaluations (dropouts were due to nonmedical reasons). There was no significant difference in weight of saliva measured at baseline or at the end of 2 weeks treatment with ipratropium bromide compared to placebo. Furthermore, post hoc analysis did not reveal any significant change on UPDRS-II item 6 between active treatment and placebo and no differences in the number of doses administered (ipratropium 66.3 ± 28.5 or placebo 63.7 ± 26.8) by patients or in the subjective assessment of drooling severity after drug intake were found. Only 1 patient reported an AE, consisting of dry nasal passages leading to nose bleeding, which was assessed as probably related to the study drug. (Quality score, 73%.)

Efficacy conclusion. Although results appear to be negative, low sample size prevents a change in the conclusion that there is *insufficient evidence* for the efficacy of ipratropium bromide spray for the treatment of sialorrhea in PD.

Glycopyrrolate (One New Study,⁸⁰ Conclusion: Efficacious). Arbouw et al. (2010)⁸⁰ conducted a 4-week, randomized, double-blind, placebo-controlled, cross-over trial with oral glycopyrrolate 1 mg administered twice daily in 23 patients with PD. The trial consisted of a first week without study medication in which the baseline level of sialorrhea was scored followed by 2 sequential treatment periods of 1 week each with a washout period of 1 week between treatments. Patients were required to have marked to severe sialorrhea (≤ 5 on a scale from 1 to 9). The severity of sialorrhea was scored 3 times a day by the patients or a caregiver directly before the time of drug administration (morning, afternoon, evening). The primary outcome measure was the difference in responder rate (ie, a $> 30\%$ decrease in the mean sialorrhea score) between glycopyrrolate and placebo. The secondary outcome measure was the difference in the mean sialorrhea scores between placebo and glycopyrrolate. Data were analyzed on an ITT basis. The mean (SD) sialorrhea score improved from 4.6 (1.7) with placebo to 3.8 (1.6) with glycopyrrolate (mean difference 0.8; 95% CI, 0.02–1.4; $P = .011$). Nine patients (39.1%) with glycopyrrolate had a clinically relevant improvement of at least 30% versus 1 patient (4.3%) with placebo ($P = .021$). There were no significant differences in AEs between glycopyrrolate and placebo treatment. Dry mouth was nonsignificantly more common in the glycopyrrolate arm (52.2%) than in the placebo arm (30.4%; $P = .18$). (Quality score, 95%.)

Efficacy conclusion. Based on this study, glycopyrrolate can be rated *efficacious* for the very short-term treatment of sialorrhea in PD. Although efficacious in 1-week treatment, the study provides insufficient evidence for the treatment of sialorrhea in PD exceeding 1 week.

Safety Conclusion Related to Muscarinic Receptor Antagonists (Ipratropium Bromide Spray and Glycopyrrolate, Conclusion: Insufficient Evidence). There were no safety concerns identified in the above reviewed study on ipratropium bromide spray and glycopyrrolate for the treatment of sialorrhea in PD. Being very poorly absorbed, AEs of inhaled ipratropium resemble those of other anticholinergics and are minimal. In normal clinical use, dryness of the mouth is a common side effect. Ipratropium was extensively studied for possible AEs on mucociliary clearance from the lungs, urinary outflow, and increased intraocular pressure, which are all well-known side effects of anticholinergic drugs. These

were not found to be a problem with ipratropium bromide spray.⁸¹ AEs of glycopyrrolate may include dry mouth, difficult urinary retention, constipation, drowsiness, and blurred visions.⁸² Since glycopyrrolate has a quaternary ammonium structure that is not able to cross the blood-brain barrier in considerable amounts, it should not worsen cognitive dysfunction in PD, although behavioral changes have been reported in children and young adults with cerebral palsy and related neurodevelopmental disabilities.⁸³ There are however only limited data available for PD patients for both ipratropium bromide spray and glycopyrrolate. Therefore there is *insufficient evidence* to make conclusions on the safety of both drugs.

Botulinum Toxin B (BTX-B) (Two New Studies,^{84,85} Conclusion: Efficacious). Ondo et al. (2004)⁸⁴ conducted a 4-week, double-blind, randomized, placebo controlled, parallel-group study that sought to assess the efficacy and safety of intraglandular BTX-B injections. Sixteen PD patients manifesting sialorrhea but not dysphagia were included in the study. Patients were evaluated at baseline and 1 month after treatment by the Drooling Rating Scale (DRS), Drooling Severity and Frequency Scale (DSFS), and a VAS assessing disability incurred by sialorrhea. Salivary gland imaging was accomplished by using a standard method before drug or placebo injection. A total of 2500 Units BTX-B were injected (each parotid gland received 1000 Units of BTX-B and each submandibular gland 250 Units BTX-B). Sixteen patients were included and 8 were assigned to each treatment arm. After 1 month, significant reductions in the DRS (BTX-B: 11.4 ± 3.5 to 7.4 ± 4.7 ; placebo: 11.9 ± 2.0 to 12.3 ± 1.7 ; $P < .05$), DSFS (BTX-B: 7.4 ± 0.9 to 5.1 ± 2.1 ; placebo: 7.4 ± 0.5 to 7.4 ± 0.5 ; $P < .001$) and on the VAS (BTX-B: 70.3 ± 16.4 to 34.0 ± 25.7 ; placebo: 62.1 ± 23.0 to 78.3 ± 14.3 ; $P < .001$) were noted in the BTX-B group compared to placebo. AEs were mild and included dry mouth ($n = 3$), worsened gait ($n = 2$), diarrhea ($n = 1$), and neck pain ($n = 1$) in the BTX-B group. (Quality score, 79%.)

Lagalla et al. (2009)⁸⁵ conducted a 4-week, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy of BTX-B treatment on PD-related drooling. Patients had to manifest complaints about social restriction due to drooling and to have a UPDRS-II item 6 score ≥ 2 to be included. Patients previously treated with BTX were excluded. Subjects received 4000 units of BTX-B or matching-placebo in each parotid gland. Patients were assessed at baseline and one month after treatment by means of the DSFS, VAS dealing with familial- and social-related embarrassment. Hypersalivation and dysphagia were also assessed by the respective UPDRS-II items and the Patient Global Impression (PGI) score. Finally, objective measurement of the amount of buccal saliva was performed by

placing dental rolls into the mouth and calculating the weight difference before and after insertion. Thirty-six subjects were included, of whom 18 were assigned to each treatment arm. There was a significant reduction in the score on sialorrhea rating scales (77.0 ± 12.2 to 40.4 ± 18.1) and in the objective measurements (2.1 ± 1.1 to 1.4 ± 0.9) for the BTX-B treated group vs. placebo (both $P < .0001$). No significant variation was observed in dysphagia scores. Three patients on BTX-B complained of mild, transient swallowing difficulties that resolved within 2 weeks of treatment. No other AEs were observed. (Quality score, 82%.)

Efficacy conclusion. Although these were 2 studies with a small sample size, due to the consistent and large effect size, BTX-B can be considered *efficacious* for the treatment of sialorrhea in PD.

Botulinum Toxin A (BTX-A) (One New Study,⁷⁷ Conclusion: Efficacious). Lagalla et al. (2006)⁷⁷ studied the effect of BTX-A on drooling in PD in a double-blind, randomized, placebo-controlled, parallel-group over 1 month. Inclusion criteria were complaints of social restrictions caused by drooling and a score ≥ 2 on UPDRS-II item 6. Patients previously treated with BTX, a UPDRS-II dysphagia score > 1 , or taking anticholinergic drugs were excluded. Subjects received 50 Units of BTX-A or a matching-placebo in each parotid gland. Patients were assessed at baseline and one month after treatment by means of a VAS dealing with familial- and social-related embarrassments as well as with drooling frequency. Dysphagia was also assessed using the respective UPDRS-II items. Finally, objective measurement of the amount of buccal saliva was performed by placing dental rolls into the mouth and then calculating the difference in weight before and after insertion. Thirty-two patients were included, of whom 16 were randomly assigned to each treatment arm. No differences in demographics or disease characteristics between the groups were observed. Information about medication consumption was not provided. Patients receiving BTX-A showed significant reductions in VAS scores (VAS-D: 77 ± 16 to 45 ± 18 ; $P < .0001$; VAS-FD: 76 ± 20 to 46 ± 18 ; $P < .001$; VAS-SD: 77 ± 23 to 53 ± 24 ; $P < .01$) and buccal saliva content (2.7 ± 1.4 to 1.3 ± 0.6 ; $P < .0001$) compared to the placebo group. At 1 month posttreatment, 37% of BTX-A-treated patients scored < 2 on the UPDRS-ADL drooling item, compared with 6% of patients in the placebo group (OR 9.0; 95% CI, 0.9–86.5). No differences in the dysphagia scores were observed. One patient complained about transient swallowing difficulties. (Quality score, 79%.)

Efficacy conclusion. Based on the placebo-controlled high quality study by Lagalla et al.⁷⁷ demonstrating efficacy of BTX-A with a large effect size, and 2 placebo-controlled studies in mixed populations including

PD patients^{86,87} supporting the efficacy, BTX-A can be rated as *efficacious* for the symptomatic control of sialorrhea in PD.

Safety Conclusion Related to Botulinum Toxin A And B (Conclusion: Acceptable Risk with Specialized Monitoring). There were no safety concerns identified in the above-reviewed studies on BTX-A and BTX-B for the treatment of sialorrhea in PD. Consistently reported side effects of BTX-A and BTX-B were dry mouth and transient swallowing difficulties including rarely severe dysphagia. Therefore BTX-A and BTX-B are considered to pose an *acceptable risk with specialized monitoring* of the training of the application of BTX-A and BTX-B, as it should be given by well-trained physicians with accession to specialized monitoring techniques.

Treatment of Sialorrhea in PD – Summary and Practice Implications

The practice implications for the treatment of sialorrhea in PD are summarized in Table 8. None of the studies exceeded study durations of 1 month. Therefore, all recommendations given here are for the short-term treatment of sialorrhea in PD.

There is *insufficient evidence* concerning the efficacy and safety of ipratropium bromide spray for the treatment of sialorrhea in PD, and the practice implications are that it is *investigational* for the treatment of sialorrhea in PD. Glycopyrrolate is *efficacious* for the very short-term treatment of sialorrhea in PD, but there is insufficient evidence for the treatment of sialorrhea in PD exceeding 1 week. There is *insufficient evidence* to make conclusions on its safety. Therefore, the practice implications are that it is *possibly useful* for the short-term treatment of sialorrhea in PD.

BTX-A and BTX-B are considered *efficacious* for the treatment of sialorrhea in PD. As far as safety is concerned, they have an *acceptable risk with specialized monitoring*. The practice implications are that they are *clinically useful* for the treatment of sialorrhea in PD.

Drugs to Treat Autonomic Dysfunction in PD

In the previous EBM reviews, disorders of sleep and wakefulness were not assessed; therefore, the task force reviewed all available RTCs in that domain. The following sleep disorders in PD are covered here: insomnia, REM sleep behavior disorder (RBD), excessive daytime somnolence (EDS), and sudden onset of sleep. As far as insomnia is concerned, several definitions are used in the literature. We have adopted a broad definition in order to be able to capture all available studies that sought to evaluate therapeutic interventions for nocturnal sleep disturbance in PD. In this way, we consider insomnia as a difficulty in initiating and maintaining sleep. Only studies in which sleep disturbance was a primary outcome were included. Regarding the etiology

of insomnia, we have excluded studies on restless legs syndrome, periodic limb movements, and sleep apnea.

Drugs to Treat Disorders of Sleep and Wakefulness:

Drugs to Treat Insomnia in PD

Five RCTs have assessed the efficacy of the controlled-release formulations of levodopa/carbidopa (levodopa/carbidopa CR)⁸⁸ at bedtime and pergolide,⁸⁹ eszopiclone⁹⁰ and melatonin^{91,92} to treat insomnia in PD. In addition, a 12-week, multicenter, randomized (in a 2:1 ratio), parallel-group, double-blind placebo-controlled trial⁹³ sought to determine the efficacy of rotigotine in treating early morning motor function and nocturnal sleep disturbance in 287 patients with PD and unsatisfactory early-morning motor symptom control. Early-morning motor function and nocturnal sleep disturbance were assessed as mean treatment differences in the 2 co-primary efficacy endpoints: UPDRS-III score measured motor function in the early morning prior to any medication intake and the modifield Parkinson's Disease Sleep Scale (PDSS)-2 total scores measured nocturnal sleep disturbance, both showed significantly greater improvement with rotigotine than placebo from baseline to end of maintenance. However, insomnia and nocturnal sleep disturbance were not defined in the inclusion criteria. Therefore, this study was not included for review. Furthermore, with the design used, we cannot conclude if the improvement in sleep is derived from primary effects of rotigotine on sleep or due to its effect on parkinsonism-related nocturnal disability leading to improved sleep. Another 10-day, randomized, parallel-group, double-blind sham stimulation-controlled trial sought to determine the efficacy of rTMS on sleep using the PDSS and actigraphy in 19 patients with PD.⁹⁴ Stimulation had no effect over actigraphic variables, while the PDSS was significantly improved by the stimulation with equal effects in the groups receiving real or sham stimulation. However, sleep disturbance was not defined in the inclusion criteria. Therefore, this study was not included for review.

Controlled-Release Formulation of L-Dopa/Carbidopa at Bedtime (One New Study,⁸⁸ Conclusion: Insufficient Evidence). Stocchi et al. (1998)⁸⁸ conducted a double-blind placebo-controlled crossover study of L-dopa/carbidopa CR (Sinemet CR 200/50) at bedtime for the treatment of sleep quality and sleep-related motor disturbances in 40 patients with PD and motor fluctuations. The trial consisted of 2 sequential treatment periods lasting 2 weeks each with a washout period of 10 days between each. Outcome measures included the number of hours of sleep, the number of times awakened (recorded on a 4-point scale: 1 = none, 4 = ≥ 4 times), sleep onset latency (recorded on a 4-

point scale: 1 = 15 minutes, 4 = >60 minutes), overall sleep rating (evaluated using a 4-point severity scale: 1 = unsatisfactory, 4 = very satisfactory), nocturnal pain (assessed using an ordinal severity scale: 0 = normal; 4 = maximal severity), and sleep-related motor disturbances including nocturnal akinesia, dystonia, and cramps (also assessed by an ordinal severity scale: 0 = normal, 4 = maximal severity). L-Dopa/carbidopa CR did not improve sleep latency (Sinemet CR: mean \pm SE 1.9 \pm 0.11, placebo: 2.6 \pm 0.1, the number of awakenings (L-dopa/carbidopa CR: 2.5 \pm 0.1, placebo: 2.6 \pm 0.1) and the overall sleep rating (very satisfactory: L-dopa/carbidopa CR: 77%, placebo: 65%). There was a trend for increased sleep time under L-dopa/carbidopa CR (mean \pm SE 6.3 \pm 0.1 hr) compared to placebo (5.8 \pm 2 hr) ($P = .07$). L-Dopa/carbidopa CR significantly improved nocturnal akinesia. Assessment of AEs is not given in the paper. (Quality score, 61%.)

Efficacy conclusion. Based on this study, there is *insufficient evidence* for conclusions to be made on the efficacy of L-dopa/carbidopa CR (Sinemet CR 200/50) administered at bedtime for the treatment of insomnia in PD.

Pergolide (One New Study,⁸⁹ Conclusion: Insufficient Evidence). Comella et al. (2005)⁸⁹ conducted a randomized, double-blind, placebo-controlled, parallel-group clinical trial to test the effectiveness and safety of pergolide as add-on therapy to L-dopa in improving sleep efficiency and sleep fragmentation. Twenty-six PD patients (4 withdrew consent before randomization) with ≥ 3 PD-attributable awakenings per night (measured by wrist actigraph) occurring ≥ 3 nights per week were randomized to receive pergolide or placebo. Patients with dementia, depression, psychosis, hallucinations, or receiving dopamine agonist treatment or sleeping medications were excluded. Sleep efficiency and fragmentation were measured by a wrist actigraph worn on the nondominant limb. The drug dosage was started at 0.05 mg 1 hr before bedtime and increased up to 1 mg in divided doses, and kept as such during the 6-week maintenance period. Four patients dropped out and complete data was available from 21 patients (9 in the pergolide group and 12 in the placebo group). All AE-related dropouts occurred in the active treatment arm, and included fainting, light-headedness, constipation, and viral hepatitis. Results showed that pergolide was associated with worse sleep quality compared to placebo: mean reduction in sleep efficiency with pergolide was 7% versus 0.6% with placebo ($P = .049$); median worsening of movement and fragmentation index with pergolide was 4 versus an improvement of 1 with placebo ($P = .034$). (Quality score, 45%.)

Efficacy conclusion. Despite of the findings suggesting a harmful outcome, the low quality score precludes definite assessment; as such there is *insufficient*

evidence for a conclusion to be made on the efficacy of pergolide for the treatment of insomnia in PD.

Safety Conclusions Related to L-Dopa/Carbidopa CR, Pergolide, and Rotigotine (See Article on the “Treatments for the Motor Symptoms of PD”). L-Dopa/carbidopa CR and pergolide are evaluated in the EBM review of the treatments for the motor symptoms of PD. The use of pergolide has an *acceptable risk with specialized monitoring*, while the use of L-dopa/carbidopa has an *acceptable risk without specialized monitoring*.

Eszopiclone (One New Study,⁹⁰ Conclusion: Insufficient Evidence). Menza et al. (2010)⁹⁰ conducted a 6-week double-blind, parallel-group RCT of eszopiclone versus placebo in 30 (n = 15 eszopiclone, n = 15 placebo) PD patients with insomnia. The primary outcome measure was patient-diary-reported total sleep time (TST). Secondary endpoints comprised wake after sleep onset, the number of awakenings, several measures of sleep quality, the CGI-S and CGI-I of sleep, daytime functioning on a 10-point Likert scale (1 unable to function; 10 normal functioning), daytime alertness on a 10-point Likert scale (1 not at all alert; 10 extremely alert), fatigue severity (FSS), QoL (PDQ-8), motor functioning (UPDRS), caregiver QoL (multi-dimensional caregiver burden inventory; MCBI), and depression (Center for Epidemiologic Studies Depression Scale [CES-D]). Inclusion criteria were defined as sleep maintenance insomnia (≥ 3 of 7 nights with ≥ 2 awakenings nightly, or a TST < 6.5 hr), or sleep latency insomnia (≥ 3 of 7 nights of sleep latency > 30 minutes), as well as clinically significant daytime distress or impairment (related to insomnia) during the 2 weeks before baseline. Nineteen patients (n = 12 eszopiclone, n = 7 placebo) completed the study. Data were analyzed using an ITT approach. Study drug dosing was stratified by age: 3 mg of eszopiclone or matching placebo at night if < 65 years; 2 mg of eszopiclone or placebo if ≥ 65 years. The results showed a nonsignificant increase in TST from 4.5 ± 1.3 to 5.7 ± 1.2 in the eszopiclone arm and from 5.3 ± 1.3 to 6.0 ± 1.2 for placebo. Significant differences, favoring eszopiclone, were found for several secondary endpoints including the number of awakenings (eszopiclone: from 2.0 ± 1.5 to 1.0 ± 1.4 ; placebo: from 1.7 ± 1.4 to 1.8 ± 1.2 ; $P = .035$), quality of sleep (eszopiclone: from 3.4 ± 2.1 to 5.0 ± 2.1 ; placebo: from 3.8 ± 1.9 to 5.3 ± 2.2 ; $P = .018$) and CGI-improvement in sleep (eszopiclone: 2.3 ± 1.2 ; placebo: 3.2 ± 1.5 ; $P = .035$). Eleven patients (37%) dropped out of the trial (3 in the eszopiclone group, 2 due to a lack of efficacy, and 1 because of nausea; 8 dropped out of the placebo arm, 6 due to lack of efficacy, 1 because of increased rigidity, and 1 who moved residency). Overall, 30% of patients reported AEs, with a similar frequency between treatment arms. Two of 15 patients in the eszo-

piclone arm reported AEs that were assessed as related to the study drug. Both of them had sedation during the day and 1 also had dizziness. (Quality score, 74%.)

Efficacy conclusion. Based on this study, there is *insufficient evidence* to conclude on the efficacy of eszopiclone for the treatment of insomnia in PD.

Safety conclusion related to eszopiclone (conclusion: acceptable risk without specialized monitoring). There were no new safety concerns identified in the above study on eszopiclone for the treatment of insomnia in PD. Eszopiclone has been shown to be safe—*acceptable risk without specialized monitoring*—and *efficacious* for the short-term treatment (2 weeks) of chronic, primary insomnia in older adults up to a dosage of 2 mg, the most common AEs of eszopiclone are unpleasant taste, headache, somnolence, dizziness, and dry mouth; neuropsychiatric AEs include aggressive behavior, confusion, agitation, auditory and visual hallucinations, and worsening of depression.^{95,96}

Melatonin (Two New Studies,^{91,92} Conclusion: Insufficient Evidence). Dowling et al. (2005)⁹¹ conducted a 10-week randomized, double-blind, placebo-controlled, crossover trial in 43 PD patients with subjective complaints of unsatisfactory nocturnal sleep. Patients were excluded if their mean sleep efficiency was $> 80\%$ or if nocturnal TST was ≥ 7 hr. The aim of the study was to compare the effects of melatonin 5 mg versus melatonin 50 mg versus placebo in improving nocturnal sleep, daytime somnolence and daytime levels of functioning. This study consisted of a 2-week screening period, 3 treatment periods lasting 2 weeks each, and two 1-week washout between periods. Melatonin or placebo was administered 30 minutes before bedtime. Three patients dropped out. Using actigraphic measures, melatonin 50 mg significantly increased nocturnal sleep time (10 minutes) versus placebo ($P < .05$). Subjective outcome measures using the General Sleep Disturbance Scale showed that melatonin 5 mg significantly improved overall sleep quality compared to placebo ($P < .05$), but this was not the case for melatonin 50 mg. Melatonin did not significantly improve EDS versus placebo, according to the ESS and the Stanford Sleepiness Scale. Two patients reported minor AEs. (Quality score, 65%.)

Medeiros et al. (2007)⁹² conducted a 4-week, double-blind, placebo-controlled, parallel-group study of melatonin 3 mg compared to placebo for the treatment of sleep dysfunction in 20 patients with PD with H&Y stages 1–3. PD patients had to be on stable anti-parkinsonian medication for 30 days prior to inclusion in the study. Inclusion criteria did not define criteria for sleep dysfunction. Exclusion criteria included the use of antidepressants or sedatives. The primary outcome variables included subjective sleep quality

(Pittsburgh Sleep Quality Index) and objective sleep quality (polysomnography; sleep latency, TST, sleep efficiency and sleep fragmentation). Secondary outcome measures included daytime somnolence (ESS) and UPDRS scores. Statistical analysis was performed on 18 patients (melatonin, $n = 8$; placebo, $n = 10$) who completed the study. According to assessment with the Pittsburgh Sleep Quality Index, melatonin improved sleep quality significantly (from a mean \pm SD of 8.3 ± 4.5 to 4.5 ± 3.1) compared to placebo (from 9.9 ± 3.7 to 8.7 ± 4.0 ; $P = .03$). No significant group differences were detected for the other outcome measures. No AEs were experienced by either study group. (Quality score, 69%.)

Efficacy conclusion. Based on these 2 studies, there is *insufficient evidence* to conclude on the efficacy of melatonin at doses of 3 to 5 mg and 50 mg for the treatment of insomnia in PD.

Safety conclusions relating to melatonin at 3 to 5 mg (conclusion: acceptable risk without specialized monitoring) and melatonin at 50 mg (conclusion: insufficient evidence). There were no safety concerns identified in the above reviewed study on melatonin for the treatment of insomnia in PD. Melatonin appears to cause very few side effects, specifically in the short term, (up to 3 months) when taken at doses from 0.3 mg to 7.5 mg by healthy individuals.^{97,98} Some AEs may include headache, nausea or next day grogginess or irritability. Given its wide availability and over-the-counter use in many countries, melatonin at doses from 3 to 5 mg can be used with an *acceptable risk without specialized monitoring*. On the other hand for melatonin at 50 mg, there is *insufficient evidence* for safety in PD.

Treatment of Insomnia in PD—Summary and Practice Implications

The practice implications for the treatment of insomnia in PD are summarized in Table 9. None of the studies exceeded a duration of 10 weeks. Therefore, all recommendations given here are for the short-term treatment of insomnia in PD.

There is *insufficient evidence* for pergolide in the treatment of insomnia in PD. Safety conclusions are that pergolide has an *acceptable risk with specialized monitoring*. The practice implications are that due to safety issues, treatment of insomnia with pergolide is considered *not useful* for conditions with chronic use.

There is *insufficient evidence* regarding the efficacy of the other drugs reviewed (L-dopa/carbidopa CR, eszopiclone, melatonin 3 mg to 5 mg, melatonin 50 mg) for the treatment of insomnia in PD. Safety conclusions are that L-dopa/carbidopa CR, eszopiclone, and melatonin 3 mg to 5 mg have an *acceptable risk without specialized monitoring* and that pergolide has an *acceptable risk with specialized monitoring*. There is *insufficient evidence* to

make conclusions on the safety of melatonin 50 mg/day. Practice implications are that these drugs are *investigational* for the treatment of insomnia in PD.

Drugs to Treat Excessive Daytime Sleepiness and the Sudden Onset of Sleep

No studies concerning the sudden onset of sleep were identified. Three RCTs have assessed the efficacy of the wake-promoting agent modafinil to treat EDS in PD.

Modafinil (Three New Studies,^{99,100} Conclusion: Insufficient Evidence). Högl et al. (2002)⁹⁹ randomized 15 PD patients with subjective complaints of EDS and an ESS ≥ 10 , in a 6-week double-blind, placebo-controlled, crossover trial in order to compare the efficacy of modafinil to placebo. Patients with MMSE ≤ 24 , atypical PD, current drug-induced psychosis and sleep disorders, including sleep-disordered breathing and RBD were excluded. The trial consisted of two 2-week treatment periods separated by a 2-week washout. Modafinil or placebo were given in a single morning dose of 100 mg in the first week and 200 mg in the second week. Outcome measures were the ESS, the Maintenance of Wakefulness Test (MWT), a sleep log, and the BDI. Twelve patients completed the trial. ESS scores significantly improved with modafinil (3.42 ± 3.90) versus placebo (0.83 ± 1.99 ; $P = .011$), but the latency to sleep in the MWT was not significantly different between modafinil and placebo ($P = .139$). The BDI scores were similar between modafinil and placebo, as were the AEs. The side effects with modafinil were mild and included insomnia ($n = 1$), constipation ($n = 1$), diarrhea ($n = 2$), and dizziness ($n = 1$). (Quality score, 60%.)

Adler et al. (2003)¹⁰¹ conducted a 7-week double-blind, crossover RCT that evaluated the effect of modafinil versus placebo in PD patients (screened 27) with subjective complaints of EDS and an ESS score ≥ 10 . Patients with an MMSE ≤ 24 , a history of a psychiatric illness, EDS related to known sleep apnea, periodic limb movement disorder (including restless legs syndrome), or shift-work were excluded. There were two 3-week treatment periods separated by a 1-week washout. Twenty-one patients received 200 mg/day modafinil or placebo without dose titration and without the possibility of adjusting dosage. One patient dropped out (personal reasons). Because of a significant carryover effect on the ESS score ($P = .013$), the statistical analysis was restricted to phase 1 of the originally planned crossover study. The primary outcome measure was the ESS, while secondary outcome measures included the patient and investigator-rated CGI-C, the EDS rating scale, the modified Fatigue Assessment Inventory, the Excessive Daytime Fatigue rating scale, the UPDRS, the H&Y stage, and the Schwab & England Activities of Daily Living

TABLE 9. Conclusions on drugs to treat disorders of sleep and wakefulness in PD

	Efficacy	Safety	Practice implications
Insomnia			
Controlled-release formulation of levodopa/carbidopa	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Pergolide	<i>Insufficient evidence</i>	<i>Acceptable risk with specialized monitoring</i>	<i>Not useful</i>
Eszopiclone	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Melatonin 3–5 mg	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Melatonin 50 mg	<i>Insufficient evidence</i>	<i>Insufficient evidence</i>	<i>Investigational</i>
Excessive daytime somnolence and the sudden onset of sleep			
Modafinil	<i>Insufficient evidence</i>	<i>Insufficient evidence</i>	<i>Investigational</i>

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds. PD, Parkinson's disease.

scale. ESS score changes from baseline significantly favored modafinil (from 17.8 ± 4.2 to 14.4 ± 5.7) versus placebo (from 16.0 ± 4.2 to 17.0 ± 5.1) (95% CI, -8.6 to -0.2 ; $P = .039$), whereas differences between modafinil and placebo were not statistically significant for secondary outcome measures. AEs were similar between modafinil and placebo. (Quality score, 83%.)

Ondo et al. (2005)¹⁰⁰ conducted a 4-week randomized, double-blind, placebo-controlled, parallel-group trial which compared the effect of modafinil versus placebo in 40 PD patients with an ESS score ≥ 10 . Patients with narcolepsy, known sleep apnea, and pregnancy were excluded. Patients were given modafinil or placebo 100 mg upon waking and at lunch (total 200 mg/day) for the first week and then the dose was doubled to 2×200 mg/day. After 1 week on 400 mg, the patients could decrease the dose to 200 mg following the occurrence of AEs. No mean study drug dose was given in the original publication. The primary outcome measure was the change in ESS score; secondary endpoints included the UPDRS, the FSI, the HDRS, the standard multiple sleep latency test (MSLT), global impressions and the SF-36. Thirty-seven patients completed the study. ITT analysis revealed no significant difference in the primary outcome between modafinil and placebo: change in ESS score with modafinil was from 15.7 ± 3.1 to 13.5 ± 4.8 and with placebo was from 16.0 ± 3.7 to 14.5 ± 4.8 ($P = .28$). Differences between modafinil and placebo were also not statistically significant for subjective secondary outcome measures; the MSLT results worsened in both groups, but did not differ significantly between modafinil (from 6.4 ± 5.1 to 4.9 ± 3.6 minutes) and placebo (from 4.5 ± 3.9 to 4.1 ± 3.4 minutes) ($P = .14$). The frequency of AEs was similar between both treatment groups. AEs in the modafinil group included, nausea and anxiety ($n = 1$), dry mouth ($n = 1$), dizziness ($n = 1$), and back pain ($n = 1$). (Quality score, 90%.)

Efficacy conclusion. Based on these 3 studies with conflicting efficacy results, there is *insufficient evidence*

to conclude on the efficacy of modafinil for the treatment of EDS in PD.

Safety conclusion with regard to modafinil (conclusion: insufficient evidence). There were no new safety concerns identified in the above reviewed study on modafinil for the treatment of EDS in PD. Rare cases of serious or life-threatening rash, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported in adults and children in worldwide postmarketing experience. Estimates of the incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.¹⁰² Psychiatric AEs have been reported in patients treated with modafinil with many, but not all patients having had a prior psychiatric history; postmarketing AEs associated with the use of modafinil include mania, delusions, hallucinations, suicidal ideation, and aggression, some resulting in hospitalization.¹⁰² As mentioned above in the section on fatigue in PD, the lack of safety data, especially over the long term, concerning modafinil's cardiovascular effects—including increase of blood pressure or elevated heart rate in elderly populations,³⁷ mean that there is *insufficient evidence* to make conclusions on its safety.

Treatment of Excessive Daytime Sleepiness in PD—Summary and Practice Implications

The practice implications for the treatment of EDS in PD are summarized in Table 9. None of the studies exceeded a duration of 4 weeks. Therefore, all recommendations given here are for the short-term treatment of EDS in PD.

There is *insufficient evidence* to conclude on the efficacy or safety of modafinil for the treatment of EDS in PD. Practice implications are that modafinil is *investigational* for the treatment of EDS in PD.

Discussion

This updated review includes RCTs from January 2002 for the treatment of the non-motor symptoms of

PD. The large number of studies indicates that this is a continually changing field and that there is a need for constant updates. Conclusions for several interventions have changed from the prior review, while for other interventions new studies have confirmed prior conclusions. Furthermore, several domains and symptoms of the non-motor symptom complex in PD were not considered previously at the time of the original review. For these indications, studies published before January 2002 were also considered by the task force.

Overall conclusions according to disease indications are summarized in Tables 3 to 8 and hereunder.

- Depression or depressive symptoms: The dopamine agonist pramipexole is efficacious, and the TCAs nortriptyline and desipramine are likely efficacious; there is insufficient evidence for any other drug or rTMS in this indication.
- Fatigue: There is insufficient evidence for modafinil and methylphenidate.
- Pathological punning: There is insufficient evidence for amantadine.
- Dementia: The cholinesterase inhibitor rivastigmine is efficacious, but there is insufficient evidence for the cholinesterase inhibitors donepezil and galantamine as well as for memantine.
- Psychosis: Clozapine is efficacious and poses an acceptable risk with specialized monitoring of blood count; and olanzapine is unlikely efficacious with an unacceptable risk of motor deterioration. There is insufficient evidence for quetiapine.
- Orthostatic hypotension: There is insufficient evidence for midodrine, fludrocortisone, dihydroergotamine, etilefrine hydrochloride, indomethacine, yohimbine and L-threo-3,4-dihydroxyphenylserine.
- Erectile dysfunction: There is insufficient evidence for sildenafil.
- Gastrointestinal motility problems: Macrogol is likely efficacious for the treatment of constipation. There is insufficient evidence for tegaserod and cisapride, which have an unacceptable risk of cardiovascular ischemic events. For the treatment of anorexia, nausea and vomiting associated with L-dopa and/or dopamine agonist treatment, domperidone remains likely efficacious, while there are still insufficient efficacy data for metoclopramide, which has an unacceptable risk in patients with PD because of an aggravation of motor symptoms.
- Sialorrhea: BTX-A and -B as well as glycopyrrolate (short term of 1 week) are efficacious, for the latter there is insufficient evidence to make conclusions on the efficacy of treatment exceeding 1 week. There is insufficient evidence for ipratropium bromide spray.
- Insomnia: For any treatment there is insufficient evidence.

- Excessive daytime sleepiness: There is insufficient evidence for modafinil.
- There were no randomized clinical trials that met inclusion criteria for the treatment of anxiety disorders, apathy, medication-related impulse control disorders and related behaviors other than pathological gambling, RBD, or urinary dysfunction. Therefore, there is insufficient evidence for the treatment of these indications.
- With the exception of 1 low-quality study, which lasted 8 months,¹⁶ all of the studies included in this review had a maximum duration of 6 months. Therefore, these recommendations refer to the short-term management of a given non-motor symptom in PD.

Overall, the treatments that are efficacious for the short-term management of the different non-motor symptoms are as follows: pramipexole for the treatment of depressive symptoms, clozapine for the treatment of psychosis, rivastigmine for the treatment of dementia, and BTX-A and -B as well as glycopyrrolate for the treatment of sialorrhea. The task force has identified a number of efficacious treatments, while for most of the other interventions there is insufficient evidence to make adequate conclusions on their efficacy. The present EBM review summarizes the best available evidence from recently published RCTs. A quality assessment for each RCT was calculated. For each indication, the available RCTs were considered using predefined criteria and efficacy, safety, and implications for clinical practice were derived from the available evidence by the task force experts. Where there was unsatisfactory evidence, this has been stated. Indeed, for several indications further RCTs are required. Several of the studies with positive outcome results included small sample sizes,^{10,15,32,73,80} and therefore did not allow a conclusion of *efficacious* to be made due to the risk of Type I or Type II errors leading to false-positive or false-negative results. Studies with positive outcome results and small sample sizes were considered to be *likely efficacious*. Several of the studies did not include a placebo arm,^{8,16,7,14,13,53,54,67,75,76} which is unsatisfactory given that there is no known standard response for the treatment of the non-motor symptoms of PD. Indeed, data from trials in major depression have shown a very high and variable placebo response.¹⁰³ Furthermore, there were no RCTs that met inclusion criteria for the treatment of anxiety disorders, apathy, medication-related impulse control disorders, and related behaviors other than pathological gambling, RBD, sweating, or urinary dysfunction. Safety profiles of most of the interventions reviewed in this update are largely based on studies performed in non-PD populations without firm evidence of efficacy from RCTs in the PD population. In the absence of such, there was

insufficient evidence to conclude on the safety for many (see Tables 3–9) of the interventions reviewed.

Although common, there is a paucity of research concerning the diagnosis and treatment of non-motor symptoms in PD. Indeed, non-motor symptoms of PD are frequently missed or undeclared during routine consultations¹⁰⁴ and well-performed large-scale RCTs for the treatment of the different non-motor symptoms in PD are lacking. However, there is an ongoing interest in this field of research which is reflected (1) by the establishment of new screening tools and rating scales to assess non-motor symptoms such as the non-motors symptom questionnaire (NMSQuest),¹⁰⁵ the non-motor symptoms scale (NMSS),¹⁰⁶ and the revised version of the UPDRS (MDS-UPDRS)^{107,108} and (2) by an increase of level-I studies over the last decade. For the first MDS EBM review⁵ a total of 7 level-I studies were available, while we were able to include 52 level-I studies for the current revised version.

The criteria for recognizing the non-motor symptoms in PD are constantly changing. For example, the clinical trials on the treatment of depression used varying inclusion criteria to define depression. Some studies required the presence of a major depressive episode as defined by DSM-IV,^{7–12} which is traditional for depression treatment studies and will result in a sample of patients with depressive symptoms of moderate-severe intensity. Other studies enrolled patients either with depressive syndromes of lesser severity (eg, minor depressive episode or dysthymia)^{13–16,17} or clinically-significant depressive symptoms on the basis of a depression rating scale score.^{18,19} There are several reasons why the definition of depression in PD used in clinical trials should be broadened: (1) milder forms of depression appear to be at least as common as major depression in PD, and emerging evidence in the general population suggests that non-major depression is of clinical significance; (2) due to ongoing questions regarding the construct validity of the DSM-IV major depressive episode criteria for depression in PD, there has been an interest in applying less restrictive depressive syndrome criteria to capture clinically significant depression in PD. Additional research is needed to further delineate and validate depression subtypes in PD, and to determine if such subtypes differentially respond to treatment. The same concerns are likely applicable to cognitive dysfunction in PD, as subtle cognitive deficits are almost universally identified, even in early PD, upon detailed neuropsychological testing.^{109,110} Cognitive dysfunction in PD without dementia has been labeled “mild cognitive impairment” (PD-MCI) by some, although the utility and validity of the term PD-MCI is subject to debate.^{110–112} Additional research is needed to further delineate and validate cognitive dysfunction and its subtypes in PD, and

to determine if such subtypes differentially respond to treatment. Indeed, very recently diagnostic criteria for dementia associated with PD were developed based on characteristic clinical features identified on a comprehensive review of the existing literature.^{110,113} Various inclusion criteria were also used to define psychosis. Some studies required the presence of psychotic features such as hallucinations or delusions, while other studies enrolled patients with visual hallucinations only or clinically significant psychotic symptoms on the basis of a psychosis rating scale score. Indeed, psychosis in PD is often used as an umbrella term encompassing a spectrum of disordered thought and perception including illusions, and delusions, hallucinations, and confusion. Illusions and hallucinations are the predominant psychotic manifestations in PD and most commonly are visual in nature.¹¹⁴ However, the use of different inclusion criteria for clinical trials may limit comparability among the trials. As there are no standardized diagnostic criteria for psychosis associated with PD, provisional diagnostic criteria for psychosis associated with PD were established. These criteria are inclusive and contain descriptions of the full range of characteristic symptoms, chronology of onset, duration of symptoms, exclusionary diagnoses, and associated features such as dementia. Although these criteria require validation, they are a potential indication for therapy development.¹¹⁵ Among the trials on insomnia, various causes of insomnia in PD were considered. Insomnia in PD is caused by a multitude of factors including primary dysfunction in the regulation of the sleep-wake cycle, secondary effects of parkinsonian motor and non-motor symptoms on sleep onset and maintenance, effects of PD medications on sleep and wakefulness as well as the impact of comorbid conditions such as restless legs syndrome/periodic limb movements of sleep or sleep-disordered breathing. Clinical trials in this field therefore have to consider and assess a multitude of factors of insomnia when designing trials for this indication.

The same or similar data reviewed by different bodies can produce seemingly different conclusions. At the same time as the MDS was working on the previous and current reviews, the Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) has developed practice parameters for the different non-motor aspects in PD, published in 3 different reports.^{116–118} The apparent discrepancies relate to different methodologies and different emphasis. This report is an EBM review of data, while the practice parameters are clinical guidelines, which by definition might take in consideration context variables. Evidence-based conclusions are only 1 component of the final data set that clinicians must use in

making treatment decisions. The usefulness of all EBM reviews in day-to-day clinical practice requires integration of level-I evidence from well conducted RCTs with a number of other factors to decide on the best therapy required for an individual patient. These factors include physicians' individual clinical experience and judgment; patient preferences as well as economic influences that all contribute to the final preferred treatment choice. EBM reports offer investigators a clear view of areas where further research is needed. In such areas the prior studies can be used as a background for the design of new studies, and given that EBM has a specific technique and methodology, new designs can be applied to provide assurance of high quality assessment scores, regardless of study outcome. As such, the authors and the MDS hope that this document will serve to encourage creative study designs anchored in the key elements and criteria to produce high evidence-based assessment rankings.

The MDS is committed to an ongoing process of updating material so that these EBM reports remain current and useful to clinicians. Ongoing plans include a more regular updating of the official reports and a program to upload new published trials that will be reviewed in the next critique to the MDS website so that investigators and clinicians can keep abreast of new developments. ■

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