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

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ABSTRACT: The objective was to update previous evidence-based medicine reviews of treatments for motor symptoms of Parkinson's disease published between 2002 and 2005. Level I (randomized, controlled trial) reports of pharmacological, surgical, and nonpharmacological interventions for the motor symptoms of Parkinson's disease between January 2004 (2001 for nonpharmacological) and December 2010 were reviewed. Criteria for inclusion, clinical indications, ranking, efficacy conclusions, safety, and implications for clinical practice followed the original program outline and adhered to evidence-based medicine methodology. Sixty-eight new studies qualified for review. Piribedil, pramipexole, pramipexole extended release, ropinirole, rotigotine, cabergoline, and pergolide were all efficacious as symptomatic monotherapy; ropinirole prolonged release was likely efficacious. All were efficacious as a symptomatic adjunct except pramipexole extended release, for which there is insufficient evidence. For prevention/delay of motor fluctuations, pramipexole and cabergoline were efficacious, and for prevention/delay of dyskinesia, pramipexole, ropinirole, ropinirole prolonged release, and cabergoline were all efficacious, whereas pergolide was likely efficacious. Duodenal infusion of levodopa was likely efficacious in the treatment of motor complications, but the practice implication is investigational. Entacapone was nonefficacious as a symptomatic adjunct to levodopa in nonfluctuating patients and noneffi-cacious in the prevention/delay of motor complications. Rasagiline conclusions were revised to efficacious as a symptomatic adjunct, and as treatment for motor fluctuations. Clozapine was efficacious in dyskinesia, but because of safety issues, the practice implication is possibly useful. Bilateral subthalamic nucleus deep brain stimulation, bilateral globus pallidus stimulation, and unilateral pallidotomy were updated to efficacious for motor complications. Physical therapy was revised to likely efficacious as symptomatic adjunct therapy. This evidence-based medicine review updates the field and highlights gaps for research. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; evidence-based medicine; levodopa; dopamine agonists; monoamine oxidase inhibitors; catechol-*O*-methyl transferase inhibitors; amantadine; anticholinergics; clozapine; neurosurgery; deep brain stimulation; exercise; physical therapy; speech therapy; occupational therapy; acupuncture

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The available treatment options for Parkinson's disease (PD) continue to expand. For the practicing clinician, the best option for an individual patient may seem daunting and confusing. Many drugs have been developed for similar indications—for example, several dopamine agonists are now available—and the decision as to which drug should be used may not always be apparent. In addition, many aspects of PD,

in particular, the nonmotor features, may not have effective treatment options. One mechanism of assisting clinicians in decision making is the use of evidence-based medicine (EBM). EBM is a strategy for the critical evaluation and uniform comparison of clinical trial data with conclusions based on predetermined efficacy criteria.[1] The process of EBM has become a key part of health policy in many fields.[2] In clinical practice, EBM offers one set of data that must be integrated with the physician's experience and judgment, patient preference, expert opinion, and medical economic determinants to arrive at a final therapeutic recommendation. EBM reviews also help to identify areas where specific evidence is lacking so future research can focus on unmet needs.

The *Movement* Disorder Society (MDS) has already performed 2 EBM reviews of treatments for PD. In 2002, the first detailed EBM analysis of pharmacological, surgical, and psychosocial interventions in the treatment of PD, including nonmotor aspects such as depression, psychosis, and autonomic dysfunction, was published.[3] In 2005 this review was updated with a focus on the pharmacological and surgical aspects of PD.[4] Since 2002, the MDS has sponsored educational events to disseminate this information to clinicians in order to broaden the applicability of these guidelines to 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 motor symptoms of PD published from January 2004 (2001 for nonpharmacological studies) to December 2010. A separate publication will focus on updates in treatments of nonmotor aspects of PD (updated from 2002). (NB: Studies available as "EPub ahead of print" up to December 2010 are included; as such, full publication dates may be cited as 2011.)

Materials and Methods

The search strategy, inclusion criteria, and evaluation methods followed those previously reported.[3,4] Literature searches were undertaken for articles published between January 2004 (2001 for nonpharmacological therapies) and December 2010, using electronic databases including Medline and the Cochrane Library central database and systematic checking of reference lists published in review articles and other clinical reports. The following inclusion criteria were adhered to.

- Randomized controlled trials (RCTs) in idiopathic PD that measured motor symptoms as the end point.
- Interventions included pharmacological, surgical, and nonpharmacological therapies that were commercially available in at least 1 country.
- In most cases, articles were only selected for review that had:
  - an established rating scale or well-described outcome measurement of end points;
  - a minimum of 20 subjects who were treated for a minimum duration of 4 weeks and that were reported in full-paper format in English.

In cases where these criteria were not applied, special exceptions were noted with a justification for inclusion.

A quality assessment for each article was calculated using predetermined criteria described in the original review.[3] Each intervention was considered for the following indications: prevention/delay of clinical progression, symptomatic monotherapy, symptomatic adjunct therapy to levodopa, prevention/delay of motor complications (motor fluctuations and dyskinesia), treatment of motor complications (motor fluctuations and dyskinesia) (Table 1). In contrast to the previous EBM reviews, efficacy conclusions were drawn for the prevention and treatment of motor complications, specifically separated into dyskinesia and motor fluctuations. For treatments for which there were no new level I studies evaluating the separate outcomes of fluctuations and dyskinesia, if the prior designation of "insufficient data" had been used for the assessment of motor complications, the conclusion in this report retained 'insufficient evidence' for both dyskinesia and fluctuations.

In addition, the terminology has been altered from "prevention" to "prevention/delay" to reflect the possibility that treatments may have a delaying effect, rather than an ability to truly prevent disease progression or motor complications.

For each intervention, there is a description of the new clinical trials followed by a summary with conclusions. In addition, the conclusions are summarized in Tables 2–8. Each table covers efficacy, safety, and implications for clinical practice, as defined in Table 1, for each of the above indications. Changes from the 2005 review listed are indicated by a gray background with italicized text, and conclusions that have not changed are listed with a white background.

Results

Dopamine Agonists

The following dopamine agonists are presented in alphabetical order.

Twenty-three new studies[5–27] were published. New studies updated efficacy conclusions for the nonergoline dopamine agonists piribedil, pramipexole, and ropinirole. There were studies using new dopamine agonists not previously reviewed including pramipexole extended release, ropinirole prolonged release (PR), and rotigotine transdermal patch (Table 2).

TABLE 1. Definitions for specific recommendations[3]

Efficacy conclusions	Definition	Required evidence
Efficacious	Evidence shows that the 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.
Nonefficacious	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.
Unlikely useful	Available evidence suggests that the intervention does not provide clinical benefit.
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit.

There were new studies using the ergoline dopamine agonists cabergoline and pergolide. Updates on newly recognized adverse effects of dopamine agonists are included, and safety concerns related to ergot agonists are reviewed.

Oral Nonergot Dopamine Agonists

Piribedil (2 new studies[7,20])—new conclusions: *efficacious* for control of motor symptoms—monotherapy.

Control of Motor Symptoms—Monotherapy. **Rascol et al (2006)**[20] compared the efficacy of piribedil monotherapy to placebo in 401 early untreated PD patients over a 7-month period. Subjects were randomized to piribedil (mean dose, 244 mg/day) or placebo. Open-label levodopa supplementation was permitted. The Unified Parkinson's Disease Rating Scale (UPDRS)–III score at the last observation carried forward on monotherapy was the primary outcome measure. Secondary end points included the proportion of responders (defined as UPDRS-III improvement $>$ 30% from baseline) and the number of patients remaining on monotherapy after 7 months. UPDRS-III improved on piribedil ($-$4.9 points) compared with worsening on placebo (2.6 points; estimated effect, 7.26 points; 95% confidence interval [CI], 5.38–9.14; $P < .0001$). The proportion of responders was significantly higher for piribedil than for placebo (42% vs 14%; odds ratio [OR], 4.69; 95% CI, 2.82–7.80; $P < .001$). This study aimed to maintain piribedil monotherapy (ie, delay levodopa rescue) for as long as possible. The proportion of patients requiring supplemental levodopa after 7 months was smaller in the piribedil group (17% vs 40%; OR, 3.72; $P < .001$). Reported adverse events (AEs) were comparable to those reported for other dopamine agonists; gastrointestinal side effects were the most common (22% piribedil vs 14% placebo). ***Quality score, 93%.***

Efficacy conclusions: This study allows a reclassification of piribedil as *efficacious* for the control of motor symptoms—monotherapy.

Control of Motor Symptoms—Adjunctive Therapy. **Castro-Caldas et al (2006)**[7] reported on a 12-month multicenter RCT assessing the efficacy of piribedil 150 mg versus bromocriptine 25 mg in 425 PD patients with motor symptoms (with or without fluctuations) insufficiently controlled by levodopa. Motor efficacy was assessed using the UPDRS III; response rate was defined as $\geq$30% improvement in score. There was no significant difference in change in UPDRS-III from baseline between piribedil and bromocriptine; baseline mean (SD) UPDRS-III score for piribedil, 23.8 (9.4), decreased by 7.9 (9.7); baseline score for bromocriptine, 24.1 (10.6), decreased by 8.0 (9.5). The significance of the change compared with baseline for each

TABLE 2. Conclusions on dopamine agonists (presented in alphabetical order)

Dopamine agonists		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Nonergot dopamine agonists						
Piribedil	Efficacy	Insufficient evidence	*Efficacious*	Efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	*Clinically useful*	Clinically useful	Investigational (F, D)	Investigational (F, D)
Pramipexole	Efficacy	Insufficient evidence	Efficacious	Efficacious	*Efficacious (F, D)*	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	*Clinically useful (F, D)*	Clinically Useful (F)
Pramipexole extended release	Efficacy	*Insufficient evidence*	*Efficacious*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	*Investigational*	*Clinically useful*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*
Ropinirole	Efficacy	Insufficient evidence	*Efficacious*	*Efficacious*	Insufficient evidence (F) Efficacious (D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	*Clinically useful*	*Clinically useful*	Investigational (F) Clinically useful (D)	Clinically useful (F) Investigational (D)
Ropinirole prolonged release	Efficacy	*Insufficient evidence*	*Likely efficacious*	*Efficacious*	*Insufficient evidence (F)* *Efficacious (D)*	*Efficacious (F)* *Insufficient evidence (D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Possibly useful*	*Clinically useful*	*Investigational (F)* *Clinically useful (D)*	*Clinically useful (F)* *Investigational (D)*
Rotigotine	Efficacy	*Insufficient evidence*	*Efficacious*	*Efficacious*	*Insufficient evidence (F, D)*	*Efficacious (F)* *Insufficient evidence (D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Clinically useful*	*Clinically useful*	*Investigational (F, D)*	*Clinically useful (F)* *Investigational (D)*
Parenteral nonergot dopamine agonist						
Apomorphine	Efficacy	Insufficient evidence	Insufficient evidence	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring when used as parenteral therapy.				
	Practice implications	Investigational	Investigational	Clinically useful	Investigational (F, D)	Clinically useful (F) Investigational (D)
Ergot dopamine agonists						
Bromocriptine	Efficacy	Insufficient evidence	Likely efficacious	Efficacious	Insufficient evidence (F) Likely efficacious (D)	Likely efficacious (F) Insufficient evidence (D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	Possibly useful	Clinically useful	Investigational (F) Possibly useful (D)	Possibly useful (F) Investigational (D)
Cabergoline	Efficacy	Insufficient evidence	*Efficacious*	Efficacious	*Efficacious (F, D)*	Likely efficacious (F) Insufficient evidence (D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	*Clinically useful*	Clinically useful	*Clinically useful (F, D)*	Possibly useful (F) Investigational (D)
Dihydroergocryptine	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	Clinically useful	Investigational	Investigational (F, D)	Investigational (F, D)
Lisuride	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	Possibly useful	Possibly useful	Investigational (F, D)	Investigational (F, D)
Pergolide	Efficacy	*Unlikely efficacious*	Efficacious	Efficacious	*Insufficient evidence (F)* *Likely efficacious (D)*	Efficacious (F) Insufficient evidence (D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	*Unlikely useful*	Clinically useful	Clinically useful	*Investigational (F)* *Possibly useful (D)*	Clinically useful (F) Investigational (D)

Treatments with new efficacy conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

drug was not stated. The number of responders was also not significantly different between piribedil and bromocriptine, 54.8% versus 55.3%, respectively. Noninferiority analysis was performed as a post hoc test on the percentage of responders and showed no difference. There were no outcome measures on motor fluctuations or dyskinesia. However, dyskinesia was reported as a side effect and occurred in 6 subjects on piribedil and 10 on bromocriptine. An overall good tolerability of piribedil was observed; AEs observed with piribedil were the same as with other dopamine agonists. ***Quality score, 78%.***

Efficacy conclusions: This study maintains the designation of piribedil as *efficacious* as adjunct therapy to levodopa in the treatment of motor symptoms of PD. Other conclusions for piribedil, brought forward from the prior report, are listed in Table 2.

Pramipexole (4 new studies[12,16,19,25])—new conclusions: *efficacious* in prevention/delay of motor fluctuations and dyskinesia.

Control of Motor Symptoms—Monotherapy. **Kieburtz et al (2010)**[25] performed a 12-week double-blind study in which 311 patients with early PD were randomized to fixed low dosages of pramipexole or placebo. Pramipexole was given at 0.5 or 0.75 mg twice daily or at 0.5 mg 3 times daily. The monoamine oxidase B (MAO-B) inhibitors, amantadine and anticholinergics were allowed if kept stable. The primary outcome measure was the change from baseline in the UPDRS total score (parts I–III). This was −4.7 points (95% CI, 2.5–6.9 points) on 0.75 mg twice a day, −4.4 points (95% CI, 2.3–6.5 points) on 0.5 mg twice a day, and −4.4 points (95% CI, 2.3–6.5 points) on 0.5 mg 3 times a day compared with placebo. All reductions were significant versus placebo ($P < .0001$). The significance of changes from baseline was not reported. Among the secondary outcome measures, somnolence (as measured on the Epworth Sleepiness Scale [ESS]) was significantly more marked in the 0.75-mg group than in the two 0.5-mg groups. Quality of life as measured on the Parkinson's Disease Questionnaire–39 improved significantly on 0.75 mg twice a day and 0.5 mg 3 times a day but not on 0.5 mg twice a day relative to placebo. Fatigue, nausea, constipation, and edema were more common in the active treatment groups than on placebo, without significant differences between dosages. ***Quality score, 85%.***

Efficacy conclusions: There is no change in the conclusion that pramipexole is *efficacious* as monotherapy.

Control of Motor Symptoms—Symptomatic Adjunct to Levodopa. **Moller et al (2005)**[16] compared pramipexole to placebo as add-on therapy over 24 weeks in 363 advanced-PD patients with motor fluctuations. The primary outcome measure was UPDRS-II and -III scores during *on* periods. There was significant improvement with pramipexole in UPDRS-II score (pramipexole, −4.3 [SD, 4.6]; placebo, −1.8 [SD, 4.2]; $P = .0001$) and in UPDRS-III score (pramipexole, −10.3 [SD, 12], baseline mean score *on,* 27.5; placebo, −4.43 [SD, 11.1], baseline mean score *on*, 29.8; $P = .0001$). AEs resulted in withdrawal of 17.8% of subjects from the pramipexole group and 36.1% from the placebo arm, with worsening parkinsonism the predominant reason. ***Quality score, 74%.***

Efficacy conclusions: This study confirms the prior designation that pramipexole is *efficacious* for the control of motor symptoms as an adjunct to levodopa treatment.

Prevention/delay of Motor Complications. **Holloway et al (the Parkinson Study Group [PSG], 2004)**[12] performed an RCT parallel group study of pramipexole compared with levodopa (CALM-PD study) in 301 early-PD patients over 4 years. In both groups, open-label levodopa was added as needed to treat residual and progressive motor symptoms. After 4 years, the mean daily pramipexole dose was 2.78 mg, and in this group, the mean levodopa dose was 434 mg/day; whereas in the levodopa arm, the mean dose was 702 mg/day. The primary outcome measure was time to first motor complication. Pramipexole significantly lowered the risk of dyskinesia (24.5% vs 54%; hazard ratio, 0.37; 95% CI, 0.25–0.56; $P < .01$) and wearing-off (47% vs 62.7%; hazard ratio, 0.68; 95% CI, 0.49–0.63; $P = .02$). Disabling dyskinesias (defined according to the UPDRS-IV) were rare, and there was no significant difference between groups—point prevalence at 48 months: pramipexole, 4.4%; levodopa, 6.9%. Levodopa resulted in a significantly lower risk of freezing (25.3% vs 37.1%; hazard ratio, 1.7; 95% CI, 1.11–2.59; $P = .01$) and greater improvement in total UPDRS (mean score reduction of 2 ± 15.4 points vs mean score increase of 3.2 ± 17.3 points in the pramipexole group, $P = .003$). AEs were similar to other dopamine agonists. Withdrawals because of AEs were higher in the pramipexole group ($n = 17$) than in the levodopa group ($n = 1$). Somnolence was significantly higher in the pramipexole group (36% vs 21%), although unexpected sleep episodes while driving were no different, occurring in 5 subjects in the pramipexole group and 2 in the levodopa group. There was significantly more edema in the pramipexole group (42% vs 15%). ***Quality score, 98%.***

An open-label follow-up of this initial RCT was reported after 6 years.[28] From the initial cohort, 108 from the pramipexole group and 114 from the levodopa group entered the open-label follow-up study. Additional levodopa use was needed in 72% of the original pramipexole arm compared with 59% in the

original levodopa monotherapy arm ($P = .001$). There were significantly fewer total motor complications (both wearing-off and dyskinesia) in the pramipexole group: 50% versus 68.4% ($P = .002$). Wearing-off occurred in 58.8% and dyskinesia in 36.8% of the original levodopa group compared with 44%, and 20.4%, respectively, in the original pramipexole groups (all $P < .01$). The ESS score was significantly worse in the pramipexole arm: 11.3 (SD, 5.8) versus 8.6 (SD, 4.7); $P < .001$. However, this open-label extension study does not fulfill level I evidence criteria and thus cannot be used for determining efficacy conclusions.

Efficacy conclusions: This study by Holloway et al allows a new designation for pramipexole as *efficacious* in prevention/delay of dyskinesia and motor fluctuations.

Treatment of Motor Complications. **Moller et al (2005)**,[16] see above, compared pramipexole to placebo as add-on therapy in 363 advanced-PD patients with motor fluctuations over 24 weeks. Pramipexole significantly improved motor fluctuations; thus, there was a reduction in *off* time with pramipexole of −2.5 hours compared with −10 minutes with placebo. Total motor complications were also improved with pramipexole, as measured using the total UPDRS-IV score, which improved by −1.1 points (SD, 2.3 points) compared with −0.5 points (2.2 points) with placebo ($P = .0114$). Dyskinesia was also assessed separately using a nonvalidated scale (Parkinson's Dyskinesia Rating Scale), and there was no significant difference in subjects who had increased, unchanged, or decreased dyskinesia ($P = 0.194$). ***Quality score, 74%***.

Poewe et al (2007)[19] compared the rotigotine transdermal patch with an active comparator, pramipexole, and placebo in 506 advanced-PD patients experiencing motor fluctuations > 2.5 hour/day *off* time/day. There was a significant improvement in daily hours of *off* time with pramipexole (−2.8 hours [SE, 0.20 hours]) compared with placebo (−0.9 hours [SE, 0.29 hours]); $P < .0001$. This study is reviewed in detail below. ***Quality score, 100%***.

Efficacy conclusions: These studies confirm the prior designation that pramipexole is efficacious for treatment of motor fluctuations. The data on dyskinesia do not allow a change in the designation of *insufficient evidence* to conclude on the treatment of dyskinesia. Other conclusions for pramipexole, brought forward from the prior report, are listed in Table 2.

Pramipexole Extended Release (1 new study[26])—new conclusions: control of motor symptoms—monotherapy, *efficacious*; all other conclusions, *insufficient evidence*.

Control of Motor Symptoms—Monotherapy. **Hauser et al (2010)**[26] reported a randomized, double-blind placebo- and active comparator–controlled trial in subjects with early PD. Two hundred and fifty-nine subjects were randomized 2:2:1 to treatment with pramipexole extended release (ER) once daily, pramipexole immediate release (IR) 3 times a day, or placebo. All subjects received 3 times a day dosing. Levodopa rescue was required by significantly more (14%) patients in the placebo group than in the pramipexole ER (2.9%) and IR (1.0%) groups. Adjusted mean (SE) change in UPDRS-II and -III scores from baseline to week 18, including postlevodopa rescue evaluations, was −5.1 (1.3) in the placebo group, −8.1 (1.1) in the pramipexole ER group ($P = .0282$), and −8.4 (1.1) in the pramipexole IR group ($P = .0153$). Adjusted mean (SE) change in UPDRS activities of daily living (ADLs) and motor scores, censoring postlevodopa rescue data, was −2.7 (1.3) in the placebo group, −7.4 (1.1) in the pramipexole ER group ($P = .0010$), and −7.5 (1.1) in the pramipexole IR group ($P = .0006$). AEs were more common with pramipexole ER than placebo but no different from pramipexole IR and included somnolence, nausea, constipation, and fatigue. ***Quality score, 95%***.

Ropinirole (4 new studies[5,9,15,21])—new conclusions: *efficacious* as symptomatic adjunct to levodopa.

Control of Motor Symptoms—Monotherapy. **Singer et al (2007)**[21] compared ropinirole, sumanirole, and placebo in a 40-week parallel, double-blind, double-dummy study in 614 early-PD patients. There was a flexible dosing schedule of sumanirole 1–16 mg/day and ropinirole 0.75–24 mg/day. The primary outcome measure was a change in combined UPDRS-II and -III scores from baseline. The mean improvement in score from baseline for ropinirole was −5.2 ± 0.78 compared with worsening 0.38 ± 0.73 with placebo ($P = .006$). As sumanirole is no longer in development, the outcomes of this group are not reviewed. No unexpected safety concerns were reported. Withdrawals because of AEs occurred in 9% of the ropinirole group and 8% of the placebo group, with the most common AEs in the ropinirole group somnolence (31%) and nausea (35%). ***Quality score, 85%***.

Giladi et al (2007)[9] compared oral ropinirole as an active comparator with the transdermal rotigotine patch in 561 early-PD patients (total UPDRS score < 10). This study is reviewed in detail below. Patients were randomized 2:2:1 to rotigotine 8 mg/day, ropinirole 24 mg/day (reached by 26%; mean dose, 14.1 mg/day), and placebo. The primary outcome measure was responder rate, defined as a ≥20% reduction in UPDRS-II and -III combined subscores compared with baseline and was significantly higher with ropinirole (68%) than with placebo (30%); $P < .0001$. Mean absolute improvement in UPDRS-II and -III subscores between baseline and end of treatments was −2.2 (SD,

±10.2) for placebo compared with −11.0 (SD, ±10.5) for ropinirole ($P < .0001$). Subgroup analysis was performed with a lower dose of ropinirole (<12 mg/day), achieved by the majority of patients, and showed equal efficacy of improvement in mean UPDRS-II and -III scores of −9 points. Thirteen percent of subjects withdrew from the ropinirole arm compared with 5% in the placebo arm. Excessive daytime sleepiness occurred in 14% of ropinirole-treated subjects and 6% of placebo-treated subjects, with no difference in sleep attacks (2% and 3%, respectively). ***Quality score, 95%***.

Efficacy conclusions: These 2 studies reinforce the prior conclusion that ropinirole is *efficacious* as monotherapy for treating the motor symptoms of PD.

Control of Motor Symptoms—Adjunctive to Levodopa. **Barone et al (2007)**[6] compared sumanirole and ropinirole as an active comparator and placebo in a 40-week parallel double-dummy study in 948 advanced-PD patients. The primary outcome measure was combined UPDRS-II and -III scores. There was significant improvement with ropinirole (mean dose, 18 mg/day) compared with placebo (−13.14 vs −4.55, $P < .001$). There were no unexpected safety concerns. High rates of nausea and somnolence were reported with ropinirole, and withdrawals because of AEs were 24% in the ropinirole group versus 8% for the placebo group. ***Quality score, 80%***.

Mizuno et al (2007)[15] compared ropinirole with placebo in an RCT with a parallel-group design in 243 advanced-PD patients (STRONG study). The inclusion criteria were broad, and patients who were included either had motor fluctuations or were stable but with an insufficient therapeutic effect, that is, a considerable disability in daily life. Results were not reported separately for stable patients and those with motor complications. The primary end point was a mean reduction in UPDRS-III score (during *on* time where applicable). There was a significantly greater reduction in UPDRS-III with ropinirole compared with placebo (−9.5 [95% CI, 7.9–11.0] vs −4.5 [95% CI 3– 5.9]; $P = .00001$). Discontinuation rates because of AEs were similar 12.4% versus 11.5%, respectively. ***Quality score, 89%***.

Efficacy conclusions: These studies allow the new designation of ropinirole as *efficacious* when used as an adjunct to levodopa for the treatment of PD motor symptoms.

Prevention/Delay of Motor Complications. There were no new studies meeting level I evidence criteria. However, **Hauser et al**[29] reported 10-year open-label follow-up of the initial 5-year double-blind study by **Rascol et al.**[30] The latter study found ropinirole efficacious in the prevention/delay of dyskinesia. In this open-label extension, 18% of the original cohort was followed, and the risk of dyskinesia was lower in the original ropinirole arm, 52.4% (22 patients), compared with 77.8% (21 patients) in the levodopa arm (adjusted OR, 0.3; 95% CI, 0.1–1.0; $P = .046$). The median time to dyskinesia was 8.6 years in the ropinirole group versus 7 years in the levodopa group (adjusted hazard ratio, 0.4; 95% CI, 0.2–0.8; $P = .007$). The incidence of moderate wearing-off (UPDRS-IV ≥ 25% of days) was significantly lower in the ropinirole group 20.5% (8 patients) compared with 48% (12 patients) in the levodopa group ($P < .03$). There were no unexpected safety issues reported in either study.

Efficacy conclusions: There is no change from the conclusion in the prior review that ropinirole is *efficacious* for the prevention/delay of dyskinesia. As there are no new level I studies since that date, there remains *insufficient evidence* for ropinirole in the prevention/delay of motor fluctuations.

Treatment of Motor Complications. **Barone et al (2007),**[5] see above, compared sumanirole and ropinirole as an active comparator and placebo in a 40-week parallel double-dummy study in 948 advanced-PD patients. Outcome measures of effect on motor complications were all improved with ropinirole compared with placebo; change in the percentage of *off* time (−14.44% vs placebo, −9.18%; $P = .0026$); *on* time without dyskinesia (ropinirole, +12.01%; placebo, +7.95%; significance not stated), and *on* time with dyskinesia (ropinirole, +2.57%; placebo, +1.36%; significance not stated). ***Quality score, 80%***.

Mizuno et al (2007),[15] see above, compared ropinirole with placebo in an RCT with a parallel-group design in 243 advanced-PD patients (STRONG study). Outcome variables included the percentage of patients with ≥20% reduction in the percentage of time spent *off*. There was a significantly greater percentage of patients with ≥20% reduction in the percentage of time spent *off* in the ropinirole than in the placebo group (58.7% vs 38.6%; $P = .03$). Dyskinesia was not measured as an end point. Discontinuation rates because of AEs were similar: 12.4% with ropinirole versus 11.5% with placebo. ***Quality score, 89%***.

Efficacy conclusions: These studies support the prior conclusions that ropinirole is *efficacious* in the treatment of motor fluctuations. There is insufficient evidence for an effect on treating dyskinesia. Other conclusions for ropinirole, brought forward from the prior report, are listed in Table 2.

Ropinirole Prolonged Release (3 new studies[18,22,24])—new conclusions: *insufficient evidence* for prevention/delay of clinical progression; *likely efficacious* in control of motor symptoms—monotherapy

and *efficacious* as adjunct to levodopa; *efficacious* in prevention of dyskinesia; *insufficient evidence* for prevention of motor fluctuations; *efficacious* for treatment of motor fluctuations; *insufficient evidence* for treatment of dyskinesia.

Control of Motor Symptoms—Monotherapy. **Stocchi et al (2008)**[22] performed a 36-week randomized, double-blind crossover study (EASE-PD monotherapy) comparing ropinirole immediate release (IR; 0.75–24 mg/day) with ropinirole PR (2–24 mg/day) in 161 early-PD patients. The study consisted of 3 phases. At the end of the titration phase, the mean (SD) dose of ropinirole PR was 18.0 (5.73) versus 7.0 (2.12) mg/day for ropinirole IR. At the end of maintenance period, the mean (SD) dose of ropinirole PR was 18.6 (5.67) versus 8.9 (4.52) mg/day for ropinirole IR. At the end of the study, when all patients had switched formulation, the mean (SD) dose of ropinirole IR release was 18.8 (5.85) versus 9.6 (5.52) mg/day for ropinirole PR. The primary end point of noninferiority of ropinirole PR versus ropinirole IR using a predefined threshold ($\leq$3 points on the upper limit of 95% CI for the difference in change in UPDRS motor score from baseline) was reached. Mean total UPDRS improvements were similar between the agents: PR, -13.7 ± 9.33, versus IR, -12.4 ± 8.49. AEs were similar in the 2 groups, 54% IR and 56% PR, and typical of dopamine agonists. The study was limited by the complex crossover design (3 maintenance periods of 8 weeks), and the forced dose–titration schedule resulted in a different titration speed and a large difference in the mean doses reached. ***Quality score, 61%.***

Efficacy conclusions: This study allows the conclusion that ropinirole PR is *likely efficacious* as symptomatic monotherapy for the control of motor symptoms.

Control of Motor Symptoms—Adjunct to Levodopa. **Pahwa et al (2007),**[18] also see below, conducted a 24-week parallel-group RCT comparing ropinirole PR (mean daily dose, 18.8 mg/day) and placebo in 393 advanced-PD patients (EASE-PD adjunct). UPDRS-III scores improved by -6.5 ± 1.81 with ropinirole PR compared with -1.7 ± 1.83 with placebo (adjusted treatment difference, -4.8; 95% CI, 6.56 to -2.98; $P < .0001$). AEs were typical of dopaminergic drugs and resulted in withdrawal of 5% of subjects from both arms. ***Quality score, 95%.***

Efficacy conclusions: This study allows the conclusion that ropinirole PR is *efficacious* in the control of motor symptoms as adjunct therapy to levodopa.

Prevention/Delay of Motor Complications. **Watts et al (2010)**[24] performed a multicenter, randomized, double-dummy, flexible-dose study to determine whether the addition of ropinirole PR in 104 PD patients not optimally controlled with levodopa (<600 mg/day) delays the onset of dyskinesia compared with increasing doses of levodopa (up to 3 times daily). The planned study duration was 107 weeks; however, the study was terminated early because of lower enrollment than expected. The calculated number of patients required was 208, and the actual duration of exposure to the study medication was around 11 months. The primary end point was time to onset of dyskinesia, measured by the investigators' assessment of clinical findings or history. During the study, 3% of the ropinirole PR group (mean dose, 10 mg/day) and 17% of the levodopa group (mean additional dose, 284 mg/day) developed dyskinesia ($P < .001$). The time to onset of dyskinesia was significantly delayed in the ropinirole group. There were no significant differences in the mean change in UPDRS-III scores from baseline in week 28 between ropinirole PR (-3.7 ± 9.3) and levodopa (-3.5 ± 7.0). There was a reduction in the percentage of subjects experiencing motor fluctuations as assessed using UPDRS-IV in the ropinirole-treated group; thus, the percentage of subjects with fluctuations in the ropinirole group was 65% at baseline and 54% at follow-up versus 56% of subjects at baseline and 57% at follow-up in the levodopa group; however, no statistical analysis was reported. AEs were rated as comparable in the 2 groups by the authors but were numerically in favor of levodopa; the ESS score was significantly better in the levodopa group. ***Quality rating, 90%.***

Efficacy conclusions: This study supports the conclusion that ropinirole PR is *efficacious* in preventing/delaying dyskinesia. There is *insufficient evidence* for prevention/delay of motor fluctuations.

Treatment of Motor Complications. **Pahwa et al (2007),**[18] see above, conducted a 24-week parallel-group RCT comparing ropinirole PR (mean daily dose, 18.8 mg/day) and placebo in 393 advanced-PD patients (EASE-PD adjunct). Patients were recruited with motor fluctuations consisting of >3 hours daily *off* time but excluded with disabling peak-dose dyskinesia. The primary end point was the reduction, in hours, of daily *off* time, as recorded using diaries. Other outcome measures were change in hours and percentage of daily *on* time, *on* time without troublesome dyskinesia, and UPDRS-III score. There was a significant reduction in *off* time with ropinirole PR of 2.1 hours/day compared with 0.3 hours/day for placebo. Mean levodopa reduction was -278 mg/day for ropinirole PR versus -164 mg/day for placebo. The mean *on* time without troublesome dyskinesia as absolute hours was not reported but increased in the ropinirole PR group, from 53.2% to 66.6%, versus 52.7% to 56% for placebo. ***Quality score, 95%.***

Efficacy conclusions: This study allows the conclusions that ropinirole PR is *efficacious* in the treatment of motor fluctuations and that there is *insufficient evidence* for dyskinesia.

Transdermal Nonergot Dopamine Agonist

Rotigotine (5 new studies[9,14,19,23,27])—new conclusions: *insufficient evidence* for prevention/delay of clinical progression; *efficacious* in control of motor symptoms—monotherapy and as adjunct to levodopa; *insufficient evidence* for prevention/delay of motor complications; *efficacious in* treatment of motor fluctuations; *insufficient evidence* for treatment of dyskinesia.

Control of Motor Symptoms—Monotherapy. **Watts et al (2007)**[23] conducted a 6-month parallel-group study in 277 early-PD patients (<5 years' duration) randomized in a 2:1 ratio to rotigotine transdermal patch (2–6 mg) or placebo patch. Patients were allowed stable doses of MAO-B inhibitor, amantadine, and anticholinergics. The method of randomization, baseline UPDRS scores, and the reasons for the withdrawal of 14 patients in the rotigotine arm and 9 in the placebo arm were not clearly stated. The primary outcome measure was a change in combined UPDRS-II and -III scores from baseline to end of the maintenance phase and responder rate (>20% change in sum of UPDRS-II and -III scores). Rotigotine (final mean dose, 5.7 mg/day) resulted in a mean improved UPDRS score of 3.98 ± 0.71 UPDRS points compared with a mean worsening of 1.31 ± 0.96 UPDRS points in the placebo group ($P < .001$). The responder rate was higher in the rotigotine group, 48%, versus 19% in the placebo-treated group ($P < .0001$). AEs were more common in the rotigotine group compared with the placebo (14% vs 6%). The most common side effect in the rotigotine-treated group was related to application site problems (erythema, pruritis, and dermatitis), occurring in 44%, versus 12% in the placebo group, leading to discontinuation in 5% of the rotigotine-treated group. Dyskinesia was not reported either as an outcome or an AE. ***Quality score, 78%.***

Giladi et al (2007)[9] compared the rotigotine transdermal patch with an active comparator, oral ropinirole, in 561 early-PD patients (total UPDRS score < 10). This was described above; data for rotigotine are presented here. Patients were randomized 2:2:1 to rotigotine 8 mg/day (reached by 92%), ropinirole 24 mg/day, or placebo. The duration of titration for ropinirole was 13 weeks compared with 4 weeks with the rotigotine patch; there was a different minimal dose maintenance of 24 weeks for ropinirole and 33 weeks for rotigotine, although blinding was maintained through the double-dummy design. The primary outcome measure was responder rate, defined as ≥20% decrease in UPDRS-II and -III combined subscores, compared with baseline, and was significantly higher in the rotigotine group (52%) compared with the placebo group (30%, $P < .0001$). The difference between rotigotine and ropinirole did not show noninferiority, but the authors state that this was not sufficiently powered. Absolute improvement in mean UPDRS-II and -III subscores between baseline and end of treatments was −2.2 ± 10.2 for placebo versus −7.2 ± 2.2 for rotigotine ($P < .0001$). A similar number of patients withdrew from the rotigotine (17%) and ropinirole (13%) groups compared with 5% for the placebo group. ***Quality score, 95%.***

Efficacy conclusions: Based on these 2 studies, the transdermal rotigotine patch can be rated as *efficacious* as monotherapy for the symptomatic control of motor symptoms of PD.

Control of Motor Symptoms—Adjunct to Levodopa. **LeWitt et al (2007)**,[14] see below, compared 2 doses of the rotigotine transdermal patch (8 and 12 mg/day) with a placebo patch over 28 weeks as add-on therapy for 351 PD patients with motor fluctuations and >2.5 hours *off* time per day. UPDRS-III scores were significantly improved from baseline with both doses of rotigotine (8 mg by −6.8 and 12 mg −8.7, compared with −3.4 with placebo; $P < .05$). Application-site reactions occurred in 36% of the 8-mg group, 46% of the 12-mg group, and 13% of those receiving placebo, resulting in a total of 1.7% withdrawals. Other AEs were dopaminergic related, and there was no difference between the rotigotine doses. ***Quality score, 90%.***

Poewe et al (2007),[19] see above, compared the rotigotine patch with an active comparator, oral pramipexole, and placebo in 506 advanced-PD patients experiencing motor fluctuations of > 2.5 hours *off* time/day. Rotigotine significantly improved the mean UPDRS-III score, −8.7 (SD 8.0), compared with placebo −4.3 (SD 9.3); $P < .001$. ***Quality score, 100%.***

Trenkwalder et al (2011)[27] reported a double-blind trial in 287 patients with unsatisfactory early-morning motor control who were randomized 2:1 to receive rotigotine (2–16 mg/24 hours) or placebo. The range of disease severity of subjects was very broad and included a range of time since diagnosis (rotigotine group, 0–23 years; mean, 4.6 years; placebo group, 0–26 years; mean, 4.9 years), as well as patients not taking levodopa (19% in the rotigotine group, 18% in the placebo group). Treatment was titrated to optimal dose over 1–8 weeks with subsequent dose maintenance for 4 weeks. Early-morning motor function and nocturnal sleep disturbance were assessed as coprimary efficacy end points using UPDRS-III measured in the early morning prior to medication, and the modified Parkinson's Disease Sleep Scale (PDSS-2). UPDRS-

III score decreased by −7.0 points with rotigotine (from a baseline of 29.6 [SD, 12.3]) and by −3.9 points with placebo (baseline, 32.0 [13.3]). Mean PDSS-2 total score decreased by −5.9 points with rotigotine (baseline, 19.3 [SD 9.3]) and by −1.9 points with placebo (baseline, 20.5 [10.4]). Improvement was significantly greater with rotigotine than with placebo on both UPDRS-III (difference, −3.55; 95% CI, −5.37 to −1.73; $P = .0002$) and PDSS-2 (difference, −4.26; 95% CI, −6.08 to −2.45; $P < .0001$). The most frequent AEs were nausea (placebo, 9%; rotigotine, 21%), application-site reactions (placebo, 4%; rotigotine, 15%), and dizziness (placebo, 6%; rotigotine 10%). ***Quality score: 98%***.

Efficacy conclusions: These studies allow a new conclusion that rotigotine is *efficacious* for the control of motor symptoms as an adjunct to levodopa in PD.

Treatment of Motor Fluctuations. **LeWitt et al (2007)**[14] (PREFER study) compared 2 doses of the rotigotine patch, 8 and 12 mg/day, with a placebo patch over 28 weeks as add-on therapy for 351 PD patients with motor fluctuations and >2.5 hours *off* time per day. The 12 mg/day group was titrated over 5 weeks (final mean dose, 9.51 mg [range, 4–11.2 mg], in the intention-to-treat [ITT] population), whereas the 8 mg/day group was titrated over 4 weeks (final mean dose, 7.16 mg [range, 4–7.73 mg]. The primary outcome measure was absolute change in *off* time (hours/day) between baseline and end of maintenance using patient-rated diaries. There was a significant reduction with rotigotine 8 mg (−2.7 hours; CI, −2.1 to −3.4 hours; $P < .001$) and rotigotine 12 mg/day (−2.1 hours; CI, −1.5 to −2.8 hours; $P < .001$) compared with placebo (−0.9 hours; CI, −0.32 to −1.51 hours; $P > .05$). Post hoc analysis showed no significant difference between the 2 doses of rotigotine. There was a high responder rate (defined as >30% reduction in absolute *off* time) in the placebo group, 34.5%, but the rate was higher in the rotigotine groups (mean for both doses, 56%). Other outcome measures included a corresponding increase in *on* time without troublesome dyskinesia by 3.5 hours in the rotigotine 8 mg group ($P < .0001$) and by 2.2 hours in the 12-mg group ($P < .001$) versus 1.1 hours in the placebo group. There was no significant difference in *on* time with troublesome dyskinesia (rotigotine 8 mg, −0.4 hours; rotigotine 12 mg, 0.1 hours; placebo, −0.1). There were small reductions in levodopa dose in each of the 3 groups: placebo, 1.8%; rotigotine 8 mg/day, 2.6%; and rotigotine 12 mg/day, 4.5%. ***Quality score, 90%***.

Poewe et al (2007)[19] compared the rotigotine transdermal patch with an active comparator, oral pramipexole, and placebo in 506 advanced-PD patients experiencing motor fluctuations > 2.5 hours of *off* time/day. Patients were randomized 2:2:1 to rotigotine 18 mg/day (mean dose achieved, 12.95 mg/day), pramipexole 4.5 mg/day (mean dose achieved, 3.1 mg/day), and placebo (double-dummy) and titrated over 7 weeks, followed by 16 weeks of maintenance. The primary outcome measure was absolute change in total *off* hours, recorded using home diaries, from baseline to end of study. There was a significant improvement in rotigotine (−2.5 hours) compared with placebo (−0.9 hours); $P < .0001$. Rotigotine significantly improved absolute *off* time from baseline compared with placebo by −1.58 hours (95% CI, −2.27 to 0.9 hours; $P < .001$). There was a corresponding increase in *on* time without troublesome dyskinesia with rotigotine of +2.8 hours compared with +1.4 hours with placebo ($P < .001$). Responder rates were significantly better for rotigotine (59.7%) versus placebo (35%); $P < .0001$. Rotigotine failed the noninferiority analysis compared with pramipexole responder rates, suggesting slightly greater efficacy of pramipexole. ***Quality score, 100%***.

Efficacy conclusions: These studies allow a new conclusion that rotigotine is *efficacious* in the treatment of motor fluctuations, but that there is *insufficient evidence* for the treatment of dyskinesia.

Parenteral Nonergot Dopamine Agonist

Apomorphine (no new studies fulfilling inclusion criteria)—no new conclusions.

Ergot Dopamine Agonists

Bromocriptine (no new studies fulfilling inclusion criteria)—no new conclusions.

Two studies (**Hely et al [2005]**[11] and **Katzenschlager et al [2008]**[13]) have been reported comparing the use of bromocriptine with levodopa in early PD as a means of preventing/delaying clinical progression, as determined from mortality outcome and motor scores, and preventing/delaying motor complications. Although important long-term studies, both were open-label follow-up studies of prior RCTs and as such do not fulfill inclusion criteria.

Cabergoline (2 new studies[6,8]**)—new conclusions: *efficacious* for control of motor symptoms—monotherapy; *efficacious* in preventing/delaying dyskinesia; *efficacious* in preventing/delaying motor fluctuations.**

Control of Motor Symptoms—Monotherapy. **Bracco et al (2004)**[6] performed a parallel-group RCT of cabergoline and levodopa in 419 early-PD patients. The initial titration period was 24 weeks, with a 5-year follow-up. The final mean daily doses were cabergoline 2.9 mg with 431 mg supplemental levodopa, compared with levodopa 784 mg. One primary outcome measure was UPDRS-III scores. Both treatments improved symptoms, but levodopa resulted in greater

improvement in mean motor disability (UPDRS-III) compared with cabergoline: 16.3 points (baseline, 28.7 ± 14 points) versus 19.2 points (baseline, 27.5 ± 14.4 points), respectively, at 5 years ($P < .01$). The overall frequency of AEs was similar in the 2 groups although cabergoline-treated patients experienced a significantly higher frequency of peripheral edema (16.1% vs 3.4%, respectively; $P < .0001$). ***Quality score, 88%***.

Efficacy conclusions: This study allows a new conclusion of cabergoline as *efficacious* for symptomatic monotherapy.

Prevention/Delay of Motor Complications. **Bracco et al (2004)**,[6] see above, performed an RCT of cabergoline and levodopa in 419 early-PD patients. The study also measured the frequency of motor complications (as defined using a checklist including predictable wearing-off and unpredictable *on–off* motor fluctuations, morning akinesia, dystonia, and dyskinesia). Total motor complications were significantly delayed ($P = .0175$) and occurred less frequently in cabergoline-treated than in levodopa-treated patients (22.3% vs 33.7%). Incidence of dyskinesia after 5 years in the cabergoline arm was 9.5% compared with 21.2% for levodopa ($P < .001$), and wearing-off was 16.1% versus 22.1%, respectively ($P = .0175$). Cox model proportional hazards regression analysis showed that the relative risk of developing motor complications was >50% lower (0.46; $P < .001$) with cabergoline compared with levodopa. ***Quality score, 88%***.

Efficacy conclusions: This study allows a change in the conclusions that cabergoline is *efficacious in prevention/delay* of dyskinesia and motor fluctuations.

Treatment of Motor Complications. **Deuschl et al (2007)**[8] performed a 12-week randomized study comparing entacapone to cabergoline as adjuncts to levodopa in 161 PD subjects older than 60 years and with ≥1 hour/day of *off* time. The age range of recruited subjects was slightly higher than usual, that is, the average age was 70 years; the reason for this higher age cutoff was not explained but may have reduced the possibility of drawing generalizing conclusions from the study. Subjects were randomized to entacapone (200 mg with each levodopa dose; mean, 698 mg/day [+ 447 mg levodopa/day]) or cabergoline (maximum, 6 mg/day; mean, 3.45 mg/day [+ 475 mg levodopa/day]). The primary aim was to demonstrate the noninferiority of entacapone compared with cabergoline with respect to change from baseline in total daily *off* time after the first daily *on* time. This goal was narrowly missed (*on* time reduction, 1.8 hours [per protocol, PP, 1.9 hours] for entacapone versus 1.7 hours [PP, 1.6 hours] reduction in the cabergoline group; upper limit of CI, 30.5 minutes [predefined noninferiority margin: 30 minutes]). For both groups, there was a significant reduction compared with baseline (mean daily *off* time, 3.8 hours for entacapone and 3.7 hours for cabergoline). Secondary outcomes showed no difference between entacapone and cabergoline in total daily *on* time, *on* time with dyskinesia, and UPDRS-III. AEs were similar between the 2 groups, apart from nausea, which was reported in 7.3% of the entacapone group versus 25.3% of the cabergoline group ($P = .0024$). Withdrawals as a result of AEs were similar, 7 in the entacapone group and 11 in the cabergoline group. Interpretation is limited, as the prespecified sample size was not achieved because of difficult recruitment, and there was no placebo group. ***Quality score, 74%***.

Efficacy conclusions: This study does not change the prior conclusion that cabergoline is *likely efficacious* in the treatment of motor fluctuations. There is *insufficient evidence* for treatment of dyskinesia. Other conclusions for cabergoline, brought forward from the prior report, are listed in Table 2.

Dihydroergocyptine and Lisuride (no new studies)—no new conclusions.

Pergolide (2 new studies[10,17])—new conclusions: *unlikely efficacious* for preventing/delaying clinical progression; *likely efficacious* in preventing/delaying dyskinesia; *insufficient evidence* in preventing/delaying motor fluctuations.

Preventing/Delaying Clinical Progression. The effects of early use of pergolide on disease progression as measured using UPDRS change was evaluated in early PD in 2 studies.[10,17]

Grosset et al (2005)[10] conducted an RCT using low-dose pergolide (0.05 mg/day) versus placebo in 106 early-PD subjects over approximately 3 years. The sample size originally calculated was not achieved. The primary outcome measure was mean time to need for levodopa, as assessed by investigators' opinion, guided by an increase in combined UPDRS-II and -III of 6–12 points. There was no significant difference between the pergolide group (520 days; SE, 50 days; 95% CI, 422–618 days) and the placebo group (434 days, SE, 39 days, 95% CI, 358–609 days). Secondary outcome measures also showed no significant effect of pergolide on Hoehn and Yahr (H&Y) score, Schwab & England scale, or the combined UPDRS-II and -III (pergolide mean increase of 11.4 vs placebo mean increase of 14.6; $P = .08$). A 4-week washout period resulted in no significant change in UPDRS (pergolide mean increase, 1.2 [95% CI, −0.8 to 3.2], vs placebo, 0.0 [95% CI, −1.6 to 1.6]; $P = .3$). The most frequent AEs were pain (pergolide, n = 17, vs placebo, n = 11) and nausea, with 1 patient withdrawing from each arm because of this problem. An additional 23 subjects were withdrawn from the study (12 from the pergolide arm and 11 from the placebo arm) for various

reasons. The dose of pergolide initially thought to be subtherapeutic turned out to have a small symptomatic effect, but there was no suggestion of a disease-modifying effect. ***Quality score, 60%***.

Oertel et al (2006)[17] reported an RCT of pergolide versus levodopa in 194 early-PD patients enrolled within 2 years of diagnosis and without prior medications (PELMOPET study). Inclusion criteria included a positive response to apomorphine. Patients were randomized to pergolide (mean final dose, 3.23 mg/day; n = 148) or levodopa (mean dose, 504 mg/day; n = 146) monotherapy for 3 years, with no open-label levodopa. Only 52% of the pergolide and 61.6% of the levodopa groups completed the study. The primary outcome measures were UPDRS-III score at 1 year and time to onset of motor complications (see below). The secondary outcome measures included disease progression after 3 years, defined as change from baseline in UPDRS total score. After 3 years, all outcome measures (total UPDRS and UPDRS-III subscores) were significantly better with levodopa compared with pergolide (all $P < .01$). AEs were similar to other dopamine agonists, and the withdrawal rate because of AEs was higher for pergolide than for levodopa (17.6% vs 9.6%). This study is the first strict dopamine agonist monotherapy study lasting 3 years, and therefore it is possible to make a true assessment of the long-term effects of pergolide compared with levodopa. However, there was a very high dropout rate, 48% from the pergolide group and 38% from the levodopa group. In addition, the maximum allowed doses (pergolide, 5 mg/day; levodopa, 1200 mg/day) do not necessarily reflect equivalent doses. Furthermore, the subjects had very low UPDRS and H&Y scores at baseline and had never been treated with other medications. ***Quality score, 73%***.

Efficacy conclusions: Pergolide is revised to be *unlikely efficacious* in the prevention/delay of clinical progression.

Prevention of Motor Complications. In a study by **Oertel et al (2006)**,[17] see above, of pergolide versus levodopa in 194 early-PD patients, a primary outcome measure was time to onset of motor complications (combined UPDRS-IV dyskinesia and motor fluctuations score); secondary outcome measures included severity of motor complications using UPDRS-IV and time to onset of motor complications over 3 years, defined as first positive score on UPDRS-IV (and subscores for dyskinesia and motor fluctuations). Time to onset of combined motor complications at 1 year was significantly longer in the pergolide group ($P = .038$). Onset of combined motor complications at 3 years was shorter with levodopa compared with pergolide; this difference was the result of a higher incidence of dyskinesia, 26%, compared with 8.2% in the pergolide group ($P < .001$). There was no difference in the incidence of motor fluctuations between levodopa (43.8%) and pergolide (30.6%). ***Quality score, 73%***.

Efficacy conclusions: This study justifies a redesignation of pergolide as *likely efficacious* for the prevention/delay of dyskinesia. There is *insufficient evidence* for prevention/delay of motor fluctuations. Other conclusions for pergolide, brought forward from the prior report, are listed in Table 2.

Safety Conclusions Related to Dopamine Agonists

New Conclusions for Bromocriptine, Cabergoline, Dihydroergocryptine, Lisuride, and Pergolide: ***acceptable risk with specialized monitoring***.

Nonergot Dopamine Agonists

There were no new safety concerns in any of these studies. Safety for the transdermal rotigotine patch is equivalent to other nonergoline dopaminergic agonists. Application-site reactions are common and can be reduced by rotation of the patch to different application sites. All studies reported typical AEs known to be associated with dopaminergic agents. The incidence of impulse control disorders (ICDs) using both ergoline and nonergoline dopamine agonists was not assessed in any of the above studies. The incidence of ICDs has been reported[31] as between 5.6% and 13.8% and is higher (13.5%) with dopamine agonists compared with levodopa alone (0.7%).[32,33] The association with any specific dopamine agonist is unclear because of the variable prescribing habits of clinics and different methods of measuring prevalence rates.[34] ICDs may respond to reducing or stopping the dopamine agonist. As noted in the prior EBM review, sleepiness can be an AE of all dopamine agonists. Sudden sleep attacks were also not specifically assessed in these studies. Monitoring sleepiness is recommended in all PD patients with regard to driving safety. Safety conclusions have not changed from the prior review and are acceptable risk without specialized monitoring.

For apomorphine administered as an injection, the safety conclusion remains *acceptable risk without specialized monitoring* (pump therapy requires special monitoring for hemolytic anemia).

Ergot Dopamine Agonists

There were no new safety concerns identified in the above-reviewed studies. However, there were ongoing concerns published elsewhere related to pleuropulmonary and retroperitoneal fibrosis with all ergot-derived dopamine agonists. This is possibly an idiosyncratic immune reaction or 5HT-mediated effect. The fibrotic process may remit when the drug is stopped.[35] Fibrotic valvular heart disease has been reported with

pergolide and cabergoline, an effect linked to 5-HT2B receptor agonist action. None of the new studies reported here provide any further information on the incidence of valvular lesions. Pharmacovigilance data have recently suggested that fibrotic heart valve changes may also be associated with bromocriptine use.[36,37] However, the true incidence of valvulopathy remains unclear because of variable methods of ascertainment; thus, moderate to severe valvular changes are reported in 23%–28% of PD patients exposed to pergolide versus 10% of PD patients on ropinirole and pramipexole versus 10% of control patients.[38] As a result of these adverse effects, pergolide was voluntarily withdrawn from the Canadian and US market but remains available in many other countries. The current product monograph states that pergolide and cabergoline should not be used in patients with a history of serious inflammation, fibrosis, or cardiac valvulopathy, and physicians are advised to reassess the risks and benefits of pergolide with pretreatment cardiovascular evaluation, and periodic monitoring for the development of valvular disease or fibrosis is recommended. As a consequence, the safety conclusions have changed for all ergot dopamine agonists to *acceptable risk with specialized monitoring*.

Dopamine Agonists Practice Implications and Summary

The practice implications for each of the 5 indications for all the above dopamine agonists are summarized in Table 2. The studies reviewed permit changes in practice implications for piribedil, pramipexole, ropinirole, cabergoline, and pergolide from the prior EBM review and new practice implications for nonergot dopamine agonists, pramipexole ER, ropinirole PR, and rotigotine that were not previously reviewed.

Thus, for prevention/delay of clinical progression, pergolide becomes *unlikely useful*, and for all other agonists, the practice implication remains or is newly designated *investigational*. For symptomatic monotherapy, piribedil, pramipexole ER, rotigotine, and cabergoline are now *clinically useful*. All other dopamine agonists reviewed previously (pramipexole, ropinirole, dihydroergocritpine, pergolide) remain clinically useful. Ropinirole PR becomes *possibly useful*, bromocriptine and lisuride remain possibly useful, and apomorphine is investigational for symptomatic monotherapy.

For symptomatic adjunct to levodopa, ropinirole, ropinirole PR, and rotigotine are *clinically useful*. Piribedil, pramipexole, apomorphine, bromocriptine, cabergoline, and pergolide all remain clinically useful, lisuride is possibly useful, and dihydroergocryptine is investigational. Pramipexole ER is newly designated *investigational*.

Pramipexole and cabergoline are now designated clinically useful in preventing/delaying motor complications, both dyskinesia and motor fluctuations. Ropinirole PR and ropinirole are clinically useful, whereas pergolide and bromocriptine are possibly useful for preventing dyskinesia, but all are investigational for preventing/delaying motor fluctuations. Pramipexole ER and rotigotine are investigational for preventing/delaying both motor complications, whereas piribedil, apomorphine, dihydroergocrytpine, and lisuride remain investigational.

For treatment of motor fluctuations, ropinirole PR and rotigotine are newly designated *clinically useful*. Pramipexole, ropinirole, apomorphine, and pergolide remain clinically useful, bromocriptine and cabergoline remain possibly useful and piribedil, pramipexole ER, dihydroergocritpine and lisuride are all investigational. For treatment of dyskinesia, all are investigational.

New safety conclusions for all ergot agonists are *acceptable risk with monitoring*. No changes to safety recommendations for nonergot dopamine agonists were made.

Levodopa Preparations

Four[39–42] new studies were reviewed using levodopa preparations. In the prior EBM review, novel formulations were not separated but referred to as "other"; however, in this review, the new preparations were reviewed separately and included rapid-onset formulations and duodenal infusion therapy.

Levodopa/Peripheral Aromatic Acid Decarboxylase Inhibitor Standard Formulation (1 new study)[39]—no new conclusions.

Prevention/Delay of Clinical Progression. **Fahn et al (2004)**[39] evaluated the possible toxic effect of levodopa in PD in a multicenter parallel-group RCT (ELLDOPA study), assessing whether early treatment with levodopa followed by a washout period would result in a worse outcome in the unmedicated state for those treated for 9 months with levodopa. Early, untreated PD subjects were randomized to placebo (n = 90), 150 mg levodopa/day (n = 92), 300 mg levodopa (n = 88), and 600 mg levodopa (n = 91) for 40 weeks, followed by a 2-week washout period. The primary end point was the change in total UPDRS score between baseline and week 42. After chronic treatment and washout for 2 weeks, the mean score increase was +7.8 points in the placebo group, +1.9 points in the levodopa 150 mg/day group, +1.9 in the levodopa 300 mg/day group, and +1.4 in the levodopa 600 mg/day group ($P < .001$), suggesting no dose–response evidence for a toxic effect of levodopa. No effect size difference between placebo and levodopa was presented. The ITT principle was stated to

TABLE 3. Conclusions on levodopa

Levodopa		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Standard formulation	Efficacy	Insufficient evidence	Efficacious	N/A	Nonefficacious (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	N/A	Not useful (F, D)	Clinically useful (F) investigational(D)
Controlled-release formulation	Efficacy	Insufficient evidence	Efficacious	N/A	Nonefficacious (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	N/A	Not useful (F, D)	Investigational (F, D)
Rapid-onset oral formulation	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F)* *Insufficient evidence (D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F)* *Investigational (D)*
Infusion formulations	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Likely efficacious (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia; N/A, not applicable.

have been applied, and only subjects who completed the 2-week washout were included in the final analysis. Dyskinesia was recorded as an AE and was higher in the 600 mg levodopa group (16.5%), compared with 3.3% in the placebo group, 3.3% in the levodopa 150 mg/day group, and 2.3% in the levodopa 300 mg/day group ($P < .001$). The short washout time and the well-established "long-duration levodopa effect" do not allow any solid conclusions to be drawn on the neuroprotection provided with levodopa, but the data establish that at a clinical level, early exposure to levodopa does not adversely affect parkinsonism, as detected after a 2-week washout condition. ***Quality score, 79%.***

Efficacy conclusions: There continues to be insufficient evidence for conclusions to be made on the efficacy of levodopa in the *prevention/delay* of clinical progression. Other conclusions for levodopa, brought forward from the prior report, are listed in Table 3.

Levodopa/Peripheral Aromatic Acid Decarboxylase Inhibitor Controlled-Release Formulations (no new studies)—no new conclusions.

Levodopa/Peripheral Aromatic Acid Decarboxylase Inhibitor Rapid-Onset Oral Formulations (2 new studies[40,41])—new conclusions: efficacious for treatment of motor fluctuations.

Treatment of Motor Complications. **Stocchi et al (2007)**[40] evaluated melevodopa, a lipophilic formulation of levodopa that is 250 times more soluble than conventional levodopa. Seventy-four PD subjects on stable levodopa were recruited with a delay of at least 45 minutes to switch *on* after the first dose of levodopa in the afternoon. Half (n = 37) were treated with melevodopa (315 mg/25 mg carbidopa) as the first dose of the afternoon, whereas the remaining 37 received regular levodopa/carbidopa 250/25 mg as an afternoon dose. All other drugs were unchanged. The primary outcome measure was time to switch *on*; subjects advised the investigator when the *on* period started and finished, and this was confirmed by a 30% improvement in UPDRS-III, as assessed in a hospital clinic. There was a significant improvement with melevodopa (n = 35, ITT) compared with standard levodopa, the difference between the latencies of the least-square means of the melevodopa and standard levodopa groups was −11.8 minutes (95% CI, −23.3 to −0.3 minutes; $P = .045$). There was no evidence that *on* time was extended overall. There was no significant change in dyskinesia, as assessed using the Abnormal Involuntary Movement Scale; no data were reported. No new AEs were reported. The primary outcome measure was not the typical one for measuring motor fluctuations, but a short time to switch *on* is a pertinent clinical goal of new treatments of motor fluctuations. ***Quality score, 83%.***

Stocchi et al (2010)[41] further evaluated melevodopa/carbidopa in PD subjects with motor fluctuations and at least 2 hours *off* time. Subjects were randomized to melevodopa/carbidopa (M/C; n = 150) or standard levodopa/carbidopa (L/C; n = 71) for 12 weeks. There

was a 4-week optimization period during which all subjects received up to 1000 mg/day of regular levodopa/carbidopa, and following randomization each subject then received the equivalent dose and scheduling of either levodopa/carbidopa and placebo or melevodopa/carbidopa and placebo that they were taking at the end of the run-in period. All other PD medications were allowed with stable dosing, except for other soluble levodopa preparations and apomorphine. The primary outcome measure was change from baseline in mean daily *off* time, as measured using patient diaries. There was no significant difference between the melevodopa/carbidopa group (mean change in *off* time, −39.4 minutes; CI, −67.08 to −11.73 minutes; ITT n = 140) compared with the levodopa/carbidopa group (+3.5 minutes; CI, −36.19 to +,43.26 minutes; ITT n = 62; $P = .07$). Secondary outcomes including adjusted mean baseline changes in *on* motor UPDRS were significantly improved in both groups (levodopa/carbidopa motor UPDRS *on* score improved −2.2; CI, −4.6 to −0.5; $P = .02$), and melevodopa/carbidopa motor *on* score improved −1.2 (CI, −3 to −0.1; $P = .03$). Totals *on* UPDRS, ADLs, and Schwab and England were all significantly improved in both groups compared with baseline. There was no difference in *on* time without dyskinesia or in responder rate (at least 20% reduction of initial *off* time) between the groups. There were no significant or unexpected AEs. The study did not reach the numbers required according to the power calculation (221 rather than 240). Differences in the number of levodopa doses and time intervals between dosing were not stated, which may have affected differences in *off* time between the 2 groups. ***Quality score, 93%***.

Efficacy conclusions: These conflicting studies suggest that there is *insufficient evidence* at this time for the use of melevodopa in the treatment of motor fluctuations.

Duodenal Infusion of Levodopa (1 new study[42])—new conclusions: likely efficacious for treatment of motor fluctuations and dyskinesia; insufficient evidence for all other indications.

Treatment of Motor Complications. **Nyholm et al (2005)[42]** assessed the efficacy of duodenal levodopa/carbidopa infusions in advanced-PD subjects, using a nasoduodenal infusion system. Nasoduodenal levodopa/carbidopa gel infusion (containing 20 mg/mL levodopa and 5 mg/mL carbidopa in carboxymethylcellulose) as monotherapy (oral levodopa was allowed overnight) was compared with optimized conventional combination therapies (oral levodopa, other PD drugs, and in 8 subjects, subcutaneous apomorphine and infused apomorphine). There was no placebo-treated group. Twenty-four PD patients experiencing motor fluctuations and dyskinesia despite individually optimized treatment were randomized in a crossover design to two 3-week treatment phases; there was no washout phase. Baseline doses of parkinsonian drugs in each group were not clear. Per protocol, 19 subjects completed the study. Infused daily levodopa doses ranged between 456 and 3,556 mg, but oral doses used in the conventional arm were not stated. Dose adjustments were allowed in week 1 of each crossover arm to optimize treatment, but this was not defined. Because of blinding difficulties with the nasogastric tube, a new Treatment Response Scale (TRS) video rating scale was devised for the study (nonvalidated). The TRS ranged from −3 (severe *off*) to +3 (*on* with severe dyskinesia), where 0 was designated *on* without any dyskinesia, as assessed by post hoc video recordings performed on 2 separate days in the hospital during each of weeks 2 and 3. Patients were videorecorded for 1–2 minutes every 30 minutes from 9 AM to 5 PM and ratings accumulated. The primary efficacy variable was the percentage of ratings within the interval −1 to +1, which represented a clinically desirable, functional *on* state accepting mild parkinsonism or mild dyskinesia. Other outcomes were electronic patient diaries and UPDRS. There was a significant effect of infusion therapy on the median percentage of ratings in a functional *on* interval (−1 to +1), which increased from 81% in conventional therapy to 100% in infusion therapy ($P < .01$). Median total UPDRS score at the end of each treatment arm was 53 with conventional therapy and 35 with infusion therapy ($P < .05$). However, there were no significant differences in UPDRS-III subscores between the 2 groups. There were no differences in AEs, with the most frequent being dyskinesia, (4 in the infusion arm, 7 in the conventional arm). ***Quality score, 60%***.

Efficacy conclusions: Duodenal infusion of levodopa is *likely efficacious* for the treatment of motor fluctuations and dyskinesia; there is *insufficient evidence* for all other indications.

Safety Conclusions with Levodopa Preparations—no new conclusions.

There were no new safety issues. Safety issues with the duodenal infusion of levodopa were not evaluated in these studies because for long-term clinical use, a permanent tube fitted via a gastrostomy is required.

Levodopa Preparations Practice Implications and Summary

The findings are summarized in Table 3. The levodopa/peripheral aromatic acid decarboxylase inhibitor standard formulation was evaluated in the first dose–response, placebo-controlled RCT, but there was insufficient evidence for any conclusions to be drawn regarding the effect on clinical progression, and the practice implications are that levodopa remains

TABLE 4. Conclusions on COMT inhibitors

COMT inhibitors		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Entacapone	Efficacy	Insufficient evidence	N/A	Efficacious[a] *Nonefficacious*[b]	*Nonefficacious (F, D)*	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	N/A	Clinically useful[a] *Not useful*[b]	*Not useful (F, D)*	Clinically useful (F) Investigational (D)
Tolcapone	Efficacy	Insufficient evidence	N/A	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	N/A	Possibly useful	Investigational (F, D)	Possibly useful (F) Investigational (D)

[a]In PD subjects *with* motor complications;
[b]in PD subjects with respect to motor function in nonfluctuating patients; both without prior use of levodopa or already on levodopa.
Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia; N/A, not applicable.

investigational for preventing/delaying clinical progression. Rapid-onset oral formulations and infusional formulations are also newly designated *investigational for preventing/delaying clinical progression*. For symptomatic monotherapy, the standard formulations of levodopa and controlled-release levodopa remain as clinically useful, with infusional formulations and rapid-onset oral release designated *investigational*.

For levodopa controlled release, the practice implication for treatment of motor complications remains investigational. There is insufficient evidence for use of the rapid-acting levodopa preparation melevodopa because of conflicting data, with 1 study showing benefit as a single afternoon dose, but the second study replacing all levodopa with melevodopa was not efficacious; thus, the practice implication is *investigational* for treatment of motor fluctuations. Short-term duodenal levodopa infusion therapy was evaluated via a nasoduodenal method compared with best medical therapy, and the conclusion was *likely efficacious* for treatment of motor complications. Although this is the first study to attempt to evaluate the efficacy of levodopa/carbidopa gel infusions in an RCT design, there are issues that limit the applicability to clinical practice including lack of evaluation of efficacy and safety with a permanent infusion tube that would be required for chronic use of this agent; thus, the practice implication is *investigational for the treatment of motor fluctuations*. There are no new safety conclusions for levodopa.

Catechol-*O*-methyltransferase Inhibitors

The currently available catechol-*O*-methyltransferase (COMT) inhibitors are entacapone and tolcapone. These drugs enhance bioavailability of levodopa and are used as adjuncts to levodopa. Studies were reported using entacapone in early-PD subjects with no motor complications as well as in advanced-PD subjects with motor complications, mostly fluctuations. Conclusions on symptomatic adjunct to levodopa and prevention/delay of motor complications with use of entacapone have been divided into PD subjects *with no* motor fluctuations (either de novo with respect to levodopa use or already on levodopa) and PD subjects on levodopa *with* established motor fluctuations (see Table 4).

Entacapone (7 new studies[43–49])—new conclusions: nonefficacious for control of motor symptoms—as adjunct to levodopa in subjects with no motor complications, but retained efficacious status as an adjunct to levodopa in subjects with motor fluctuations; nonefficacious in prevention/delay of motor fluctuations and dyskinesia.

Control of Motor Symptoms—Adjunct to Levodopa in De Novo Subjects (with No Prior Levodopa Use and No Motor Complications). Two studies assessed the effects of starting treatment with entacapone combined with levodopa as symptomatic treatment, in early-PD patients with no prior levodopa use. **Hauser et al (2009)**[43] assessed the efficacy of entacapone as symptomatic therapy in early-PD subjects requiring levodopa treatment with combined UPDRS-II and -III scores > 18. Amantadine, anticholinergics, selegiline, rasagiline, and coenzyme Q10 were all permitted. A total of 423 PD patients were randomized to levodopa/carbidopa/entacapone (LCE) 100/25/200 mg (n = 208) or levodopa/carbidopa (LC) 100/25 mg (n = 215) 3 times/day for 39 weeks. Treatment assignment was stratified according to whether or not the subject was taking other allowed PD medications. The power calculation was reported as needing 424 subjects, 212 per group, but this was not achieved. The analysis was ITT, with 177 subjects in the LCE group and 190 in the LC group completing. Subjects were allowed open-label levodopa up to a maximum of 750 mg/day

(10.1% in the LCE group and 15.3% in LC groups required open-label levodopa); no subject required >750 mg/day levodopa. The primary outcome measure was combined UPDRS-II and -III, as assessed < 90 minutes before the third levodopa dose of the day. There was a small but significant difference in favor of LCE in the adjusted mean difference in combined UPDRS-II and -III between groups, 1.7 (SD, 0.84); $P = .045$. However, there was no difference in UPDRS-III motor subscores. Diarrhea occurred more frequently in the LCE group and led to discontinuation (LCE, n = 8, 3.9%, vs LC, n = 0, 0.0%). Nausea was reported by 26.6% of subjects in the LCE group and 13.5% of subjects in the LC group. ***Quality score, 83%***.

Stocchi et al (2010),[44] see below, assessed the effects of early entacapone combined with levodopa/carbidopa as a single formulation and placebo/levodopa/carbidopa as a single formulation on preventing the development of dyskinesia over 134 weeks in a multicenter RCT (STRIDE-PD). Outcomes included change in UPDRS-II and -III scores, which were both improved compared with baseline, but with no significant difference between the 2 groups ($P = .18$). ***Quality score, 86%***.

Efficacy conclusions: These studies establish that entacapone is *nonefficacious* for the control of motor symptoms as an adjunct to levodopa in de novo PD subjects with no prior exposure to levodopa and no motor complications.

Control of Motor Symptoms—Adjunct in Subjects Already on Levodopa But with No Motor Complications. **Olanow at al (2004)**[45] conducted a 26-week double-blind RCT of entacapone (n = 373) versus placebo (n = 377). All subjects were on stable levodopa (maximum, 400 mg immediate release or 300 mg controlled release) and had *no* motor complications. The primary outcome measure was change from baseline to week 26 in UPDRS-III, as assessed in office 1–2 hours following the morning levodopa dose. There was no significant difference between the 2 groups; the mean adjusted change between baseline and final treatment visit was -0.9 ± 0.35 in the entacapone group and -0.8 ± 0.35 in the placebo group ($P = .83$). Levodopa dose significantly decreased in the entacapone group, by −4.9 mg, versus an increase of +12.5 mg in the placebo group. There were no outcome measures evaluating the presence of motor complications; dyskinesia was reported as an AE, and there was no difference between groups (entacapone vs placebo, 12.6% vs 0.9%, respectively). There was no difference in other AEs between groups. ***Quality score, 95%***.

Efficacy conclusions: This study is sufficiently robust to designate entacapone as *nonefficacious* as an adjunct to levodopa in patients without motor fluctuations at baseline.

Control of Motor Symptoms—Adjunct in Subjects on Levodopa with Motor Complications. Three studies[46,47,49] have assessed entacapone combined with levodopa in PD subjects with motor fluctuations as a treatment for wearing-off. All studies also measured motor benefit as adjunct and are briefly reviewed here; full descriptions of the studies are in the section below on Treatment of Motor Complications.

Fung et al (2009),[46] see below, assessed the effect of entacapone. One hundred and eighty-four PD subjects were randomized to levodopa/carbidopa/entacapone or levodopa/carbidopa. UPDRS-III scores improved from baseline to week 12 in both treatment groups, but the difference in mean change was not significant ($P = .087$). ***Quality score, 69%***.

Reichmann et al (2005),[47] see below, assessed the effect of entacapone in 270 PD subjects. Entacapone reduced the UPDRS-III score (mean baseline UPDRS-III score, 37.6 ± 13.2, compared with placebo, 38.6 ± 17; mean change, −1.9; 95% CI, 3.7–0.2; $P = .03$). ***Quality score, 70%***.

Rascol et al (2005),[49] see below, compared rasagiline (1 mg/day) with entacapone (200 mg/dose of levodopa) and placebo in 687 PD patients (LARGO study) over 18 weeks. There was a significant improvement in UPDRS-III *on* score with entacapone compared with placebo of −2.73 points ($P < .0001$). ***Quality score, 100%***.

Efficacy conclusions: There is no change from the prior conclusion that entacapone is *efficacious* for the control of motor symptoms as an adjunct to levodopa in subjects already experiencing motor fluctuations.

Prevention/Delay of Motor Complications. **Hauser et al (2009)**,[43] see above, assessed the efficacy of entacapone as symptomatic therapy in 423 early-PD subjects requiring levodopa treatment and who had combined UPDRS-II and -III scores > 18. Outcome measures included the presence of wearing-off motor fluctuations and dyskinesia as assessed by blinded raters at all scheduled visits. Wearing-off was observed in 29 subjects (13.9%) in the LCE group and 43 (20.0%) in the LC group ($P = .099$). No difference in new onset of dyskinesia was seen. ***Quality score, 83%***.

Stocchi et al (2010)[44] assessed the effects of early entacapone combined with levodopa therapy on preventing the development of dyskinesia over 134 weeks in a multicenter RCT (STRIDE-PD). PD patients, within 5 years of diagnosis and requiring levodopa therapy were randomized to levodopa/carbidopa/entacapone (end-of-study total mean levodopa dose, 305.2 mg/day; n = 373) or levodopa/carbidopa (total mean levodopa dose, 306.8 mg/day; n = 372) as 4 doses spaced 3.5 hours apart. Both groups had subjects already on antiparkinsonian medications, 70.5% in the levodopa/carbidopa/entacapone group and 71.5% in the levodopa/carbidopa group, including 58%

dopamine agonists in both groups. Amantadine use was excluded. The primary end point was time to onset of dyskinesia, as noted by the blinded rater either through direct questioning of the patient or observation at study visit. Analysis was performed on the ITT population and stratified according to dopamine agonist use at baseline. Subjects randomized to levodopa/carbidopa/entacapone had a greater risk of developing dyskinesia than subjects receiving levodopa/carbidopa (hazard ratio, 1.29; CI, 1.0–1.65; $P = .038$; survival time estimates for first quartile of patients, 90.7 weeks [65.3–104.0 weeks] in the LCE group vs 117.1 weeks [92.1–132.6 weeks] in the levodopa/carbidopa group). The use of levodopa/carbidopa/entacapone resulted in significantly more dyskinesia in PD subjects who were taking a dopamine agonist (hazard ratio, 1.55; CI, 1.13–2.13; $P = .006$; frequency of dyskinesia, 41.9% levodopa/carbidopa/entacapone vs 31.3% levodopa/carbidopa), in subjects with disease duration < 2 years ($P < .01$), and in subjects on MAO-B inhibitors ($P = .005$). There was no significant difference in time to dyskinesia between use of LCE and LC in PD subjects not taking a dopamine agonist (frequency of dyskinesia, 34% in the levodopa/carbidopa/entacapone group vs 35.5% in the levodopa/carbidopa group). There was no significant difference in frequency of wearing-off between the levodopa/carbidopa/entacapone and levodopa/carbidopa groups (44.2% vs 50.8% at 208 weeks) or time to developing wearing-off (mean, 72.9 vs 78.5 weeks; hazard ratio, 0.94 [0.76–1.17]; $P = .6$).

Although there was no difference in mean levodopa dose at the end between the 2 groups (see above) because of the effect of entacapone on increased bioavailability of levodopa, calculation of a ''levodopa-equivalent dose'' demonstrated that the levodopa/carbidopa/entacapone group was receiving a higher levodopa-dose equivalent at the final study visit (mean, 524.1 mg) compared with 432.6 mg in the levodopa/carbidopa group ($P < .001$). There was a higher drop-out rate because of AEs in the levodopa/carbidopa/entacapone group (10.2%) compared with the levodopa/carbidopa group (6.5%). These were typical of dopaminergic and COMT actions. ***Quality score, 86%***.

Efficacy conclusions: These studies establish that entacapone is *nonefficacious* in preventing/delaying dyskinesia and motor fluctuations in PD subjects.

Treatment of Motor Complications. Four studies[46–49] have assessed entacapone combined with levodopa in PD subjects with motor complications as a treatment for wearing-off.

Fung et al (2009),[46] see above, conducted a 12-week randomized, double-blind multicenter study to assess the effect of entacapone on quality of life in PD subjects; secondary outcome measures included improvement in motor symptoms. This study was included as it enrolled a large number of subjects. PD subjects (n = 184) on stable levodopa (3–4 doses/day) with predominantly wearing-off consisting of <3 hours of nondisabling *off* time over 48 hours (reported in 78.5% of the LCE group and 84.6% of the LC group) and no dyskinesia were randomized to levodopa/carbidopa/entacapone or levodopa/carbidopa. Subsequent reduction in daily levodopa doses was permitted until day 14, but patients had to remain on at least 3 equal doses per day. Treatment with dopamine agonists, selegiline, anticholinergics, or amantadine at stable doses was permitted. Total doses of levodopa or entacapone at the end of study were not stated. UPDRS-IV and wearing-off as assessed by questionnaire were not significantly different between the levodopa/carbidopa and levodopa/carbidopa/entacapone groups. AEs were not significantly differrent between the 2 groups, and the most common were nausea and diarrhea. ***Quality score, 69%***.

Reichmann et al (2007),[47] see above, assessed the effect of entacapone on quality of life and ADLs in 270 PD subjects with motor fluctuations. Secondary outcome measures focused on improvement in UPDRS-III and -IV and mean *off* time recorded in patient diaries. This study was included in this review as a large number of subjects were enrolled. Subjects were randomized 2:1 to entacapone 200 mg with each dose of levodopa or placebo. The levodopa dose could be up- or down-titrated at the discretion of the investigator; the final doses of levodopa and entacapone were not reported at the end of the study. There was no significant difference in mean *off* time change from baseline, as recorded in the patient diaries (−1.0 [1.9] hours with entacapone and −0.9 [2.0] hours with placebo). There was a decrease in the proportion of patients with predictable wearing-off in both groups but no significant difference between entacapone and placebo (no data given). Total UPDRS-IV fluctuation subscore was reported as improved with entacapone (−0.3 [CI, −0.5 to 0.1]; $P = .02$), but no data reported. Dyskinesia increased in both the entacapone and placebo groups, but there was no significant difference, as assessed using UPDRS-IV subscore. ***Quality score, 70%***.

Mizuno et al (2007)[48] assessed low and standard doses of entacapone in 341 Japanese PD subjects. Patients with >3 hours *off* time and receiving at least 3 doses of levodopa/day were randomized 1:1:1 to entacapone 100 mg, entacapone 200 mg, or placebo for 13 weeks. The baseline doses of levodopa (average, 450 mg) were lower than in most previous RCTs of entacapone (average, 700–800 mg/day). Analysis was performed PP, and 300 subjects completed, 107, 95, and 98 members of the groups, respectively. The primary outcome measure was change in *on* time when awake, as assessed from patient diaries; secondary outcome measurements were change in *off* time

and UPDRS. There was a significant increase in *on* time (mean, 1.4 hours) for the entacapone 100- and 200-mg groups compared with placebo (0.5 hours). *Off* time was decreased by 1.3, 1.1, and 0.4 hours with entacapone 100 mg, entacapone 200 mg, and placebo, respectively; significance not stated. There was more dyskinesia (UPDRS-IV item 32) with entacapone versus placebo (data not reported). Overall, there were no significant differences in outcomes between the entacapone 100- and 200-mg groups. There were more AEs in the entacapone groups compared with placebo, with worsening or new onset of dyskinesia reported in 22.8% of the 200-mg entacapone arm, 21.2% of the 100-mg entacapone arm, and 13.3% of the placebo arm. At the end of the study, there was no significant difference in the decrease in levodopa between groups; although 10.5% in the 200-mg entacapone group required reduction because of dyskinesia versus 7.1% in the 100-mg entacapone group and 5.3% in the placebo group. The final dosing of entacapone was not reported. ***Quality score, 61%***.

Rascol et al (2005),[49] see below, compared rasagiline (1 mg/day) with entacapone (200 mg/dose of levodopa) and placebo in 687 PD patients (LARGO study) over 18 weeks. Subjects were on at least 3 doses of levodopa a day with at least 1 hour *off* time a day. The primary outcome measure was change in *off* time using patient-completed diaries. There was a significant reduction in adjusted mean *off* time compared with baseline of −0.8 hours (−0.2 to −0.41 hours) with entacapone ($P < .0001$). There was no difference between rasagiline and entacapone in absolute reduction in *off* time (rasagiline, −1.18 hours; entacapone, −1.2 hours). Daily *on* time without troublesome dyskinesia was correspondingly increased by 0.85 ± 0.17 hours with entacapone compared with placebo, 0.03 ± 0.17 hours ($P = .0005$). There was no increase in troublesome dyskinesia. There were no new AEs. ***Quality score, 100%***.

Efficacy conclusions: These studies confirm the prior conclusion that entacapone is *efficacious* in the treatment of motor fluctuations. There is *insufficient evidence* for treatment of dyskinesia. Other conclusions for entacapone, brought forward from the prior report, are listed in Table 4.

Tolcapone (no new studies)—no new conclusions.

Safety Conclusions with COMT Inhibitors—no new conclusions.

AEs with entacapone were consistent with prior EBM reviews; the most common included nausea and diarrhea. ICDs were assessed in Stocchi et al 2010[44] and occurred equally between the 2 groups: 14 of 103 levodopa/carbidopa/entacapone subjects (12 were on a dopamine agonist) and 15 of 102 LC subjects (10 were on a dopamine agonist). The FDA released a drug safety communication[50] concerning a greater number of cases of prostate cancer in subjects taking levodopa/carbidopa/entacapone (n = 9) compared with levodopa/carbidopa (n = 2) in the STRIDE-PD study. This is in contrast to other studies using entacapone that did not report any increased risk. The FDA recommends no change in use of entacapone and that normal monitoring for prostate cancer should be performed using current screening guidelines until any further information is available.

In addition, the FDA released a second communication[51] related to the STRIDE-PD study reporting an ongoing safety review of possible increased cardiovascular disease risk with combined levodopa/carbidopa/entacapone. Thus, there were 7 myocardial infarctions and 1 cardiovascular death in the levodopa/carbidopa/entacapone group compared with no myocardial infarctions or cardiovascular deaths in the levodopa/carbidopa group. However, no definitive conclusions can be made at this time, as most of the subjects had preexisting heart disease, and a meta-analysis of other studies using combined levodopa/carbidopa/entacapone (excluding the STRIDE-PD study) did not show a statistically significant increased risk of cardiovascular complications. The current recommendation is that there should be no change in use of combined levodopa/carbidopa/entacapone but that PD subjects with known cardiovascular disease should be regularly evaluated.

The safety issues of tolcapone include elevation in liver enzymes, requiring regular monitoring. In the last EBM review, tolcapone was considered ''acceptable but requiring special monitoring in fluctuating patients who have failed other therapies and unacceptable risk in patients who can otherwise be treated.'' Lees and colleagues[52] performed an RCT safety study of tolcapone in 677 PD patients. Subjects were randomized to receive placebo (n = 342) or tolcapone 100 mg 3 times (n = 335) daily, added to standard doses of levodopa. Liver transaminase were elevated above the upper limit of normal (ULN) in 20.2% of subjects in the placebo and 27.5% in the tolcapone groups; with increases > 3 times ULN in 1.2% and 1.8%, respectively ($P = .5$). Liver transaminase values returned to normal in 65% of placebo- and 80% of tolcapone-treated patients. No instances of serious hepatotoxicity were seen. Diarrhea was the most commonly reported AE (36 of 342 patients [11.0%] in the placebo group vs 98 of 335 patients [29.0%] in the tolcapone group) and caused discontinuation in 9.9% of tolcapone-treated patients.

COMT Inhibitor Practice Implications and Summary

These studies permit changes for entacapone and no changes for tolcapone use (Table 4). There are no

changes from the prior review that there is insufficient evidence on the role of entacapone or tolcapone in preventing/delaying clinical progression and the unchanged practice implication is *investigational*. Entacapone remains efficacious as a symptomatic adjunct to levodopa in PD subjects with motor fluctuations; thus, the practice implication remains clinically useful. However, in subjects with *no* motor complications, entacapone is nonefficacious, and the new practice implication is that entacapone is *not useful as a symptomatic adjunct in nonfluctuating PD subjects not taking prior levodopa or in subjects already on levodopa*. Tolcapone remains possibly useful as symptomatic adjunct in PD subjects with motor fluctuations.

In preventing/delaying motor complications, the practice implication is that entacapone is *not useful* in preventing motor complications, both dyskinesia and motor fluctuations, in subjects with no prior levodopa use. Tolcapone remains investigational for this indication. Entacapone and tolcapone both remain clinically useful in the treatment of motor fluctuations. Safety conclusions for entacapone are still acceptable risk without specialized monitoring. Monitoring of liver transaminases remains important for the use of tolcapone, but with monitoring, the drug can be used safely, and the safety conclusion remains acceptable with specialized monitoring.

MAO-B Inhibitors

Selective MAO-B inhibitors extend the duration of action of levodopa by reducing metabolic breakdown. Six studies were reviewed using the most widely available MAO-B inhibitors, selegiline and rasagiline, as treatments in early disease to assess efficacy in preventing/delaying clinical progression, for control of motor symptoms as monotherapy, and in advanced disease to treat motor fluctuations. A new orally disintegrating tablet preparation of selegiline that bypasses hepatic metabolism was also reviewed in 2 studies.

Selegiline (1 new study[53])—no new conclusions.

Prevention/Delay of Clinical Progression. **Palhagen et al (2007)**[53] reported the 7-year outcome of a study that originally enrolled 157 previously untreated early-PD subjects taking selegiline 10 mg/day or placebo.[54] In this extension combination study, 71 subjects initially taking selegiline and 69 on placebo were treated with levodopa therapy (150 mg/day for 1 month and then adjusted according to clinical need) and evaluated at 7 years. Mean daily levodopa dose at the end of the study was significantly higher on placebo (631.0 ± 186.3 mg vs selegiline 529.0 ± 145.6 mg; $P < .001$). Subjects were evaluated in a double-blind fashion until the requirement for further antiparkinsonian drugs including dopamine agonists or slow-release levodopa. The primary end point was time to development of motor fluctuations or time to require further treatment interventions. Secondary end points were UPDRS total and subscores. There was no difference in the number of subjects reaching termination point (selegiline, 13%; placebo, 17%). There was a trend toward more motor fluctuations on placebo, 34%, versus selegiline, 20% (analyses of total monotherapy and combination therapy; $P = .053$; HR, 0.55; $P = .076$). No difference was seen in incidence of dyskinesia (40% with placebo vs 35% with selegiline) or in time to onset of dyskinesia between the 2 groups. Total UPDRS and UPDRS-III subscores were significantly lower in the selegiline group after 48 months but not after 60 months. At 60 months, tremor and bradykinesia subscores were significantly lower in the selegiline group ($P < .05$). Sixty-four patients dropped out, and 28 were withdrawn because of an AE (selegiline, 12; placebo, 16). Data on UPDRS scores were only available for 19 subjects in the selegiline arm and 28 on placebo, and thus the results are hard to interpret. The other coprimary results were not clearly stated. Adverse events were as previously described with selegiline. ***Quality score, 57%***.

Efficacy conclusions: This study confirms the earlier designation of insufficient evidence for selegiline in prevention/delay of clinical progression. Other conclusions for selegiline, brought forward from the prior report, are listed in Table 5.

Oral Disintegrating Tablet (ODT) Preparation of Selegiline (2 new studies[55,56])—new conclusions, insufficient evidence as treatment of motor fluctuations; insufficient evidence for all other indications.

Treatment of Motor Complications. **Waters et al (2004)**[55] compared ODT selegiline (1.25 mg/day for 6 weeks, followed by 2.5 mg/day for 6 weeks) with placebo in 140 PD patients with >3 hours/day *off* time. The primary outcome variable was average percentage reduction in *off* time at weeks 10 and 12 combined, as assessed by diaries. There was a significant reduction in the percentage of daily *off* time in the selegiline group compared with placebo (13.2% vs 3.8%, respectively; $P < .001$; mean time in *off* state, 2.2 vs 0.6 hours, respectively; percentage dyskinesia free *on* time, 9.5% vs 3.3%, respectively; $P = .038$). Overall 32% of the selegiline group and 21% of the placebo group had treatment-related AEs, but only 3 and 1, respectively, discontinued. ***Quality score, 88%***.

Another study, by **Ondo et al (2007)**,[56] evaluated selegiline ODT in 150 PD subjects using the same design as above. There was no change in the percentage of daily *off* time with selegiline compared with placebo (11.6% vs 9.8%). There were similar overall AE rates, 73% versus 72%, with dizziness occurring in 13% versus 6%; discontinuations were 7% in the

TABLE 5. Conclusions on MAO-B inhibitors

MAO-B inhibitors		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Selegiline	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F) Nonefficacious (D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	investigational	Investigational (F) Not useful (D)	Investigational (F, D)
Oral disintegrating selegiline	*Efficacy*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*
Rasagiline	*Efficacy*	Insufficient evidence	Efficacious	*Efficacious*	Insufficient evidence (F, D)	*Efficacious (F)* *Insufficient evidence (D)*
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	*Clinically useful*	Investigational (F, D)	*Clinically useful (F)* *Investigational (D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

selegiline group and 0% in the placebo group. ***Quality score, 80%***.

Efficacy conclusions: Based on these 2 studies with conflicting outcomes, there is *insufficient evidence* for selegiline ODT in the treatment of motor complications.

Rasagiline (5 new studies[49,57–60])—new conclusions: efficacious for control of motor symptoms—adjunct to levodopa and efficacious as treatment of motor fluctuations.

Rasagiline has been assessed in 2 studies in early PD for prevention/delay of clinical progression and 1 study for the control of motor symptoms—monotherapy. Two studies were performed in advanced PD for the treatment of motor complications.

Prevention/Delay of Clinical Progression. The Parkinson Study Group (**PSG**) **2004**[57] in a delayed-start design assessed the efficacy of rasagiline monotherapy in 404 early-PD patients not requiring dopaminergic therapy. Subjects were randomized into 3 groups: rasagiline 1 mg/day for 1 year, rasagiline 2 mg/day for 1 year, and placebo for 6 months, followed by rasagiline 2 mg/day for 6 months (delayed 2-mg group). The primary outcome measure was the change in the total UPDRS score from baseline to 52 weeks or last observation carried forward (LOCF). There was a significant effect of lower long-term UPDRS scores in the group treated with early and continuous rasagiline 2 mg/day. The change from baseline in total UPDRS scores for rasagiline 1 mg versus delayed 2 mg was −1.82 (−3.64 to 0.01; $P = .05$) and for rasagiline 2 mg/day versus delayed 2 mg was −2.29 (−4.11 to 0.48; $P = .01$). Total average UPDRS scores were higher in subjects in the delayed 2-mg group at 52 weeks: 27.45 ± 14.18, 27.10 ± 11.90, and 28.02 ± 14.17 for the 1-mg, 2-mg, and delayed 2-mg groups, respectively. The only concern is that LOCF may not be appropriate for all the subjects who end-pointed along the way. Between 61% and 65% completed the full follow-up period in the 3 arms, and LOCF was used to compute data for the remainder. It is unclear if this is an appropriate method for missing data. There were no significant AEs. ***Quality score, 89%***.

Olanow et al (2009)[58] assessed the effect of rasagiline 1 mg, 2 mg, and placebo in a delayed-start design study in 1176 early-PD subjects (ADAGIO study). Untreated patients with disease duration < 18 months were randomized to 72 weeks of treatment in 2 phases: phase 1, placebo (delayed start) or rasagiline 1 or 2 mg (early start) for 36 weeks; followed by phase 2, all rasagiline for 36 weeks. Four groups were assessed: delayed-start rasagiline 1 mg (n = 300), early-start rasagiline 1 mg (n = 288), delayed-start rasagiline 2 mg (n = 295), and early-start rasagiline 2 mg (n = 293). There were 3 hierarchical end points that had to be achieved: change in total UPDRS/week (slope of the line between weeks 12 and 36) between the 2 rasagiline groups and placebo, change in UPDRS between baseline and week 72 between early and delayed start, and noninferiority of the slope (rate of change in UPDRS between weeks 48 and 72) between early and delayed start. Secondary outcomes included change in total UPDRS score between baseline and the last observed value in phase 1. The total number of subjects included in the primary end point analysis was 1164 subjects, with 996 in the second and third

end points, and 910 completing with no difference in the groups. Rasagiline 1 mg reached significance in all 3 end points: early-start rasagiline 1 mg had less worsening in UPDRS score between baseline and week 72 (2.82 ± 0.53) than the delayed-start group (4.50 ± 0.56); $P = .02$. Rasagiline 2 mg did not reach significance in all primary end points. There were no significant differences in AEs; 1 subject in the rasagiline 1 mg group developed a melanoma. The unusual statistical design, small (but significant) overall change in UPDRS, lack of dose response, and inconsistent finding with an earlier study[57] make interpretation of clinical relevance difficult. ***Quality score, 83%.***

Efficacy conclusions: Based on these 2 studies, there is *insufficient evidence* for a role of rasagiline in prevention/delay of clinical progression of PD.

Control of Motor Symptoms—Monotherapy. **Stern et al (2004)**[59] compared rasagiline 1, 2, and 4 mg/day and placebo in 56 patients with early, untreated PD. There was a 3-week escalation and 8-week steady state. The primary outcome was safety and tolerability; secondary outcome measures were changes from baseline in total UPDRS. The study was included in this review as a higher dose (4 mg) was evaluated in the trial, although the study was not powered to detect change in total UPDRS. There was significant improvement in total UPDRS compared with baseline with rasagiline 2 mg (−3.6 ± 1.7 points), $P < .05$, but not rasagiline 1 mg (+1.8 ± 1.3 points), rasagiline 4 mg (−3.6 ± 1.2 points), or placebo (−0.5 ± 0.8 points). AEs were similar to placebo, and only 1 subject in the 1-mg rasagiline arm discontinued, because of visual hallucinations and dizziness. ***Quality score, 76%.***

Efficacy conclusions: This report reinforces the prior conclusion that rasagiline is *efficacious* as monotherapy for the symptomatic treatment of PD motor symptoms.

Control of Motor Symptoms—Adjunct to Levodopa. **PSG (2005),**[60] see below, compared rasagiline 0.5 and 1.0 mg/day and placebo in 472 levodopa-treated PD subjects with at least 2.5 hours/day *off* time (PRESTO study). *On* period UPDRS-III improved with both doses of rasagiline adjusted for placebo (rasagiline 0.5 mg, −2.91 [−4.59 to −1.23]; rasagiline 1 mg, −2.87 [−4.58 to 1.16]; both $P < .001$). ***Quality score, 98%.***

Rascol et al (2005),[49] see above, compared rasagiline (1 mg/day) with entacapone (200 mg/dose of levodopa) and placebo in 687 PD patients (LARGO study) over 18 weeks. Rasagiline improved on period motor UPDRS-III scores compared with placebo by −2.94 points ($P < .0001$). ***Quality score, 100%.***

Efficacy conclusions: These studies allow rasagiline to be newly designated as *efficacious* for treating the motor symptoms of PD as an adjunct to levodopa.

Treatment of Motor Complications. **PSG (2005),**[60] see above, compared rasagiline 0.5 mg/day, 1.0 mg/day and placebo in 472 levodopa-treated PD subjects with at least 2.5 hours/day off time (PRESTO study). The primary outcome was change in total daily *off* time over 26 weeks, as measured with patient-completed diaries. Exploratory end points included daily *on* time with dyskinesia and UPDRS-IV dyskinesia subscores. Rasagiline 0.5 mg/day significantly reduced *off* time by −0.49 hours (−0.91 to −0.08 hours; $P = .02$), as did rasagiline 1 mg/day by −0.94 hours (−1.36 to −0.51 hours; $P < .001$), adjusted for placebo. There was a corresponding increased *on* time, with daily *on* time without dyskinesia increased in both groups compared with placebo, 0.51 hours (0–1.03 hours; $P = .05$) and 0.78 hours (0.26–1.31 hours; $P = .004$) for rasagiline 0.5 and 1 mg, respectively. However, troublesome dyskinesia was increased with rasagiline 1 mg/day, 32% of increased *on* time, whereas with rasagiline 0.5 mg, there was no troublesome dyskinesia. Dyskinesia subscore was significantly increased with rasagiline 1 mg/day (+0.37 points [0.04–0.7 points]; $P = .03$) but not with rasagiline 0.5 mg/day. There was significantly more weight loss, vomiting, and anorexia in the rasagiline 1 mg/day group, but no difference in dropouts because of AEs between the groups. ***Quality score, 98%.***

In the study by **Rascol et al (2005),**[49] as described above, rasagiline (1 mg/day) was assessed in 687 PD subjects with motor fluctuations and compared with entacapone and placebo. The primary outcome measure was change in daily *off* time using patient-completed diaries. There was a significant reduction in *off* time of 0.78 hours (−1.18 to −0.39 hours) with rasagiline. There was a corresponding increase in daily *on* time without troublesome dyskinesia with rasagiline by 0.82 hours (0.36, 1.27 hours) compared with placebo ($P < .0005$). ***Quality score, 100%.***

Efficacy conclusions: These studies allow rasagiline to be newly designated as *efficacious* for treating motor fluctuations. For the treatment of dyskinesia, there remains *insufficient evidence*. Other conclusions for rasagiline, brought forward from the prior report, are listed in Table 5.

Safety for MAO-B Inhibitors—no new conclusions.

There were no safety issues with these studies. **Katzenschlager (2008)**[13] assessed selegiline 10 mg/day combined with levodopa (n = 271) compared with levodopa alone (n = 249) and bromocriptine (n = 262) in early untreated PD subjects. This study has

been discussed above in the section on bromocriptine. The selegiline arm was stopped in 1995 because of concerns regarding excess mortality in the patients taking selegiline with levodopa. Long-term mortality outcomes showed no significant difference after a mean 14-year follow-up (HR, 1.17, levodopa/selegiline compared with levodopa alone). Restriction of tyramine-containing foods when using rasagiline is no longer necessary.

RCTs using rasagiline have renewed interest in the issues related to the risk of skin cancer, particularly melanoma, in PD patients. Recent rasagiline studies reported very small numbers of subjects with melanoma either developing during the study, for example, 1 subject in the ADAGIO study and 2 subjects in the PRESTO study. In the latter study, 1 subject had a melanoma prior to the start of treatment; thus, disease mechanisms related to PD itself may be a factor. To date, there is no evidence linking rasagiline to melanoma or skin cancers. Overall, there is a 1- to 3-fold increased incidence of melanoma in PD subjects compared with controls; however, the cause is unknown and is not consistently related to any dopaminergic medication per se.[61] In addition, nonmelanoma skin cancers have also been reported more frequently in PD subjects, but the data are less robust. At present, there are no specific safety recommendations, although PD subjects should have regular dermatological review regardless of medication usage.

For both selegiline and rasagiline, the concomitant use of certain antidepressants has a theoretical risk of serotonin syndrome; however, the studies of early rasagiline[57,58] allowed certain antidepressants, with no cases of serotonin syndrome reported. However, vigilance should be maintained with all coprescriptions of antidepressants and MAO-B inhibitors, and patients should be counseled about known drugs that are contraindicated with use of MAO-B inhibitors.

MAO-B Inhibitors Practice Implications and Summary

Conclusions on selegiline are unchanged, and there are new conclusions on rasagiline and ODT selegiline (Table 5). There remains insufficient evidence for selegiline and rasagiline in preventing/delaying clinical progression, and the practice implication remains as investigational for preventing clinical progression.

For symptomatic monotherapy, selegiline and rasagiline both remain clinically useful. There is insufficient evidence for ODT selegiline, and as such the practice implication is *investigational for symptomatic monotherapy*. For symptomatic adjunct to levodopa, rasagiline is newly designated *clinically useful*, whereas ODT selegiline is *investigational*. The prior EBM review reported that selegiline was "possibly useful" as symptomatic adjunct therapy, although there was insufficient evidence; this error has been corrected in Table 5, and the practice implication is now investigational.

In prevention/delay of motor fluctuations, ODT selegiline is newly designated *investigational*, whereas selegiline and rasagiline remain investigational. Selegiline also remains not useful in prevention/delay of dyskinesia. In the treatment of motor complications, both fluctuations and dyskinesia, ODT selegiline is *investigational*, whereas selegiline remains investigational. For treatment of motor fluctuations, rasagiline is newly designated *clinically useful* but *investigational* for dyskinesia. There is no change in the safety conclusions that there is an acceptable risk without specialized monitoring for selegiline, selegiline ODT, and rasagiline.

Other Therapies, Anticholinergics, Amantadine, Clozapine, Zonisamide

Anticholinergics (no new studies)—no change in conclusions.

Amantadine (1 new study[62])—no change in conclusions.

Amantadine, a nonselective NMDA receptor antagonist, was reported as clinically useful in the treatment of dyskinesia in the prior EBM review. One new study evaluated long-term efficacy in PD subjects with dyskinesia.

Treatment of Motor Complications. **Wolf et al (2010)**[62] performed an RCT parallel-group study to assess the long-term antidyskinetic effect of amantadine. Thirty-two PD patients with a mean disease duration of 16.8 years who had been on stable amantadine therapy (mean dose, 298 mg/day) for dyskinesia for at least 1 year (mean, 4.8 years) were randomized in a double-blind manner to amantadine (at the same dose) or placebo and followed for 3 weeks. The study was included despite the shorter duration of follow-up, as it evaluates the long-term efficacy of amantadine. The primary outcomes were dyskinesia duration and intensity, as assessed by change in UPDRS-IV items 32 and 33 between baseline and week 3, by between-group comparison of the change in UPDRS items 32 and 33, and by patients' diaries. There was a significant increase in dyskinesia, as measured on UPDRS items 32 and 33, in patients who had been switched to placebo, from 3.06 (95% CI, 2.1–4.03) at baseline to 4.28 (95% CI, 3.1–5.4) at the 3-week follow-up ($P = .02$), whereas there was no significant change between baseline and follow-up (3.2 [95% CI, 2.1–4.4] vs 3.6 [95% CI, 2.3–4.8]) in patients continuing on amantadine. Diary data also showed a significant increase in time spent *on* with

TABLE 6. Conclusions on anticholinergics, amantadine, clozapine, and zonisamide

Drug		Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Anticholinergics	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Investigational (F, D)
Amantadine	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F) Efficacious (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Possibly useful	Possibly useful	Investigational (F, D)	Investigational (F) Clinically useful (D)
Clozapine	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence (F, D)	*Insufficient evidence (F)* *Efficacious (D)*
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	*Investigational (F)* *Possibly useful (D)*
Zonisamide	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Efficacious*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Clinically useful*	*Investigational (F, D)*	*Investigational (F, D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

troublesome dyskinesia (from 1.7 to 3.5 hours/day) in the placebo group only. The difference in UPDRS items 32 and 33 between the 2 randomized groups failed to reach significance, which, as the authors comment, may have been a result of insufficient power, as the calculated required sample size was not achieved because of recruitment issues. ***Quality score, 88%.***

Efficacy conclusions: This study reinforces the prior conclusion that amantadine is efficacious for treating dyskinesia. Other conclusions for amantadine, brought forward from the prior report, are listed in Table 6.

Safety Issues with Amantadine—no new conclusions.

No new safety issues were reported. There are case reports of reversible corneal edema in PD patients on amantadine.[63] To date, routine ophthalmological monitoring is not currently recommended for patients using amantadine, but clinicians need to be vigilant about patients reporting sudden visual changes.

Clozapine (1 new study)[64]—new conclusions: efficacious in treatment of dyskinesia.

Treatment of Motor Complications. Clozapine has been investigated as a treatment for dyskinesia. The exact mechanism of action is unclear but may relate to the rate of binding to striatal dopamine D2 receptors or serotonergic properties.[65] There is 1 new study[64] evaluating clozapine as a treatment for dyskinesia.

Durif et al (2004)[64] conducted an RCT in 50 PD patients with disabling dyskinesia using clozapine (average, 39.4 ± 4.5 mg/day) over 10 weeks. The primary end point was change in *on* time with and without dyskinesia and *off* time between baseline and end of study, using home diaries. Secondary outcomes included an acute levodopa challenge before and after 70 days, with post hoc video scoring using a dyskinesia severity scale in resting and activation by mathematical calculations. There was a significant reduction in mean *on* time with dyskinesia with clozapine, −1.7 hours compared with placebo, −0.74 hours ($P = .003$). No changes were seen in *off* time duration. Thirty-eight patients completed the levodopa challenge (PP group), with a significant reduction in dyskinesia severity at rest, from an average 6.7 to 4.5 points (maximum score possible, 28; $P = .05$). There was no significant effect with dyskinesia rated during activity. The change in dyskinesia measured at rest is of unclear clinical significance. ***Quality score, 90%.***

Efficacy conclusions: This study allows a new conclusion of clozapine as *efficacious* in the treatment of dyskinesia. There is *insufficient evidence* for the treatment of motor fluctuations Other conclusions for clozapine, brought forward from the prior report, are listed in Table 6.

Safety for Clozapine—no new conclusions.

Clozapine use requires mandatory blood testing because of the risk of agranulocytosis, which occurs in 0.7%. In the above study, 3 patients were withdrawn from the clozapine group for reversible eosinophilia, but no significant change in white cell count occurred. There were no new issues (see also, nonmotor section on clozapine use in PD for psychosis).

Zonisamide (1 new study[66])—new conclusions: efficacious as symptomatic adjunct to levodopa; insufficient evidence for all other indications.

Zonisamide is an agent with multiple potential modes of action including a possible increase in dopamine synthesis as well as glutamate release inhibition and MAO-B inhibition.[67] Although originally developed for use in epilepsy, studies have suggested a potential use in PD, and zonisamide is licensed for use in PD in Japan.

Control of Motor Symptoms—Adjunct to Levodopa and Treatment of Motor Complications. **Murata et al (2007)**[66] conducted a multicenter parallel-treatment RCT of zonisamide as adjunctive treatment to levodopa in 347 PD patients. The inclusion criteria were very broad and included PD patients who showed "insufficient response to levodopa" and had a variety of motor fluctuations. Subjects were given placebo for 2 weeks as a single-blind run-in phase and then randomized to 12 weeks' treatment with zonisamide (25, 50, or 100 mg/day) or placebo, in addition to levodopa. The primary end point was change from baseline in the UPDRS-III score. Secondary end points included changes from baseline in total daily *off* time (as determined from patient diaries), parts I, II, and IV UPDRS scores, and modified H&Y score. There was a significant improvement in the primary end point in the 25- and 50-mg groups versus placebo (−6.3, −5.8, and −2.0 points, respectively; $P = .001$ and $P = .003$); the 4.6-point decrease in UPDRS-III score in the 100-mg group did not reach statistical significance ($P = .066$). The duration of *off* time was significantly reduced in the 50- and 100-mg groups versus placebo (by 1.30, 1.63, and 0.20 hours/day, respectively). There were no significant differences between the zonisamide and placebo groups with respect to changes from baseline in the UPDRS-I, -II, and -IV scores and in the modified H&Y score. Dyskinesia frequency was not increased in the zonisamide groups. The incidence of AEs was similar among the 25-mg, 50-mg, and placebo groups but higher in the 100-mg group; the most common AEs were somnolence, apathy, weight loss, and constipation. However, the average daily dose of levodopa that subjects were taking was low, 350 mg/day, making applicability to PD patients with motor fluctuations unclear. ***Quality score, 85%.***

Efficacy conclusions: This study allows a conclusion of *efficacious* for the control of motor symptoms as an adjunct to levodopa but *insufficient evidence* for treatment of motor complications.

Anticholinergics, Amantadine, Clozapine, and Zonisamide Practice Implications and Summary

There are no changes in the conclusions for anticholinergics or amantadine, whereas new studies with clozapine permit new conclusions, and zonisamide was not reviewed previously (Table 6). The practice implications for anticholinergics remain as clinically useful as both monotherapy and symptomatic adjunct therapy; all other indications are investigational. Amantadine also remains as clinically useful as monotherapy, as an adjunct symptomatic therapy to levodopa as well as for treatment of dyskinesia. Other uses are investigational.

Clozapine was evaluated in the 2002 EBM review for nonmotor symptoms of PD, and this will be updated in an accompanying EBM update on treatments for nonmotor symptoms of PD. There remains insufficient evidence for the use of clozapine as an adjunct to levodopa, with the practice implication as investigational for use as symptomatic adjunct in the treatment of PD tremor. Clozapine was efficacious in treatment of motor complications (dyskinesia); however, to date, only 1 study with short-term follow-up has shown this, and combined with potential safety issues, the practice implication is that clozapine is *possibly useful in the treatment of levodopa-induced dyskinesia*. Zonisamide is effective as a symptomatic adjunct to levodopa, with the practice implication that it is *clinically useful*. There was insufficient evidence for any other efficacy conclusions, with the practice implications that zonisamide is *investigational* for all other indications. Safety conclusions for anticholinergics and amantadine remain unchanged, and zonisamide is designated as *acceptable without specialized monitoring*. The safety conclusions for clozapine also remain unchanged from the 2002 review: the use of clozapine has an *acceptable risk with specialized monitoring*.

Surgical Treatments

Eight level I studies[68–75] were reviewed involving the subthalamic nucleus (STN), pallidum, and thalamus as targets, using either deep brain stimulation (DBS) or lesioning. In all cases, surgery was performed for the indication of symptomatic adjunct to levodopa and/or to treat motor complications. Some surgical studies[73,74] used quality of life as the primary outcome measure but included comprehensive reporting of motor outcomes and were included in this review. The study by Weaver et al,[75] which pooled STN and globus pallidus (GPi) DBS into a single DBS group to address the question of surgical versus best medical treatment, did not provide data that allow efficacy evaluations of these procedures separately and therefore is not discussed further. Because some studies[68–71] examined a given surgical intervention relative to bilateral STN DBS, the latter surgery is discussed first.

Control of Motor Symptoms—Adjunct to Levodopa and/or Treatment of Motor Complications

Bilateral STN DBS (5 new studies[68,69,71–74])—new conclusions*: efficacious* for the treatment of both dyskinesia and motor fluctuations.

Anderson et al (2005)[68] conducted a double-blind comparison of bilateral STN versus bilateral GPi stimulation in advanced-PD patients (10 patients in each group with 12 months of follow-up). Changes from baseline were reported for each group, but the statistical analysis was restricted to comparisons between groups and not within each group (baseline to end of study). *Off* medication UPDRS motor scores (the primary outcome measure) were improved after 12 months of both STN and GPi stimulation (reduced from 51 ± 13 to 27 ± 11 points and from 50 ± 23 to 30 ± 17 points, respectively, ie, improvement of 48% vs 39%; $P = .40$). Bradykinesia tended to improve more with STN than with GPi stimulation (44% vs 33%; $P = .06$). Levodopa dose was reduced by 38% in STN stimulation patients compared with 3% in GPi stimulation patients ($P = .08$). Dyskinesia was reduced by both STN and GPi DBS (62% vs 89%; $P = .27$). Cognitive and behavioral complications were observed only with STN stimulation, including 2 patients who experienced persistent cognitive changes. Although concluding that there was "no clear superiority of STN over GPi stimulation," the authors acknowledged that some of the differences between targets that were statistically insignificant in the study may be significant in the context of a larger trial. ***Quality score, 58%***.

Deuschl et al (2006),[72] in the German Parkinson Study Group, reported on a large randomized controlled multicenter unblinded trial of bilateral STN stimulation versus best medical therapy (BMT) in patients with severe motor complications. The study included 156 patients < 75 years (mean age, about 60 years) who were randomly assigned in pairs to receive either STN DBS in combination with BMT or BMT alone. The primary outcome measures were the changes (from baseline to 6 months) in health-related quality of life (Parkinson's Disease Questionnaire–39 [PDQ-39] score; range, 0–100, with higher scores indicating worse function) and *off* medication UPDRS-III score. According to the ITT analysis of the 78 pairs of patients, in 50 pairs (64%), the patient treated with DBS had greater improvement in the PDQ-39 summary index score than the patient assigned to BMT ($P = .02$), and in 55 pairs (71%), the patient treated with DBS had greater improvement in the stimulator *on*/*off* medication UPDRS-III score compared with the paired non-DBS subject evaluated in the *off* medication state ($P < .001$). This result was obtained despite rigid criteria for the replacement of missing data that gave an advantage to BMT in the results. Regarding the treatment of motor complications, dyskinesia score improved by 54% in the DBS group (by a mean of 3.4 ± 4.5 points; 95% CI, 2.3–4.5 points), but remained unchanged in the BMT group ($P < .001$). Significant improvements in diary records of *on* time without troublesome dyskinesia (from a mean of 3.2 to 7.6 hours/day), *on* time with troublesome dyskinesia (2.0 to 1.0 hours/day), and *off* time (6.2 to 2.0 hours/day) occurred in the DBS group, but these remained unchanged in the BMT group. These improvements occurred in the context of a significant reduction in dopaminergic equivalents (50% in the DBS group compared with only 8% with BMT; $P < .001$). Serious AEs were more common with DBS than with BMT alone (12.8% vs 3.8%, $P < .04$) and included a fatal intracerebral hematoma and a suicide, although the total number of AEs tended to be higher in the BMT group (64.1% vs 50.0%, $P = .08$). ***Quality score, 80%***.

Esselink et al (2006)[71] conducted a rater-blinded comparison of unilateral pallidotomy (n = 14) versus bilateral STN stimulation (n = 20) at 12 months in patients with advanced PD; 6-month data were published in 2004 and previously reviewed in the 2005 EBM guidelines. Statistical significance was reported for between-group but not for within-group changes in outcome measures. After 1 year, the median *off* medication UPDRS-III score (the primary outcome measure) improved by 53% in the STN stimulation patients and by 31% in the pallidotomy patients ($P = .002$). The Schwab and England scale improved more in the STN group than in the pallidotomy group (20-point difference in median change scores; $P = .04$). Dyskinesia severity, as assessed by the Clinical Dyskinesia Rating Scale and UPDRS-IV items 32 and 33, improved substantially in both treatment groups, with no significant between-group differences. The PDQ-39 improved in both groups (median change of 23.5 points in the STN group vs 11 points in the pallidotomy group [185-point scale]; $P = .25$). Dopaminergic drug reduction was larger in the STN group (29.4% vs 9.5%), but again the difference between the treatment groups was not significant. The authors acknowledged that the lack of consistently significant differences in favor of STN stimulation could be a result of the small sample size. One patient in each group had a severe AE (1 pallidotomy patient committed suicide 3 weeks after successful surgery; 1 STN patient had severe cognitive deterioration). ***Quality score, 86%***.

Four-year follow-up data were subsequently reported.[70] This study showed long-term superiority in the efficacy of bilateral STN DBS over pallidotomy, with median change scores (compared with preoperative baseline) in *off*-medication UPDRS-III of 46% versus 27% ($P = .04$). The study could not demonstrate significant between-group differences with respect to dyskinesia severity, ADL functioning, quality of life, or levodopa equivalent dose; the authors attributed this to the small sample size studied. The frequency of adverse events was approximately the same in both groups, with drooling and emotional lability the most frequent in the pallidotomy and STN DBS groups, respectively. ***Quality score, 93%***.

Schupbach et al (2006)[73] randomized 20 patients with a short duration of PD symptoms (5–10 years; mean, 6.8 ± 1.0 years), young age (<55 years), and relatively mild motor symptoms and complications to either immediate bilateral STN DBS (n = 10) or optimized medical treatment (n = 10). Patients were included in pairs and matched (for age, duration and severity of disease, and impairment in socioprofessional functioning) before randomization; despite this, patients randomized to surgery had a higher mean *off* medication score (32.7 ± 13.4 vs 25.3 ± 8.7). Disease-specific quality of life (the primary end point, using the PDQ-39 summary index), UPDRS-III, cognition, and psychiatric morbidity were assessed at inclusion and after 6, 12, and 18 months. Quality of life was significantly improved, by 24%, in the surgical group (within-group change did not reach statistical significance), but did not change in nonsurgical patients, resulting in a significant end-of-study difference in the 2 groups ($P < .05$). After 18 months, the severity of *off*-medication parkinsonian motor signs was reduced by 69% in operated-on patients but increased by 29% in the medically treated group ($P < .05$).

Regarding the treatment of motor complications, the UPDRS-IV (motor complications of levodopa) score improved by 83% in operated-on patients but worsened by 15% in the medically treated group ($P < .05$); there was no separation of dyskinesia and fluctuations. Daily levodopa dose was reduced by 57% in operated-on patients but increased by 12% in the medically treated group ($P < .05$). AEs were mild or transient, and overall psychiatric morbidity and anxiety improved in the surgical group (no change in the medical group). Neuropsychological tests remained stable in both groups. ***Quality score, 74%***.

Follett et al (2010)[69] randomly assigned 299 patients to undergo either bilateral STN DBS (n = 147) or bilateral GPi DBS (n = 152); 23% of patients were ≥ 70 years. The results of GPi DBS are discussed further in the section below. The primary outcome was the change from baseline to 24 months in *off*-medication, *on*-stimulation UPDRS-III score, which was blindly assessed by clinicians (patients remained unaware of the surgical target for the duration of the study). There was a mean reduction of 10.7 points (95% CI, 8.5–12.9 points) in the *off*-medication, *on*-stimulation UPDRS-III score at the end of the study in the STN DBS group. Statistical significance was reported for between-group but not within-group changes in the other outcome measures. Diary comparisons between baseline and 24 months documented a mean increase of 4 hours/day with good motor function without troublesome dyskinesia; furthermore, *on* time with troublesome dyskinesia was reduced by 2.6 hours/day and *off* time by 2.5 hours/day. Overall quality of life, as measured by the PDQ-39, improved by 4.2 points. Daily levodopa-equivalent dose decreased by 408 mg. There were no significant differences in either overall or serious AEs between the 2 treatment groups. ***Quality score, 90%***.

In the multicenter open-label trial from the United Kingdom of **Williams et al (2010)**,[74] patients were randomized to surgery and BMT (n = 183) or to BMT alone (n = 183). Although according to the protocol, lesional surgery or DBS, either STN or GPi, was allowed at the discretion of the local clinician, in practice, 98% of the patients allocated to surgery underwent STN DBS, and in all but 2 cases, the procedure was performed bilaterally. The primary end point was patient self-reported quality of life on the PDQ-39. At 1 year, the mean improvement in the PDQ-39 summary index score compared with baseline was 5.0 points in the surgery group and 0.3 points in the medical therapy group ($P = .001$), with significant differences seen in the domains of mobility ($P = .0004$), activities of daily living ($P < .0001$), and bodily discomfort ($P = .004$). The between-group difference in mean change in the off-medication UPDRS-III score was 16.8 points in favor of surgery ($P < .0001$).

Regarding the treatment of motor complications, UPDRS-IV items 32 (proportion of the waking day that dyskinesia is present) and 39 (proportion of the waking day that the patient is *off*) improved across all categories in the surgery group versus the medical therapy group ($P < .0001$ for both dyskinesia and *off* periods). There was a significant 34% reduction in mean levodopa equivalents in the surgery group. The authors noted that in this study antiparkinsonian drug treatment in the medical group might have been better than in other studies because apomorphine could be included; 45 patients in each group (25%) were on apomorphine at study entry, but by 1 year, this had decreased to 13 in the surgery group and increased to 63 in the medical therapy group. ***Quality score, 80%***.

Efficacy conclusions: All the above studies confirm the 2005 conclusion that STN DBS is *efficacious* as an adjunct to levodopa. The new evidence on improvements in dyskinesia and motor fluctuations permit the designation of *efficacious* for the treatment of both dyskinesia and motor fluctuations. Other conclusions for STN DBS, brought forward from the prior report, are listed in Table 7.

Bilateral GPi DBS (2 new studies[68,69]—new conclusions: *efficacious* for control of motor symptoms—adjunct to levodopa; *efficacious* for the treatment of dyskinesia and motor fluctuations.

The studies by Anderson et al[68] and Follett et al[69] (bilateral GPi DBS vs bilateral STN DBS) were reviewed in the section above on STN DBS. They demonstrated that motor improvement from bilateral GPi DBS is equivalent to STN DBS, the latter designated as efficacious (see above). The summary here focuses on the GPi group in the study by Follett et al.

TABLE 7. Conclusions on surgery

Surgery		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Bilateral subthalamic nucleus (STN) stimulation	Efficacy	Insufficient evidence	Insufficient evidence	Efficacious	Insufficient evidence (F, D)	*Efficacious (F, D)*
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	Clinically useful	Investigational (F, D)	*Clinically useful (F, D)*
Bilateral pallidal (GPi) stimulation	Efficacy	Insufficient evidence	Insufficient evidence	*Efficacious*	Insufficient evidence (F, D)	*Efficacious (F, D)*
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	*Clinically useful*	Investigational (F, D)	*Clinically useful (F, D)*
Unilateral pallidotomy	Efficacy	Insufficient evidence	Insufficient evidence	Efficacious	Insufficient evidence (F, D)	*Efficacious (F, D)*
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	Clinically useful	Investigational (F, D)	*Clinically useful (F, D)*
Unilateral thalamotomy	Efficacy	Insufficient evidence	Insufficient evidence	*Likely efficacious*	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	*Possibly useful*	Investigational (F, D)	Investigational (F, D)
Thalamic stimulation (unilateral or bilateral)	Efficacy	Insufficient evidence	Insufficient evidence	*Likely efficacious*	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	*Possibly useful*	Investigational (F, D)	Investigational (F, D)
Subthalamotomy	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	Investigational (F, D)
Human fetal cell transplantation	Efficacy	Insufficient evidence	Insufficient evidence	Nonefficacious	Insufficient evidence (F, D)	Nonefficacious (F, D)
	Safety	Unacceptable risk				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	Investigational (F, D)

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

The primary outcome of the **Follett et al (2010)**[69] study was the change from baseline to 24 months in *off*-medication, *on*-stimulation UPDRS-III scores; this improved by a mean of 11.8 points (95% CI, 9.5–14.1 points) in the GPi DBS group. Diary comparisons between baseline and 24 months documented a mean increase of 4.9 hours/day with good motor function without troublesome dyskinesia in the GPi treatment group (vs 4 hours/day in the STN DBS group, $P = .09$). *On* time with troublesome dyskinesia was reduced by 3.2 hours/day after GPi stimulation (vs 2.6 hours/day with STN DBS, $P = .20$) and *off* time by 2.7 hours/day (vs 2.5 hours/day with STN DBS, $P = .61$). PDQ-39 improved by 4.8 points in the GPi DBS group (vs 4.2 points in the STN DBS group, $P = .69$). Daily levodopa-equivalent dose was decreased less than in the GPi DBS group compared with the STN DBS group (243 vs 408 mg; $P = .02$). The authors concluded that patients had similar improvements in motor function after either GPi or STN DBS but noted that extended follow-up is needed to determine whether these improvements would remain stable over a longer period. ***Quality score, 90%.***

Efficacy conclusions: Based on these new studies, there is sufficient evidence to designate GPi DBS as *efficacious* as adjunctive treatment to levodopa and as *efficacious* for the management of both dyskinesia and motor fluctuations. Other conclusions for GPi DBS, brought forward from the prior report, are listed in Table 7.

Unilateral Pallidotomy (1 new study with 2 reports[70,71] on outcomes at 2 times)—no new conclusions.

In the 2005 EBM review, the text designated pallidotomy as efficacious for the treatment of motor complications (both dyskinesia and motor fluctuations [the printed table designating likely efficacious was an error]). This conclusion was based primarily on the high-quality study by Vitek et al[76] comparing unilateral pallidotomy with medical therapy (quality score, 82%), which documented significant improvements in

both dyskinesia and motor fluctuations after pallidotomy ($P < .0001$ for between-group changes). These conclusions are reinforced by 2 new reports.[70,71]

The 2006 and 2009 reports by **Esselink et al**[70,71] (unilateral pallidotomy vs bilateral STN DBS) were reviewed in the section above on STN DBS. In brief, the study demonstrated superiority in efficacy of bilateral STN DBS over pallidotomy with respect to *off*-medication UPDRS-III scores (the primary outcome measure) at 12 months and at 4 years. There was a substantial improvement in the Clinical Dyskinesia Rating Scale score in the pallidotomy group (median change of 3.5 points at 12 months and at 4 years vs 5 points in the STN DBS group; *P* value not significant for between-group differences).

Efficacy conclusions: In the absence of conflicting level I data, the above studies permit no change in the conclusion of *efficacious* for pallidotomy as a symptomatic adjunct to levodopa and a new conclusion of *efficacious* for both motor fluctuations and dyskinesia. Other conclusions for pallidotomy, brought forward from the prior report, are listed in Table 7.

Unilateral Thalamotomy and (Unilateral or Bilateral) Thalamic DBS (1 new study[77])—new conclusions: both procedures are *likely efficacious* as a symptomatic adjunct to levodopa.

Schuurman et al (2008)[77] compared the efficacy of unilateral thalamotomy versus unilateral or bilateral thalamic DBS for the treatment of drug-resistant tremor in 45 PD patients. Twenty-three patients were randomized to receive thalamotomy, and 22 received DBS. The primary outcome measure was change from baseline in functional status, measured by the Frenchay Activities Index (FAI; range of scale, 0–60, with higher scores indicating better functioning). The severity of arm tremor (assessed using the UPDRS; range of scores, 0–4) was a secondary outcome measure; at baseline, all patients in both treatment groups had either grade 3 (moderate) or grade 4 (severe) tremor. Six-month results were published in 2000 and reviewed in the 2002 EBM review. This article reported 2- and 5-year outcomes. The difference in mean FAI scores between thalamic DBS and thalamotomy was 4.4 after 6 months ($P < .05$), 4.1 after 2 years (P = NS), and 7.0 after 5 years ($P < .05$) in favor of stimulation. Absolute FAI scores worsened over time in both treatment groups (back to baseline in the stimulation group and below baseline in the thalamotomy patients at 5 years), probably because of disease progression (worsened postural instability and gait). However, 93% of patients with thalamotomy (13 of 14) and 88% of patients with thalamic DBS (15 of 17) still experienced satisfactory tremor suppression at 5 years, with tremor scores of 0 (= absence of tremor) or 1 (= occasional slight tremor). As previously reported in 2000, AEs such as cognitive deterioration, dysarthria, and gait and balance disturbance were more often seen after thalamotomy. However, the 1 death related to surgery (perioperative cerebral hemorrhage) was in a DBS-treated patient, and 6 equipment-related complications occurred in the DBS group, all requiring surgery. ***Quality score, 62%***.

Efficacy conclusions: These studies allow a change in the conclusion for thalamotomy or thalamic DBS to *likely efficacious* as a symptomatic adjunct to levodopa. Other conclusions for thalamic surgery, brought forward from the prior report, are listed in Table 7.

All Other Surgeries: Subthalamotomy, Cell Transplantation (no new studies)—no changes in conclusions.

Recently, Alvarez et al (2009)[78] reported on the effects of unilateral subthalamotomy in a large number of PD patients followed up for up to 3 years. The procedure produced marked improvement in contralateral parkinsonian features, but the study is not discussed further here as it did not meet level I criteria. The 2 level I studies by Coban et al[79] (unilateral pallidotomy vs unilateral subthalamotomy) and Merello et al[80] (bilateral STN DBS vs bilateral subthalamotomy vs unilateral subthalamotomy plus contralateral STN DBS) were not included in our review because of their small sample sizes (10 and 16 patients in total, respectively).

Safety for Surgery—no change in conclusions.

No new safety issues were identified for thalamotomy, pallidotomy, or thalamic DBS; these have previously been covered in the earlier EBM reviews. Weaver et al[75] reported that 40% of patients undergoing bilateral GPi or STN DBS experienced at least 1 serious AE (significantly higher than the 11% rate in the medically treated group). These were most commonly surgical-site infections. There were also significantly more falls in the DBS group. In this study, patients undergoing bilateral DBS also demonstrated small decrements in working memory, processing speed, phonemic fluency, and delayed recall. When Follett et al[69] compared the GPi and STN groups, no significant differences in either overall or serious AEs were found. Both groups had similarly slight decrements in all measures of neurocognitive function that were not significantly different between the 2 groups, except for processing speed index, which declined more after STN DBS. Witt et al[81] reported that bilateral STN DBS in a highly selected group of patients did not reduce global cognitive functioning, although there was a selective decrease in frontal cognitive functions and verbal fluency, but these cognitive changes had no effect on quality of life. Similarly, Williams et al[74] found that patients undergoing bilateral STN DBS showed a decline in verbal fluency and vocabulary compared with a medical therapy control group.

There were more serious AEs in the surgery group, and these were mainly related to surgery; 20% of patients in this group had serious surgery-related AEs (most commonly infections). Since the 2004 EBM report, multiple studies have also reported on a broader range of AEs that can be seen after STN DBS, both motor and nonmotor.[82] Many of these can occur despite significant improvement in overall motor function, including dysarthrophonia,[83] impairment of cognitive-motor performance,[84] emotional lability,[70] impulsive-compulsive behaviors,[85] suicide,[86] apathy,[87] social maladjustment,[73] and weight gain.[88,89] It should be noted, however, that the apparently higher incidence of side effects with STN DBS (compared with, for example, GPi DBS) may be a result—at least in part—of the greater number of STN cases being performed. Psychiatric complications such as mania[90] and hypersexuality[91] have also been reported to occur after GPi DBS for PD. A final important AE in fetal transplant studies has been the emergence of dyskinesia, even when patients do not take dopaminergic drugs (runaway dyskinesia), although case reports suggest that DBS may actually treat this surgical complication.[92]

Surgical Treatment Practice Implications and Summary

Prior conclusions regarding bilateral STN DBS, bilateral GPi DBS, unilateral pallidotomy, unilateral thalamotomy, and thalamic DBS (unilateral or bilateral) have been modified in this review (see Table 7). Although there is usually a concomitant reduction in dopaminergic medication dose that may result in reduction of dyskinesia, bilateral STN DBS is considered efficacious and *clinically useful for the treatment of motor fluctuations and dyskinesia*. Bilateral GPi DBS is considered efficacious and *clinically useful for the symptomatic control of PD* as an adjunct to levodopa and efficacious and *clinically useful for the control of motor complications* (both motor fluctuations and dyskinesia). Pallidotomy is efficacious and *clinically useful* in the treatment of motor fluctuations and dyskinesia. Thalamotomy and thalamic DBS are likely efficacious as symptomatic adjuncts to levodopa therapy, and the practice implications are changed to *possibly useful*. No qualified studies of surgical treatments were identified for other indications. Conclusions for all other procedures, including subthalamotomy and human fetal cell transplantation, remain unchanged. Safety conclusions remain unchanged as acceptable risk with specialized monitoring.

Nonpharmacological Therapies

Nonpharmacological therapies, including physical, occupational, and speech therapy were last reviewed in the EBM review in 2002.[3] These interventions were not included in the 2005 review and are now updated. Studies using acupuncture were also reviewed.

Physical Exercise Therapy (14 new studies[93–106])—new conclusions: likely efficacious as treatment of motor symptoms—adjunct to levodopa.

A wide variety of physical therapy treatments are used in PD patients. This review includes RCTs using these various techniques as adjuncts to levodopa. For this section, studies are grouped into 3 classes of interventions: physiotherapy, movement strategy training with cuing devices or focused attention, and formalized patterned exercises.

Control of Motor Symptoms—Adjunct to Levodopa: Physiotherapy. This intervention includes stretching, walking, and use of conventional exercise machinery with guidance from expert physiotherapists. Seven studies were identified involving a mixture of general physiotherapy (PT) techniques and treadmill training, and 1 study was multidisciplinary using PT, occupational therapy, and speech therapy.[95]

Ellis et al (2005)[93] performed a single-blind, crossover, RCT in 68 PD patients with at least H&Y stages II or III. All subjects were on stable medication, but no information on type and dose was provided. Patients were randomized to either 6 weeks of group PT in twelve 90-minute sessions that included strengthening, gait, treadmill, and relaxation or to the usual medical therapy. Each assignment was followed by crossover to the other treatment with no washout period for 6 weeks. Patients were assessed at the end of each treatment and further assessed 6 and 24 weeks later when no specific interventions were dictated. The primary end points included change in UPDRS-III, Sickness Impact Profile (SIP-68, including the mobility portion), and timed comfortable walking speed (CWS) after 6, 12, and 24 weeks. Blinding of these assessments was not stated. There was improvement in UPDRS-III of −3.5 (8.6) points and −1.5 (6.7) points in the 2 groups at 24 weeks but no significant difference in effect between groups or over time on the UPDRS-III. There was a significant difference in effect between groups and over time in SIP-mobility scores and CWS, although this was only over 6 weeks and possibly lost after 24 weeks. The 2 study site patients differed in some baseline features, UPDRS-III, CWS, and SIP motor and subgroup analysis by site was not performed. ***Quality score, 50%***.

Ashburn et al (2007)[94] performed a single blind RCT of a home-based personalized exercise program in 142 PD patients independently living at home and having had 1 fall in the prior year. Home PT consisted of 6 once-weekly exercise sessions for improving strength and balance and preventing falls. In addition, subjects were expected to perform exercises at home,

and monthly telephone contact encouraged compliance. The control PD groups received the usual care, which included visits from a PD nurse. Patients were followed up for 6 months, but no further details were given. The primary outcome measures were changes in self-reported number of falls/near-falls using a diary at 8 weeks and 6 months. There was no significant difference in percentage of falls or injuries sustained because of falling between the 2 groups (at 6 months, unadjusted exercise vs control difference, −5% [−20% to 10%; $P > .05$]). In comparing 6-month unadjusted exercise versus control differences, the exercise group showed a significant reduction in near-falls of −11% (−24.1%) and repeated near-falling of −21% (−35% to −6%). Objective outcome measures included a functional reach test that was significantly better in the exercise group compared with control at 6 months; other timed test differences were not significant. Although an equal number of patients in both groups were receiving usual PD-related rehabilitation external to the trial (24% exercise group vs 22% control), this proportion increased over the study period in the control group and was 34% at 6 months. ***Quality score, 55%***.

Cakit et al (2007)[95] performed a single-blind study in 54 advanced-PD patients who were at least H&Y stage 3. The baseline characteristics of the 2 groups were not well defined. Patients were randomized to a training group, in which they received supervised stretching and treadmill training (3 times/week for 40 minutes for 8 weeks), or to a control group. No details were given regarding the latter group's activity level. There was a high dropout rate from the control group (>50%), mostly because of loss to follow-up, changes in medications, and superimposed medical issues. The outcome measures were change at 8 weeks in timed tests on the treadmill, the Berg Balance Test, the Dynamic Gait test, and the Falls efficiency scale. There was a significant improvement in all measures in the training group (all $P < .01$) but not in the control group. Although changes in UPDRS scores were stated as an outcome measure, no such results were reported or compared between the training and control groups. Two patients developed ventricular extrasystoles on ECG monitoring but this did not require withdrawal. ***Quality score, 43%***.

Kurtais et al (2008)[96] investigated the effects of treadmill training in 30 PD patients over 7 weeks. Patients were randomized to an exercise group and received supervised gait training (a treadmill 3 times weekly for 40 minutes over a 6-week period) or to a nonintervention control group. Both groups were taught exercises for flexibility and movement, although this was not detailed further. The baseline and changes in PD medications throughout the study were not reported. The primary outcome measures were change in functional lower limb tests (eg, walking time, standing on 1 limb); all these improved in both groups, but the changes were only statistically significant for the exercise group. Ergospirometric exercise testing was also significantly improved in the treadmill group but not the control group. No other outcomes measures were used, so relevance to overall motor effects in PD is unclear. ***Quality score, 34%***.

Tickle-Degnen et al (2010)[97] performed an RCT of self-managed rehabilitation for 6 weeks. Three groups were studied: a high-intensity group receiving 27 total hours of rehabilitation (4.5 hours weekly; n = 39), a midintensity group receiving 18 hours of rehabilitation (3 hours weekly; n = 37), and a control group receiving 27 hours of best medical therapy and no rehabilitation (n = 41). The intervention consisted of a self-guided mixture of individual and group sessions of physical, occupational, and speech therapy with a mixture of exercise, speech therapy, daily functioning examples, gait training, and group discussion covering multiple coping strategies. The control group receiving BMT received no active rehabilitation intervention. Although evaluators not conducting the therapy sessions performed outcome measures, unblinding occurred for 14% of participants. The primary outcome was change in the PDQ-39 at 2 and 6 months. This study was included despite quality-of-life rating being the primary outcome measure, as subscores in the PDQ-39 measured motor outcome, and a large number of subjects were enrolled. There was an overall beneficial effect of rehabilitation, both in the high-intensity ($P = .03$) and in the midintensity ($P = .02$) groups compared with the control group at the end of 6 weeks, and both improvements were maintained at the 6-month follow-up. The adjusted mean PDQ-39 mobility subscore controlling for baseline in the ITT analysis was significant at the 6-month follow-up in the 27-hour group compared with the 0-hour group (mean score, 29.7 [1.9], compared with 36 [1.9]; $P = .03$). ***Quality score, 72%***.

A secondary outcome from the above study, walking activity calculated as a percentage of time spent walking using an activity monitor and a distance covered in a 2-minute walking test, was reported in a separate article.[107] There was no significant difference in the 3 groups for any of the outcomes, although subgroup analysis suggested improved 2-minute walking test scores following rehabilitation in those subjects with a lower baseline walking endurance score. The clinical importance of the outcomes measured with an activity monitor and the 2-minute walking test is unclear. The effect of PD medications was not included in the analysis. There was a large loss of data because of malfunction of the activity monitor with 74 complete sets of data. ***Quality score, 48%***.

Ebersbach et al (2010)[98] assessed a physical therapy program termed "BIG" with 2 active intervention groups in 60 moderate-PD patients. Subjects were

randomized equally into 3 groups of active intervention that differed in the amount of training and numbers of individuals involved in training sessions; group 1 (n = 20, ''BIG'') received individual training in the BIG technique, which emphasizes large-amplitude movements over 4 weeks (16 sessions); the second group (n = 20, ''WALK'') received instructions in Nordic walking (16 sessions over 8 weeks) in subgroups of 4–6 people; and the third group (n = 20, ''HOME'') received 1 hour of training in home exercises. All groups were encouraged to exercise at home. There were small adjustments in medications (documented as changed in levodopa-dose equivalents) in each group, but these were not significantly different between the groups. The primary outcome was change from baseline UPDRS-III between the groups after 16 weeks, as determined by blinded video rating. There was a significant improvement of −5.05 (3.91) points in the BIG group compared with +0.58 points (3.17 points) in the WALK group and +1.68 points (5.95 points) in the HOME group (ANCOVA, $P < .001$). Secondary outcomes were objective timed tests; the BIG group was superior to the WALK and HOME groups in mean timed-up-and-go (by −0.75 seconds; $P < .03$). ***Quality score, 71%***.

Allen et al (2010)[105] performed an RCT with blinded assessment to determine the effect of a 6-month minimally supervised exercise program (targeting leg muscle strength, standing balance, and gait freezing) on fall risk factors. Forty-eight participants with PD who had fallen or were at risk of falling were randomized into exercise or control groups. The exercise group attended a monthly exercise class and exercised at home 3 times weekly. The primary outcome measure was a PD falls risk score. The exercise group showed greater improvement than the control group in the falls risk score, which was not statistically significant (between-group mean difference of −7%; 95% CI, −20% to 5%; $P = .26$). There were statistically significant improvements in the exercise group compared with the control group for 2 secondary outcomes: the Freezing of Gait Questionnaire ($P = .03$) and sit-to-stand time ($P = .03$). ***Quality score, 70%***.

Yang et al (2010)[106] assessed the effect of ''downhill'' walking in 33 PD subjects at H&Y stages 1–3 and able to walk independently. Subjects (n = 16) were randomized to receive 4 weeks of ''downhill-walking'' training on a treadmill with the gradient initially set at −3.0% and then increased to a mean of −8.53% (1.92%) for 30-minute sessions, 3 times a week. A second group received conventional therapy (n = 17) consisting of 30-minute sessions, 3 times a week for 4 weeks, of balance training, flat surface walking, flexibility, and strengthening exercises. The primary outcomes were objective measurements performed in the *on*-drug state of gait, including walking speed, cadence, and stride length as well as muscle strength using a dynameter and degree of postural abnormality using a goniometer at baseline, immediately after the 4 weeks training and following an additional 4 weeks without training. Downhill walking improved walking speed ($P = .033$), stride length ($P = .05$), and knee extensor strength ($P = .047$) all compared with conventional therapy at 4 weeks, but this benefit was lost after an additional 4 weeks. Power analysis calculated a required sample size of 64 subjects; however, this was not reached. No PD-related rating scales were used, and thus the effect of this intervention on overall motor functioning including gait, balance, and falls is unclear. ***Quality score, 61%***.

Movement Strategy Training with Cuing or Focused Attention

Three studies investigated cued training for PD patients with freezing and falls.

Nieuwboer et al (2007)[99] performed a single-blind crossover multicenter 12-week study in 153 PD patients with gait disturbance of at least 1 on UPDRS item 29 and in H&Y stages 2–4 (RESCUE trial). The mean number of patients with at least 1 fall was 40%. Patients were randomized to either an early- or late-intervention group. The early-intervention group underwent nine 30-minute sessions of a cueing program lasting 3 weeks; this was followed by 3 weeks of no training and a follow-up of 6 weeks. The late intervention group received no training for the first 3 weeks, then cueing sessions, as described above, for 3 weeks, followed by the 6-week follow-up. There was no washout period. During the first week of intervention, the staff provided individualized exposure to specifically developed devices: an auditory beep signal apparatus, diodes placed on the patients' glasses to emit light flashing cues, and pulsed vibrations from a wristband for somatosensory cues. During the first week of training all patients tried all these devices, and cued practice was used in different tasks and environmental situations and included gait initiation, heel strike and push off, stepping, and walking on various surfaces. At the end of the first week of training, patients chose their preferred method: 67% chose auditory, 0% selected visual, and 33% chose somatosensory cuing. The primary outcome measure was a change in the UPDRS composite posture and gait subscore (items 13–15 and 29–30) without the use of the cueing device during the assessments. Secondary measures were timed walking tests, the Freezing of Gait Questionnaire, and a falls diary. Assessments were carried out before randomizations and after 3, 6, and 12 weeks. The posture and gait subscore (maximum score, 20) improved by 4.2% after intervention ($P = .005$). Gait speed improved by 5 cm/second ($P = .005$), and step length improved by 4 cm ($P < .001$). Freezing of Gait Questionnaire scores did not improve

($P = .25$); however, subgroup analysis on PD patients with at least a weekly freezing episode showed a significant reduction of 5.5% of freezing severity ($P = .007$). PDQ36 and Care Strain Index were not changed. All parameters were worse 6 weeks after training completion. The improvement in outcome measures is significant, but very small, and clinical relevance is not clear. ***Quality score, 59%***.

Morris et al (2009)[100] conducted a single-blind study in 33 PD inpatients at H&Y stages 2–3. Patients were randomized to either 16 sessions of up to 45 minutes over 2 weeks of movement strategy training using external cues, including attention strategies, functional mobility, and aerobic training or an exercise training group consisting of relaxation, musculoskeletal exercises, and aerobic training. Both groups received these interventions as part of an inpatient program and were followed 3 months later as outpatients. During the posthospital phase the outcome measures were change in UPDRS-II and -III after 2 weeks and retention of training 3 months after discharge. Movement strategy training significantly improved UPDRS-II and -III after admission compared with exercise training (mean difference, 4 ± 4.7 vs 1.9 ± 5.7; $P < .05$). Other outcome measures, including timed tests and the balance pull test, were also significantly improved in the cuing movement group but not in the exercise group, although the improvements were not fully maintained at the 3-month follow-up. ***Quality score, 45%***.

Sage and Almeida (2009)[101] performed an RCT in 53 PD subjects to evaluate the efficacy of specific sensory attention-focused exercises (PD-SAFEx group) involving walking, stretching, and positioning that enhance body awareness (n = 18) compared with lower limb exercise using a semirecumbent elliptical machine (aerobic group; n = 13) and nonexercise/maintenance of normal exercise (control group; n = 15). No information was given on antiparkinsonian drugs or the presence of motor fluctuations. There were differences in some baseline measurements between groups; the aerobic group had worse step length and velocity of gait, as assessed by objective gait analysis, compared with the other 2 groups. Participants in each intervention group undertook 3 sessions/week for 10–12 weeks, although no information was provided on the amount of exercise performed by the control group. The primary outcome measure was change in *on*-drug UPDRS-III; secondary outcome measures were posture and gait subscores and timed walk tests. In the PD-SAFEx group, there was a significant improvement in UPDRS-III compared with baseline: -5.6 points ($P < .001$) versus -1.8 points ($P = .016$) and $+1.2$ points ($P = .37$) for the aerobic and control groups, respectively. There was also nonsignificant improvement in the posture and gait subscores with PD-SAFEx compared with the controls. There was no effect on timed tests. ***Quality score, 57%***.

Formalized Patterned Exercises Including Tai Chi and Qigong

Burini et al (2006)[102] performed a single-blind crossover study over 6 months in 26 PD patients at H&Y stages 2 or 3. No patients with motor fluctuations were included. Patients were randomized to 7 weeks of treatment consisting of 20 group Qigong sessions or 20 group aerobic cycling exercise sessions, followed by 8 weeks of washout and then crossover to the other treatment for an additional 7 weeks. Twenty subjects attended all sessions. There was no information on antiparkinsonian drugs or changes in drugs during the study. Two patients withdrew because of injury: 1 due to a fall and hip fracture after the Qigong session and the second as a result of back pain after aerobic exercise. There were no further details on other dropouts during the program. The primary outcome measures were UPDRS-II and -III, and there was no significant effect of Qigong exercise or aerobic exercise on the scores. Secondary measures involving timed tests, and cardiopulmonary tests were significantly better with aerobic exercise but not Qigong. ***Quality score, 48%***.

Schmitz-Hubsch et al (2006)[103] performed a 6-month study comparing Qigong with no intervention in 56 PD patients. Subjects could be at any disease stage—11 of 32 in the Qigong group and 9 of 24 in the nonintervention group had motor complications. Patients were randomized to weekly group Qigong sessions lasting 60 or 90 minutes for two 2-month periods, with a 2-month pause in-between. All Qigong patients continued other pharmacological and nonpharmacological (massage, physiotherapy) therapies throughout the study. Nonpharmacological therapies were reported by 50% of participants in both groups at baseline and at 1-year follow-up; no subgroup analysis was performed on the groups with additional therapies concurrent with the Qigong. The primary outcome measure was between-group difference in the number of responders (>20% improvement in UPDRS-III compared with baseline). Follow-up took place at 3 months (after the completion of the first 2-month course), at 6 months, and at 1 year. Assessments were carried out by unblinded raters. ITT analysis was used in the intervention group only; 19 of 24 in the control group were analyzed. There was a significantly greater number of patients with improved UPDRS-III in the Qigong group at 3 months (52%) versus the control (14%) but not at 6 months (35% in the Qigong group vs 10% in the control group) or at 12 months. One major confounder is that 40% of the Qigong group and 26% of the control group had increased doses of antiparkinsonian medications. ***Quality score, 55%***.

Hackney et al (2008)[104] performed a single-blind study comparing tai chi (20 one-hour sessions) over 13 weeks compared with no intervention in 33 PD patients at H&Y stages 1.5–3. Important baseline

TABLE 8. Conclusions on nonpharmacological treatments

Therapy		Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Physical therapy	Efficacy	Insufficient evidence	Insufficient evidence	*Likely efficacious*	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	*Possibly useful*	Investigational (F, D)	Investigational (F, D)
Speech therapy	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient (F, D) data	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	*Possibly useful*	Investigational (F, D)	Investigational (F, D)
Occupational therapy	Efficacy	Insufficient evidence	Insufficient evidence	insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	Possibly useful	Investigational (F, D)	Investigational (F, D)
Acupuncture	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

characteristics of the 2 groups were not compared, including the number of patients with motor fluctuations or the total daily levodopa equivalence. Outcome measures included the Berg Balance Scale, UPDRS-III scores rated by a blinded rater using videotaped recordings, timed testing, and kinematic testing. There was a significant mean improvement of UPDRS-III of -1.5 ± 6.6 points in the tai chi group (n = 13) compared with a mean worsening of $+4.3 \pm 5.6$ points in the control group (n = 13); $P < .05$. There were small, significant improvements in other measures in the tai chi group but not in the control group. The Berg Balance Scale improved by 0.1% ($P < .001$) and the 6 minute walk by 0.2% ($P = .046$); kinematic testing was not significant. The clinical relevance of these changes is unclear. ***Quality score, 45%***.

Efficacy conclusions: The quality scores for most of these studies is not high, and the outcome measures as well as the physical therapy–specific interventions vary widely. Despite these limitations, the evidence is sufficiently robust and consistent to conclude that physical therapy, considered globally as a therapeutic intervention, is *likely efficacious*. From the description of the studies, it is most likely that most subjects were on levodopa, so the report categorizes the designation under ''adjunct to levodopa,'' but admittedly, the reports did not consistently specify medications. Other conclusions for physical therapy, brought forward from the prior report, are listed in Table 8.

Occupational Therapy (1 new study[97])—no change in conclusions.

One new study was identified and is described above.[97] In this study by Tickle-Degnen et al, subjects in the intervention group received a mixture of physical, occupational, and speech therapy. However, the separate effects of occupational therapy from physical therapy on outcome measures was not reported. Thus, no conclusions can be drawn in terms of efficacy. Other conclusions for occupational therapy, brought forward from the prior report, are listed in Table 8.

Speech Therapy (2 studies[108,109])—no new conclusions.

Ramig et al (2001)[108] evaluated the effects of the Lee Silverman Voice Treatment (LSVT) form of speech therapy over 4 weeks. Three groups were included: PD subjects (n = 14) who received speech therapy; PD subjects (n = 15) who had no speech therapy; and age-, sex-matched normal, non-PD controls (n = 14) who had no speech therapy. No information was given on baseline characteristics of PD subjects, including disease severity or medications, and the method of randomization of the PD subjects into the treatment and nontreatment groups is not clear. The enrolled PD subjects in the speech therapy group underwent 4 weekly sessions of speech therapy using the LSVT, which places a focus on speech volume. The outcome measures included sound pressure level (dB) of voice recorded during talking and vocalization tasks, at baseline, immediately posttreatment, and at the 6-month follow-up. There was a significant improvement in sound pressure levels in all tasks posttreatment and at the 6-month follow-up in the PD LSVT speech therapy group compared with baseline (all $P < .01$). The LSVT speech therapy group also improved in all tasks compared with the nontreatment PD group ($P < .001$) and in some tasks (sustained

note and reading a passage [$P < .005$] but not monologue and picture description) compared with normal controls. At 6 months, these improvements were maintained The number of subjects analyzed and the blinding of investigators performing analysis of the intervention group are not stated. ***Quality score, 45%***.

Ramig et al (2001)[109] evaluated 2 speech therapy techniques in 33 PD subjects. Subjects were randomized to LSVT therapy (n = 21) or another form of speech therapy using high respiratory rate, termed respiratory effort treatment (RET; n = 12). There was no significant difference in baseline age, sex, disease duration, or UPDRS scores (mean baseline, 27.7 ± 12 in LSVT group; 12.9 ± 12.4 in RET group). There were subjects lost to follow-up, and variable numbers were included in each end point; not all patients were accounted for after randomization. Treatment consisted of four 1-hour sessions/week for 4 weeks. Subjects were evaluated pretherapy, within 1 week of completing speech therapy, and 6, 12, and 24 months later at the same time on all assessments relative to their medication doses. The primary outcome measures were voice level (sound pressure level) and voice inflection (semitone standard deviation) recorded during sustained-note, talking, and vocalization tasks and UPDRS-III scores. The LSVT significantly improved both voice level and inflection during all 3 tasks (sustained note, talking, and vocalization) at 24 months compared with pretreatment and with RET therapy. Compared with baseline, the RET group failed to significantly improve voice level or inflection for all measures except a reading-aloud task. There were no significant differences in UPDRS scores between the 2 groups, either at baseline or over the 24 months of treatment. Although some clinical variables were reported, others pertinent to speech were not, such as the presence of motor fluctuations and total daily levodopa doses; these limit interpretation of the results. ***Quality score, 51.5%***.

Efficacy conclusions: There is no change to the prior EBM conclusions that for symptomatic therapy adjunct to levodopa, there is *insufficient evidence* for speech therapy. Other conclusions for speech therapy, brought forward from the prior report, are listed in Table 8.

Acupuncture (1 study[110])—new conclusions: insufficient evidence as symptomatic adjunct to levodopa; and all other indications.

Huang et al (2009)[110] conducted a study to evaluate the clinical efficacy of linear scalp-acupuncture (hereafter referred to as "acupuncture") and that of a herbal formula (comprising many different herbs). One hundred and fifty PD patients were randomized into 4 groups in a 2 × 2 design: 88 patients were treated by a combination of acupuncture (3 cycles of 10 treatments per cycle) and herbs; 20 patients were treated by acupuncture only; 20 patients were treated by herbs only; and 22 patients were continued on their usual dopaminergic medications. Treatments were administered over 3 months. The response rate (defined as ≥30% improvement on the modified Webster score) was 89.8% in the group receiving acupuncture and herbal therapy and 86.4% in the group receiving neither but only continuing their standard medications ($P > .05$). Similarly, there was no difference in response rate between the group receiving acupuncture only and the group receiving their standard medications (80.3% vs 86.4%; $P > .05$). ***Quality score, 41%***.

Efficacy conclusions: There is *insufficient evidence* to conclude on the role of acupuncture as an adjunct therapy to levodopa.

Nonpharmacological Therapy Practice Implications and Summary

Physical Therapy. The 2002 EBM review[3] concluded that there was insufficient evidence for exercise/physical therapy as symptomatic adjunct therapy to levodopa and a need for further studies was indicated. These new studies now enable the conclusion to be changed to *likely efficacious*, and the practice implication is that physical therapy is *possibly useful as symptomatic adjunct therapy*. Trial design in exercise therapy still limits quality scores. Several problems are inherent in the intervention itself, although many investigators have tried to overcome these. For example, it is not always clear whether patients have problems with freezing or falls on starting the study or whether it is only the "good" patients who are being recruited to these studies. Many studies do not document compliance with the therapy, that is, how many sessions' subjects attend the proposed schedule. Blinding is usually single blind, as patients have to know their intervention, which may lead to bias in some motor performance tests. Control groups are generally treated differently than active groups and in some cases may not receive any intervention, which in itself may be less motivating to the patient. Antiparkinsonian drug treatments are rarely taken into account as potential confounders, and studies often do not document the drugs patients are taking at the time of assessments or the presence of motor fluctuations and dyskinesia. Several publications have recently reviewed the challenges of assessing physical therapy as an intervention in PD.[111,112] All studies to date have been for symptomatic adjunctive therapy in PD patients who are at least H&Y stage 1.5. Preclinical evidence has suggested that exercise may enhance dopaminergic function,[113] thus investigating exercise for disease progression may be a future area of study. There are no changes in safety conclusions.

Occupational Therapy. In the 2002 EBM review,[3] occupational therapy was included in the overall section of physical therapies, and conclusions were for both. Again, no level I studies assessing occupational therapy alone in PD were reported. However, 1 study did include occupational therapy as a component of the intervention, but because of the lack of subscore analysis, the efficacy conclusion cannot change from *insufficient evidence* for a symptomatic adjunct to levodopa. Despite a lack of level I evidence, there is no change in practice implications as *possibly useful*. There are no changes in safety conclusions.

Speech therapy was last reviewed in the 2002 EBM review.[3] The studies available with evidence for evaluation are largely restricted to LSVT. The current conclusion is that there is insufficient evidence for LSVT because of issues with study design (see below) However, the practice implication remains that LSVT speech therapy is *possibly useful as a symptomatic adjunct to levodopa*. There was not sufficient evidence to make any conclusions on other forms of speech therapy at the time of this report. As noted above, studies of nonpharmacological interventions are inherently penalized in EBM scoring systems. An additional factor affecting inclusion of studies evaluating speech therapy studies is the low numbers of subjects; thus fewer than 20 subjects are frequently recruited, and as such these studies do not meet our inclusion criteria. However, for such interventions, these small numbers of participants still reflect adequate power calculations and valid statistical outcomes. Reviews of speech therapy in PD.[114–116] all indicated the need for more level I studies in speech therapy.

Acupuncture has not been reviewed previously. Apart from the study by Huang et al,[110] several other randomized clinical trials of acupuncture in PD have been published (some of which were negative for efficacy outcomes), but these did not meet the inclusion criteria for our review, mainly because of non-English-language publication. A recent systematic review of these studies by Lee et al[117] concluded that the quality of trials was too low to draw any firm conclusions. Thus, the practice implication for acupuncture is *investigational as symptomatic adjunct therapy* in the treatment of PD. As there is insufficient evidence, the practice implication is that acupuncture is also *investigational for all other indications*. The safety conclusion is *acceptable risk without specialized monitoring*.

Discussion

This updated evidence-based review includes RCTs from 2001 for physical, occupational, and speech therapy and from 2004 for pharmacological and surgical interventions for the treatment of the motor symptoms in PD. The large number of studies indicates a continually changing field and the need for ongoing updates. Conclusions for several interventions have been changed, whereas other new studies resulted in no changes to the prior conclusions.

Overall conclusions according to disease indications are summarized here.

- *Prevention/delay of clinical progression:* pergolide is *unlikely efficacious*; and there is insufficient evidence for any other treatment.
- *Control of motor symptoms—monotherapy*: piribedil, pramipexole, pramipexole PR, ropinirole, rotigotine, cabergoline, dihyrdoergocryptine, pergolide, standard and controlled-released (CR) formulations of levodopa, selegiline, and rasagiline are all *efficacious*. Ropinirole PR, bromocriptine, lisuride, anticholinergics, and amantadine are *likely efficacious*. There is *insufficient evidence* for rapid-onset oral formulations, infusion formulations of levodopa, or orally disintegrating selegiline. All other therapies reviewed likewise have *insufficient evidence* to judge efficacy.
- *Control of motor symptoms as an adjunct to levodopa:* the dopamine agonists piribedil, pramipexole, ropinirole, ropinirole PR, rotigotine, apomorphine, bromocriptine, cabergoline, and pergolide are all *efficacious*. Tolcapone, rasagiline, zonisamide, bilateral STN stimulation, bilateral GPi stimulation, and unilateral pallidotomy also are all *efficacious*. Entacapone is *efficacious* in treating motor symptoms in PD subjects with motor fluctuations but nonefficacious in PD subjects without motor fluctuations. Lisuride, anticholinergics, amantadine, unilateral thalamotomy, thalamic DBS, and physical therapy are *likely efficacious*. There is *insufficient evidence* to judge the remaining treatments.
- *Prevention/delay of motor complications:* pramipexole and cabergoline are *efficacious* for the prevention of both motor fluctuations and dyskinesia. For preventing/delaying dyskinesia, ropinirole and ropinirole ER are *efficacious*, and bromocriptine and pergolide are *likely efficacious*, with *insufficient evidence* for the ability to prevent/delay motor fluctuations. There is *insufficient evidence* for the prevention/delay of any motor complication with piribedil, pramipexole ER, rotigotine, apomorphine, dihydroergocrypitne, or lisuride. Entacapone and levodopa CR are *nonefficacious* in the prevention of both motor complications. Selegiline is *nonefficacious* for the prevention/delay of dyskinesia, *with insufficient evidence* for motor fluctuations. There is *insufficient evidence* for tolcapone or rasagiline in the prevention/delay of motor complications.
- *Treatment of motor complications: for treatment of motor fluctuations,* pramipexole, ropinirole,

ropinirole ER, rotigotine, apomorphine, pergolide, standard oral levodopa, entacapone, tolcapone, rasagiline, bilateral STN DBS, bilateral GPi DBS, and unilateral pallidotomy are all *efficacious*. Bromocriptine, cabergoline, and infusion formulations of levodopa are *likely efficacious*. There is *insufficient evidence* for all other interventions including piribedil, pramipexole ER, dihydroergocrytpine, lisuride, rapid-onset oral levodopa, CR levodopa, selegiline, oral disintegrating selegiline, or zonisamide. For the *treatment of dyskinesia*, clozapine, amantadine, bilateral STN DBS, bilateral GPi DBS, and unilateral pallidotomy are all efficacious, and infusion of levodopa is *likely efficacious*; there is *insufficient evidence* for other therapies.

EBM reviews are only as good as the "evidence" available, that is, the quality of published clinical trials. For several indications reviewed above, further RCTs are required. Thus, the evidence for the effectiveness of therapies to delay/prevent clinical progression is inherently penalized, as long-term studies are difficult to conduct because of the cost and practicalities of running an RCT over several years; subject attrition resulting in smaller numbers of subjects and open-label levodopa/other PD therapies added over time bias results. These difficulties are in addition to issues concerning the interpretation of results in which therapies may have both "disease-modifying" and "symptomatic" benefits and current difficulties in methods of effectively measuring the 2 separately. Thus, pragmatic, well-conducted shorter-term studies with more specific and sensitive outcome measures (biomarkers) are required to determine conclusions on the efficacy for this indication. Similarly, issues inherent in the design of studies using physical therapy, speech, and occupational therapies to date have biased the ability to make conclusions. Thus, the lack of "active" interventions in control groups, small numbers recruited, and lack of information in publications regarding clinical features and medications used by patients all penalize these potentially useful interventions. We strongly encourage well-designed studies in these areas.

The Cochrane library also provides EBM reviews of treatments for PD. The Cochrane process, in addition, includes a meta-analysis of RCT outcomes to provide a measure of the comparative effectiveness of interventions that is not possible in a single RCT. Recent updates of the Cochrane reviews are in agreement with our review and have reported that adjuvant therapies with dopamine agonists, MAO-B inhibitors, and COMT inhibitors are all effective in the treatment of motor fluctuations, with dopamine agonists being more efficacious in reducing *off* time (dopamine agonists, −1.54 hours/day; COMT inhibitors, −0.83 hours/day; MAO-B inhibitors, −0.93 hours/day; test for heterogeneity between drug classes, $P = .0003$).[118] Another recent review of the use of dopamine agonists in early PD reported efficacy in the prevention of motor complications; thus, PD subjects treated with dopamine agonists are less likely to develop dyskinesia (OR, 0.51; 95% CI, 0.43–0.59; $P < .00001$) or motor fluctuations (OR, 0.75; 95% CI, 0.63–0.90; $P = .002$) than levodopa-treated participants.[119] There was no difference in outcome between different types of dopamine agonists.

Evidence-based conclusions are only one 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 and patient preferences, as well as economic influences, which all weigh in to the final preferred treatment choices. In certain countries, the concept of comparative effectiveness research,[120] which is the study of the relative costs of different treatments for the same disease or condition, is being embraced by both governments and researchers and will hopefully enhance EBM recommendations and improve the overall quality and cost effectiveness of daily health care.

EBM reports offer investigators a clear view of areas remaining to be studied. In domains of unmet need, the prior studies can be used as 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 scores, regardless of study outcome. As such, the authors and the MDS hope that this document will serve to encourage creative study designs always anchored to the key elements and criteria for high evidence-based 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 more regular updating of the official reports and a program to load new published trials that will be reviewed for the next critique on the MDS Web site so that investigators and clinicians can keep abreast of new developments. ■

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