Movement Disorders
Vol. 20, No. 5, 2005, pp. 523–539

Research Review

Evidence-Based Medical Review Update: Pharmacological and Surgical Treatments of Parkinson's Disease: 2001 to 2004

Christopher G. Goetz, MD,[1]* Werner Poewe, MD,[2] Olivier Rascol, MD, PhD,[3] and Cristina Sampaio, MD, PhD[4]

[1]*Department of Neurological Sciences, Department of Pharmacology, Rush University Medical Center, Chicago, Illinois, USA*
[2]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*
[3]*Department of Pharmacology, Clinical Investigation Center, Toulouse University Hospital, Toulouse, France*
[4]*Department of Clinical Pharmacology and Therapeutics, Faculdade de Medicina de Lisboa, Lisbon, Portugal*

Abstract: The objective of this study is to update a previous evidence-based medicine (EBM) review on Parkinson's disease (PD) treatments, adding January 2001 to January 2004 information. The *Movement* Disorder Society (MDS) Task Force prepared an EBM review of PD treatments covering data up to January 2001. The authors reviewed Level I (randomized clinical trials) reports of pharmacological and surgical interventions for PD, published as full articles in English (January 2001–January 2004). Inclusion criteria and ranking followed the original program and adhered to EBM methodology. For Efficacy Conclusions, treatments were designated *Efficacious*, *Likely Efficacious*, *Non-Efficacious*, or *Insufficient Data*. Four clinical indications were considered for each intervention: prevention of disease progression; treatment of Parkinsonism, as monotherapy and as adjuncts to levodopa where indicated; prevention of motor complications; treatment of motor complications. Twenty-seven new studies qualified for efficacy review, and others covered new safety issues. Apomorphine, piribedil, unilateral pallidotomy, and subthalamic nucleus stimulation moved upward in efficacy ratings. Rasagiline, was newly rated as *Efficacious* monotherapy for control of Parkinsonism. New Level I data moved human fetal nigral transplants, as performed to date, from *Insufficient Data to Non-efficacious* for the treatment of Parkinsonism, motor fluctuations, and dyskinesias. Selegiline was reassigned as *Non-efficacious* for the prevention of dyskinesias. Other designations did not change. In a field as active in clinical trials as PD, frequent updating of therapy-based reviews is essential. We consider a 3-year period a reasonable time frame for published updates and are working to establish a Web-based mechanism to update the report in an ongoing manner. © 2005 Movement Disorder Society

Key words: Parkinson's disease; evidence-based medicine; levodopa; dopamine agonists; monoamine oxidase inhibitors; COMT inhibitors; amantadine; anticholinergics; neurosurgery; deep brain stimulation; neurotransplantation

Evidence-based medicine (EBM) offers a strategy for the critical evaluation and uniform comparison of clinical trial data.[1] This method is anchored in predetermined criteria for inclusion of trials for analysis and a ranking of treatments based both on the trial designs and the demonstrated treatment effects. EBM reviews provide information that can be used along side expert opinion and the clinician's own personal experience to arrive at a clinical decision to fit a patient's individual profile and expectations. In 2002, *Movement* Disorders published a detailed EBM analysis of pharmacological, surgical, and psychosocial interventions in the treatment of Parkinson's disease (PD), including nonmotor elements of PD such as depression, psychosis, and dysautonomia.[2] Since that publication, the *Movement* Disorder Society has sponsored courses on this material to update clinicians. The current report, authored by the faculty of those courses, incorporates new data up to January 2004 and summarizes the status of available PD treatments based

*Correspondence to: Dr. Christopher G. Goetz, Rush University Medical Center, Suite 755, 1725 W. Harrison Street, Chicago, IL 60612. E-mail: cgoetz@rush.edu
Received 16 November 2004; Accepted 19 November 2004
Published online 6 April 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20464

on a systematic methodology to evaluate clinical evidence (see Table 1). This article focuses on updates only in the pharmacological and surgical realms as applicable to motor aspects of PD.

METHODOLOGY

Search, inclusion, and evaluation methods matched those defined in the initial review.[2] The new literature covered January 2001 to January 2004. Literature searches used electronic databases including Medline (2001–2004), the Cochrane Library central database (2001–2004), and systematic checking of reference lists published in review articles and other clinical reports. Papers selected for review focused on PD and not other parkinsonian disorders, used established scales for measuring target symptoms, had a minimum of 20 subjects treated for a minimum of 4 weeks, and were reported in full-paper format in English. If these criteria were not used, special exceptions were noted with a justification for inclusion. A quality assessment for each article was calculated based on predetermined criteria described in the original critique.[2] Data were considered for the following indications: prevention of clinical progression; symptomatic control of Parkinsonism as monotherapy and as adjunct to levodopa; prevention of motor complications both fluctuations and dyskinesias; and control of motor complications. For each intervention, a summary table with conclusions follows a description of the new clinical trials, with changes from the original report listed in shaded background, covering the issues of Efficacy, Safety, and Implications for Clinical Practice as defined in Table 1 (see Tables 2–7). Conclusions that have not changed are listed with a white background.

RESULTS

Levodopa (Four New Studies, No Change in Conclusions)

Three Level I studies using standard formulation L-dopa as an active comparator concerned effects on disease progression. In addition a single, small-scale Level I study investigated the efficacy of a new soluble L-dopa formulation to control motor fluctuations.

The PSG (2002)[3] reported 4-year results on 84 subjects with early PD included in a double-blind randomized monotherapy trial comparing pramipexole and L-

TABLE 1. *Definitions for specific recommendations*

Conclusions/implications	Definition	Required evidence
Efficacy conclusions		
Efficacious	Evidence shows that the intervention has a positive effect on studied outcomes	Supported by data from at least one high-quality (score ≥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 1 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 1 data
Non-efficacious	Evidence shows that the intervention does not have a positive side effect on studied outcomes	Supported by data from at least one high-quality (score ≥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 conclusions		
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 is insufficient to conclude that the intervention provides clinical benefit	
Investigational	Available evidence is insufficient to support the use of the intervention in clinical practice, but further study is warranted	
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit	
Unlikely useful	Evidence suggests that the intervention does not have a positive effect on studied outcomes. Supported by data from any Level I trial without conflicting Level I	

RCT, randomized controlled trial.

dopa (CALM-PD). Subjects underwent sequential β-CIT (2β-carboxymethoxy-3β-{4-iodophenyl}tropane) single photon emission computed tomography (SPECT) investigations at baseline and after 22, 34, and 46 months to assess dopamine-transporter binding as a surrogate index of progressive nigrostriatal terminal dysfunction. The primary endpoint was the percentage change from baseline in striatal β-CIT uptake at month 46. Secondary endpoints included percentage change from baseline in tracer uptake at months 22 and 34 as well as changes from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) total and Motor scores measured in the practically defined *off* at months 22, 34, and 46. Two-year results were published as a planned interim-analysis[4] and failed to demonstrate statistically significant differences in β-CIT binding between the two trial arms. The 4-year analysis[3] was performed with an improved reconstruction algorithm for the SPECT data and identified statistically significant differences in the mean percentage decline of striatal β-CIT binding at month 46 with a relative difference of approximately 40% in favor of the dopamine agonist (−16.0% vs. −25.5%; $P = 0.01$). Similar differences were found at month 22 (−7.1% vs. −13.5%; $P = 0.004$) and month 34 (−10.9% vs. −19.6%; $P = 0.009$). The imaging findings, however, were not paralleled by differences in mean UPDRS Motor *off* scores between patients treated with pramipexole or L-dopa (0 vs. −2.5 points at month 22, $P = 0.04$; 0.2 vs. −0.5 points at month 34, $P = 0.57$; 1.0 vs. 2.1 at month 46, $P = 0.84$). Lack of a clinical correlate, the absence of a placebo control and the unresolved issue of potential regulatory effects of dopamine agonists or L-dopa on the imaging marker preclude conclusions from this trial about modifying effects on disease progression by pramipexole or L-dopa (Quality Score, 70%).

After a small trial using [^{18}F]dopa positron emission tomography (PET) to study effects of ropinirole or L-dopa monotherapy on disease progression had been underpowered to detect differences between treatments on the imaging endpoint,[5] Whone and associates[6] included 186 patients with early, untreated PD in another monotherapy trial with an [^{18}F]dopa PET endpoint (REAL-PET). Subjects were randomly assigned 1:1 to monotherapy with L-dopa or ropinirole and followed up for 2 years. The primary outcome measure was percentage decline of the putaminal Ki value of [^{18}F]dopa uptake from baseline after 24 months of treatment. Secondary outcomes included changes in UPDRS Motor scores, Clinical Global Improvement (CGI) ratings, and the incidence of dyskinesias assessed by UPDRS Item 32. At 2 years, the mean daily doses were 12.2 mg of ropinirole and 555.7 mg of L-dopa. Open-label supplementary L-dopa was allowed and was used in 15 patients in the ropinirole group and in 7 patients in the L-dopa arm. The trial excluded patients from the final analyses whose baseline scan was within the normal range (n = 21). Analysis of all patients with abnormal baseline scans eligible for analysis (n = 162) revealed statistically significant differences in the decline of putaminal Ki values assessed in favor of the dopamine agonist. In the region-of-interest analysis, the decline was 13.4% for ropinirole patients (n = 68) versus 20.3% for L-dopa–treated patients (n = 54; $P = 0.022$). Similar to the pramipexole versus L-dopa β-CIT study, this trial does not allow for conclusions about L-dopa effects on disease progression due to the absence of a placebo arm and the possibility of L-dopa– or ropinirole-induced influences on striatal decarboxylase activity. With regard to symptomatic control of Parkinsonism in the REAL-PET study, the mean UPDRS score change from baseline demonstrated significantly greater improvement with L-dopa compared to the agonist (improvement of 5.6 vs. a decline of 0.7; 95% confidence interval [CI], 3.54–9.14; Quality Score, 74%).

For treatment effects on motor fluctuations, a single randomized controlled study assessed the efficacy of an alternative L-dopa formulation on motor fluctuations in PD. Djaldetti and coworkers[7] included 62 patients with motor fluctuations and prominent missed or delayed *on* periods in a randomized double-blind study comparing an oral solution of L-dopa–ethyl ester and standard L-dopa–carbidopa tablets. Randomized double-blind treatment was restricted to the first morning and first afternoon dose, and patients took their regular open-label L-dopa regimen for all other scheduled L-dopa doses. Efficacy was assessed by measuring time to switching to *on* after the first morning dose or postlunch dose and by recording the number of failures to switch *on* within 90 minutes after dosing. At 4 weeks, mean "time-to-*on*" for the morning dose was significantly reduced in the oral L-dopa–ethyl ester group (from mean 46 to 36 minutes; −21%) versus L-dopa–carbidopa (from 47 to 43 minutes; −9%; $P < 0.005$), and similar findings occurred for the afternoon dose. The proportion of "no-*on*" episodes was also significantly different between the two treatment groups in favor of the L-dopa–ethyl ester group. Although the results are encouraging, the unusual design and outcome measures do not permit conclusions on the efficacy of oral solutions of L-dopa–ethyl ester in reducing fluctuations (Quality Score, 87%). Safety findings reported in these new Level I trials were comparable to those already summarized in the previous MDS EBM report.[2]

TABLE 2. *Conclusions on levodopa*

Levodopa	Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Standard formulation					
Efficacy	Insufficient data	Efficacious	Not applicable	Non-efficacious	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Clinically useful	Not applicable	Not useful	Investigational
Controlled-release formulation					
Efficacy	Insufficient data	Efficacious	Not applicable	Non-efficacious	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Clinically useful	Not applicable	Not useful	Investigational
Other formulations					
Efficacy	Insufficient data	Insufficient data	Not applicable	Insufficient data	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Investigational	Not applicable	Investigational	Investigational

Present conclusions show no change from the original (see Reference 2).

L-dopa Summary.

Overall, new Level I trials using surrogate markers of progressive nigrostriatal terminal dysfunction in PD fail to provide conclusive evidence on effects of L-dopa on disease progression. The ethyl ester study design was unusual and failed to demonstrate differences that can be translated into the practical management of motor complications. None of these new level studies assessing L-dopa adds new safety information or concerns. No studies addressed the issues of prevention of clinical progression or prevention of motor complications. Conclusions, therefore, remain the same as in the original report (see Table 2).

COMT Inhibitors

Currently available catechol-*O*-methyltransferase (COMT) inhibitors are entacapone, available internationally, and tolcapone, which has more restricted distribution. These drugs enhance bioavailability of L-dopa and, therefore, are not used in clinical situations other than as adjuncts to L-dopa.

Entacapone (Four New Studies, No Change in Conclusions).

Among new studies focusing on symptomatic control of Parkinsonism, Myllyla and colleagues[8] conducted a 12-month safety study comparing entacapone and placebo treatments in 326 L-dopa–treated patients with and without motor fluctuations. The study focused on withdrawal decline after treatment ceased and monitored the UPDRS Activities of Daily Living (ADL) and Motor scores. Mean ADL scores deteriorated by 1 point after entacapone withdrawal and remained unchanged after withdrawal of placebo ($P < 0.001$), whereas mean Motor impairment scores increased by 2.9 points with entacapone cessation and remained unchanged after placebo withdrawal ($P < 0.01$; Quality Score, 79%).

Brooks and colleagues[9] enrolled 172 fluctuating and 128 nonfluctuating L-dopa–treated PD patients into a randomized placebo-controlled, double-blind study comparing entacapone to placebo over 6 months. The primary efficacy measure in the nonfluctuating group was the change of the UPDRS ADL at month 4 and 6 versus baseline. Secondary efficacy variables included changes in the UPDRS Motor score and sum scores of Parts I+II+III, as well as changes in the daily L-dopa dose. Entacapone treatment resulted in a reduction of 0.6 points (from 10.6 [5.7] to 10.0 [5.7]) in the mean scores of the UPDRS Part II at month 4 and 6 (combined) versus baseline compared with a reduction of 0.1 points in the placebo group (from a mean of 9.5 [4.2] to 9.4 [5.7]; $P < 0.001$), whereas the other UPDRS measures did not show significant differences between entacapone and placebo. The mean daily L-dopa dose increased by 7 mg in the entacapone group compared to an increase by 47 mg in the placebo group ($P < 0.01$). Given the very small effect of size on the primary efficacy variable and the absence of an effect on UPDRS Motor scores or the combined UPDRS Parts I+II+III score, this study does not add new information and specifically does not provide sufficient evidence for the symptomatic efficacy of entacapone in patients without motor fluctuations (Quality Score, 93%).

To study effects on control of motor fluctuations, Poewe and associates[10] randomly assigned 301 L-dopa–treated patients to a 6-month randomized placebo-controlled double-blind study of entacapone versus placebo. A total of 260 subjects had motor fluctuations, and the primary outcome was absolute change in hours *on* at 6 months versus baseline. Entacapone prolonged daily *on*

time by a mean of 1.7 hours from 10.0 at baseline to 11.7 at week 24 compared to an increase from 9.7 to 10.7 with placebo ($P < 0.05$). The difference versus placebo was greatest in the subgroup of patients taking more than 5 daily doses of L-dopa (n = 174), where the gain on *on* time over placebo was 1.2 hours ($P < 0.05$). Mean UPDRS ADL scores improved by 1.1 points in patients treated with entacapone and deteriorated by 0.2 points in patients on placebo ($P < 0.05$), and Motor scores improved by 3.3 points versus 0.1 points, respectively ($P < 0.01$; Quality Score, 88%).

In the already cited study by Brooks and coworkers[9], the group of 172 L-dopa–treated patients with motor fluctuations were assessed for changes in fluctuations, using the primary outcome of the proportion of daily *on* time while awake at month 4 and 6 (combined) versus baseline. Compared to placebo treatment, entacapone induced a significant increase in *on* (mean 67.6% at baseline vs. 64.8% at months 4 and 6) versus placebo (59.3% at baseline versus 60.6% at months 4 and 6; $P < 0.05$). Mean absolute *on* time increased by 1.3 hours on entacapone versus 0.1 hours on placebo ($P < 0.001$; Quality Score, 93%).

Fenelon and colleagues[11] performed a 3-month randomly assigned double-blind placebo-controlled study of 122 L-dopa–treated patients with fluctuations. Patients were randomly assigned to entacapone or placebo in a 3:2 ratio, and the primary efficacy measure was waking *on* time derived from patient diaries. Diary data showed unusual degrees of variability in both the entacapone and placebo groups, and observed increases in *on* time were not statistically different between the two treatment groups (mean, 44.0 minutes for entacapone vs. 37.2 minutes for placebo; Quality Score, 80%). Safety findings reported in these new Level I trials were comparable to those already summarized in the previous MDS EBM report.[2]

Tolcapone (Two New Studies, No Changes in Conclusions).

Two new randomized controlled trials assessed the efficacy of tolcapone on symptomatic control of motor fluctuations in PD patients on L-dopa. Shan and coworkers[12] randomly assigned 40 patients to tolcapone or placebo and performed gait analyses both during practically defined *off* and optimal *on* periods at baseline and after 6 weeks of treatment. This study did not have a predefined primary endpoint, but the report included assessments of change of percentage *off* time as assessed by patient diaries. Tolcapone treatment induced a mean 43.5% improvement of total daily *off* time versus a mean 3.3% change on placebo ($P < 0.005$). The *on* UPDRS Motor scores slightly improved with both treatments without statistically significant differences (Quality Score, 71%).

Koller and colleagues[13] compared efficacy and safety of tolcapone or pergolide as adjuncts to L-dopa in 203 patients with motor fluctuations in a 12-week, randomized, open-label, blinded-rater, parallel-group study. The primary outcome was the change from baseline in the proportion of *off* time during the waking hours after 4 and 12 weeks of treatments assessed by home diaries. Secondary endpoints included changes in UPDRS ADL and Motor scores and quality of life assessments. Tolcapone doses ranged from 300 to 600 mg daily. The proportion of *off* time was significantly reduced from baseline to 4 and 12 weeks with both pergolide and tolcapone. The change was reported to correspond to "approximately 2 to 3 hours *off* time per day" with increases in daily *on* time of 18.2% with pergolide and 17.9% with tolcapone, but no numerical values of absolute changes were reported. Both treatments had similar effects on UPDRS Motor scores. Confusion, hypotension, constipation, and abdominal pain were more frequent with pergolide, whereas diarrhea and urine discoloration occurred more often with tolcapone. Overall, more patients on pergolide withdrew because of adverse events (15 vs. 5 on tolcapone; Quality Score, 70%). Safety findings reported in these new Level I trials were comparable to those already summarized in the previous MDS EBM report (see Table 3).[2]

COMT Inhibitor Summary.

Based on these studies, for both entacapone and tolcapone, efficacy conclusions have remained unchanged. With regard to safety issues, tolcapone is considered *Acceptable but Requiring Special Monitoring* in fluctuating patients who have failed other therapies, but *Unacceptable* in patients who otherwise can be treated.

MAO Inhibitors

Three new Level I studies add to the body of evidence regarding efficacy of MAO-B inhibitors for the treatment of PD. Two studies address the role of selegiline on preventing motor complications, and one assessed the efficacy of monotherapy with rasagiline in early PD.

Selegiline (Two New Studies, New Conclusion: Selegiline Is *Non-efficacious* for Prevention of Dyskinesias).

Caraceni and Musicco[14] randomly assigned a total of 473 untreated, early PD patients to monotherapy with L-dopa (n = 156), the dopamine agonists bromocriptine or lisuride (n = 172), or selegiline (n = 155). The primary endpoint was the occurrence of motor fluctua-

TABLE 3. *Conclusions on COMT inhibitors*

COMT inhibitors	Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Entacapone					
Efficacy	Insufficient data	N/A	Efficacious[a]	Insufficient data	Efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	N/A	Clinically useful[a]	Investigational	Clinically useful (F)
Tolcapone					
Efficacy	Insufficient data	N/A	Efficacious[b]	Insufficient data	Efficacious (F)
Safety	Acceptable risk with specialized monitoring[c]				
Practice Implications	Investigational	N/A	Possibly useful	Investigational	Possibly useful

Present conclusions show no change from the original (see Reference 2).
[a]Fluctuators only.
[b]Subjects with minimal or no fluctuations.
[c]Due to liver toxicity concerns, this designation applies only to subjects who have failed other treatments for motor fluctuations; otherwise, tolcapone safety designation is Unacceptable risk.
F, fluctuations; N/A, not applicable.

tions or dyskinesias after "approximately 3 years". At a median follow-up of 34 months, agonists and selegiline treatment showed a reduced relative risk of motor fluctuations compared to L-dopa (0.5 and 0.6, respectively). For dyskinesias, the relative risk was 0.6 for agonists and 0.8 for selegiline relative to L-dopa. However, the lower frequency of motor complications in patients assigned to selegiline was no longer statistically significant when a multivariate analysis included effects of age, disease duration, and baseline severity scores based on Hoehn and Yahr stages and Schwab and England scores. Additional treatment, (unspecified but presumably L-dopa) was started in 41% of the dopamine agonist patients and 64% of the selegiline patients during the course of the trial (Quality Score, 73%).

Shoulson and associates[15] performed a second independent randomization of 368 patients of the original DATATOP cohort who had been treated with selegiline and, by early 1993, required L-dopa treatment to either continue therapy with selegiline or switch over to placebo under double-blind conditions. Patients were followed up for 2 years, and the primary outcome was the time until the first development of wearing-off, dyskinesias, or *on–off* motor fluctuations. Secondary outcome measures included the times until first development of the single events of wearing-off, dyskinesias, or *on–off* motor fluctuations as well as the occurrence of freezing of gait, confusion, and dementia.

At the final visit after 2 years, the mean daily L-dopa dose was lower in the selegiline group compared to the placebo group (508 vs. 602 mg; $P = 0.003$). The frequency of new occurrence in any the three prespecified primary outcome events of wearing-off, dyskinesias, or *on–off* motor fluctuations was not significantly different between the two arms (86 of 176 placebo subjects vs. 87 of 191 selegiline subjects; hazard ratio, 0.87; 95% CI, 0.63–1.19; $P = 0.38$). Separate assessment of specific motor complication subtypes revealed more placebo patients with new onset of wearing-off (52.4% vs. 41.5%, $P = 0.18$) or *on–off* motor fluctuations (8.7% vs. 3.2%, $P = 0.02$) compared to those treated with selegiline, while there was a statistically significant greater incidence in dyskinesias in the selegiline group (33.8% vs. 19.4%, $P = 0.006$). Freezing of gait occurred more commonly in placebo versus selegiline-treated patients (28.9% vs. 15.5%; $P = 0.003$). There were no significant differences in the occurrence of confusional episodes or dementia or rates of withdrawal from the trial, incidence of adverse events, or deaths (Quality Score, 75%). Safety findings reported in these new Level I trials were comparable to those already summarized in the previous MDS EBM report.[2]

Rasagiline (One New Study, New Conclusion: Rasagiline Is *Efficacious* as Monotherapy for Symptomatic Control of Parkinsonism).

By the time of the original review, insufficient data were available to assess the efficacy of rasagiline. In the current time frame, one Level I study (TEMPO) assessed the efficacy of monotherapy with rasagiline in PD patients (Parkinson Study Group, 2002).[16] This trial enrolled 404 patients with early PD not requiring dopaminergic therapy into a multicenter randomized double-blind placebo-controlled trial comparing rasagiline, 1 or 2 mg daily, with placebo (placebo, n = 138; rasagiline 1 mg/day, n = 134; rasagiline 2 mg/day, n = 132). The primary outcome measure was the change in the total UPDRS score between baseline and 26 weeks of treatment. Secondary endpoints included changes in UPDRS Parts I, II, and III scores as well as symptom-based subscores (tremor, rigidity, bradykinesia, and postural instability/gait disorder), Hoehn and

TABLE 4. *Conclusions on MAO-B inhibitors*

MAO-B inhibitors	Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Selegiline					
Efficacy	Insufficient data	Efficacious	Insufficient data	Non-efficacious (D); Insufficient data (F)	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Clinically useful	Possibly useful	Not useful (D); Investigational (F)	Investigational
Rasagiline					
Efficacy	Insufficient data	Efficacious	Insufficient data*	Insufficient data	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Clinically useful	Investigational*	Investigational	Investigational

Table data are shaded gray where present conclusions differ from those of the previous report (see Reference 2).
*After the closing of this report, new data on rasagiline as an adjunct to levodopa appeared and may affect future conclusions.
MAO-B, monoamine oxide type B; F, fluctuations; D, dyskinesias.

Yahr stage, Schwab and England scale, the PDQUALIF scale, and the need for L-dopa. All subjects experiencing a decline of less than 3 points of their total UPDRS score were classified as responders.

For the primary efficacy analysis, adjusted total UPDRS score mean changes from baseline to week 26 were calculated using analysis of covariance with baseline UPDRS score and rating investigator as covariates. Adjusted mean changes in total UPDRS scores were −4.20 comparing 1 mg of rasagiline to placebo ($P < 0.001$) and −3.56 for 2 mg of rasagiline versus placebo ($P < 0.001$). Unadjusted changes were 0.1 points for 1 mg, 0.7 points for 2 mg, and 3.9 points for placebo. The responder analysis also showed significant effects of active treatment versus placebo (placebo 49% vs. 66% for 1 mg [$P = 0.004$] vs. 67% for 2 mg [$P = 0.001$]). Kaplan–Meyer analysis did not show statistically significant differences in the time to need L-dopa. Both active treatment groups showed significant improvements in PDQUALIF scores relative to placebo (−2.91 for 1 mg and −2.74 for 2 mg of rasagiline). Adverse events were equally frequent with active treatment and placebo, and there were no differences in laboratory test results, electroencephalogram abnormalities, or standing blood pressure. The only difference was seen for supine systolic blood pressure with a mean increase of 4.04 mm Hg on 2 mg of rasagiline versus placebo (Quality Score, 85%).

MAO-B Inhibitor Summary.

Conclusions on MAO-B inhibitors are presented in Table 4. Based on the two cited selegiline trials, initial monotherapy with selegiline is *Non-efficacious* in preventing motor complications once L-dopa is initiated. As such, it is also not useful for this indication. For rasagiline, the high quality score and positive findings of the cited rasagiline trial allow the 'Efficacy' conclusion that monotherapy rasagiline is *Efficacious* in reducing the motor symptoms of Parkinson's disease over 6 months. *Insufficient Data* preclude conclusions for other indications. For 'Safety Conclusions', rasagiline use is *Acceptable Without Specialized Monitoring*. For 'Clinical Practice Implications', rasagiline is considered *Useful* as a monotherapy in early PD and *Investigational* in all other settings.

Dopamine Agonists

Since the previous report, 11 published Level I clinical trials fulfilling the predefined inclusion criteria have been published using bromocriptine, pergolide, apomorphine, piribedil, pramipexole, or ropinirole. No studies concerned cabergoline, lisuride, or DHEC. Overall, these new data modify previous conclusions concerning apomorphine and piribedil. Other conclusions on dopamine agonists remain unchanged. New safety concerns related to agonists recently have included valvular heart disease, so far, most extensively reported with pergolide. Whether this effect is drug- or class-specific is not yet known, so clinicians prescribing agonists should use monitoring vigilance.

Bromocriptine (Three New Studies, No Changes in Conclusions).

Mizuno and coworkers[17] conducted a three-arm study of bromocriptine versus pramipexole versus placebo in a 12-week parallel, double-blind study of 325 L-dopa–treated patients with advanced PD. The primary endpoints were the change from baseline in UPDRS ADL scores averaged for *on* and *off* function and *on* UPDRS Motor scores. Bromocriptine (mean daily maintenance dose, 17.75 mg) improved both indices significantly better than placebo (mean UPDRS ADL improvement of 3.25 vs. 2.03 on placebo ($P = 0.007$) with a mean UPDRS-III improvement of 9.98 on bromocriptine versus 5.55 on placebo ($P < 0.001$; Quality Score, 83%).

Lees and colleagues[18] published 10-year results from an open-label parallel trial of 782 patients with early,

mild PD, randomly assigned to bromocriptine, L-dopa alone, or L-dopa with selegiline. In 1995, the selegiline arm was terminated after an interim analysis that raised safety concerns (see data in the previous MDS EBM Review).[2] The main 10-year endpoint of the study was mortality, and there was no significant difference between the bromocriptine and L-dopa arms (hazard ratio, 1.15; 95% CI, 0.90–1.47). Throughout the study, patients initially randomly assigned to bromocriptine experienced slightly worse Webster disability scores than those randomized to L-dopa, although this difference was statistically significant only during the first years. However, patients initially randomized to bromocriptine had a significantly lower incidence of dyskinesia (hazard ratio, 0.73; 95% CI, 0.57–0.97). Although the study was compromised by the early loss of one of the study arms, it has value because of its large sample size, long follow-up, and independence from industrial sponsors (Quality Score, 60%).

Montastruc and colleagues[19] reported 10-year follow-up data and mortality from a trial that initially included 60 patients with early PD randomly assigned to bromocriptine or L-dopa. Like the Lees study,[18] this study found no difference in mortality at 10 years between the 2 groups (8 of 29 on L-dopa vs. 9 of 31 on bromocriptine; Quality Score, 66%). Bromocriptine's safety findings reported in these three new trials were comparable to those summarized in the previous MDS EBM report.[2]

Pergolide (One New Study, No Changes in Conclusions).

Koller and associates[13] reported a 12-week open-label, blind-rater, parallel-group Level I trial involving 203 L-dopa–treated patients with motor fluctuations, randomly assigned to receive tolcapone or pergolide (mean final dose, 2.2 mg/day; see section on COMT Inhibitors). Efficacy was similar for pergolide and tolcapone, but there were more side-effect related drop-outs with pergolide (Quality Score, 70%).

With regard to safety, since 2001, there have been a growing number of publications that raise concerns about the risk of valvular heart disorders with pergolide. Van Camp and colleagues[20] reported that 26 of 78 (33%) PD patients treated with pergolide had signs of restrictive valvular heart disease of multiple types at echocardiography, whereas none had such abnormalities among 18 PD patients never treated with an ergot-derived dopamine agonist. In the absence of objective and reliable pharmacoepidemiological data, it is still impossible to establish what are the real prevalence and incidence rates of this adverse drug reaction. Hence, the true implication of such a side effect for clinical practice remains a matter of debate. Based on the evidence published until early 2004, the MDS EBM safety conclusions on pergolide remain unchanged, but ongoing reports and regulatory concerns may alter this statement in the future. The mechanism responsible for this effect remains unknown but may involve $5HT_2$ receptors. If such a mechanism is confirmed, other agonists that share such serotonergic mechanisms with pergolide might also share comparable safety concerns.

Apomorphine (One New Study, New Conclusions: *Efficacious* as Adjunct to L-dopa for Symptomatic Control of Parkinsonism and *Efficacious* for Control of Motor Fluctuations).

Dewey and colleagues[21] published a prospective, randomized, double-blind, placebo-controlled, parallel-group, 4-week trial in 32 patients suffering from at least 2 hours of *off* time daily despite optimized treatment. Although only 29 patients qualified for intention to treat analysis, a smaller number than the standard inclusion criteria used for this critique, the panel believed the study should be included because it is the only published randomized Level I trial. The primary efficacy factor was the predose to postdose change in UPDRS Motor score (inpatient), the correction of *off* state, and total daily time spent *off* according to daily diaries (outpatient). Apomorphine was delivered as individualized subcutaneous injections whenever the patient needed to correct *off* states. Apomorphine (mean dose, 5.4 mg) induced a significantly greater effect than placebo ($P < 0.001$) and resulted in 62% improvement (mean UPDRS Motor score, 39.7 before vs. 15.8 ± 2.4 after injection), whereas the effect of placebo was unchanged (mean UPDRS Motor score, 36.3 before vs. 36.2 after injection). In the subsequent outpatient phase, apomorphine treatment (average of 2.5 doses per day) aborted 95% of the *off* period compared to 23% for placebo ($P < 0.01$) and a 2-hour reduction in *off* time compared to no reduction with placebo ($P < 0.02$). The most frequent adverse drug reactions reported in this trial were injection site complaints, yawning, somnolence, dyskinesia, and nausea or vomiting (Quality Score, 95%).

Piribedil (One New Study, New Conclusion: *Efficacious* as an Adjunct to L-dopa for Symptomatic Control of Parkinsonism).

Ziegler and associates[22] conducted a prospective, randomized, placebo-controlled, parallel-group, 4-month study in 115 L-dopa–treated PD patients with no motor fluctuations. The primary efficacy criterion was the per-

centage of responders, defined by a 30% reduction from baseline on the UPDRS Motor score. Piribedil (150 mg/day) significantly increased the percentage of responders compared with placebo (56.4% vs. 37.7%, $P = 0.04$). These findings remained significant at the 6-month analysis, after L-dopa dose adjustment had been allowed. The most common adverse reactions on piribedil were gastrointestinal symptoms, sweating, and hypotension (Quality Score, 89%).

Pramipexole (Four New Studies: No Change in Conclusions).

As already summarized in the L-dopa section of this review, the Parkinson Study Group[3] published the 4-year neuroimaging results of the CALM-PD study. The mean percentage loss in striatal uptake from baseline was reduced in the pramipexole group compared with the L-dopa group, but the absence of a placebo arm, the lack of clinical correlate, and the potential pharmacodynamic impact of chronic dopamine treatments on the primary outcome measure preclude conclusions (Quality Score, 70%).

Pogarell and colleagues[23] reported a prospective, 11-week, randomized, placebo-controlled, parallel study in 84 patients with PD and "drug-resistant" tremor. Pramipexole or placebo was added as an adjunct to stable optimized antiparkinsonian medications. The primary endpoint was the absolute change in the sum of tremor items of the UPDRS. Pramipexole induced the greater mean change score by 4.4 points (95% CI, −6.2 to −2.5), corresponding to a difference in the mean relative change of 34.7%. A specific effect of pramipexole on parkinsonian tremor remains unclear, because the report did not clarify how antiparkinsonian medications were "optimized" at baseline and because no Level I trial specifically compared pramipexole to any other active antiparkinsonian agent on this symptom (Quality Score, 93%). The third new Level I study on pramipexole by Mizuno and colleagues[17] was already discussed in the Bromocriptine section. This randomized, three-arm placebo versus bromocriptine versus pramipexole double-blind, parallel-group study involved 325 patients with advanced PD experiencing motor fluctuations, freezing phenomena, or suboptimally treated Parkinsonism. The primary outcome measures were the change from baseline of the total score of the UPDRS ADL and the total score of the UPDRS Motor sections on the final maintenance dose. The total scores of both UPDRS ADL and Motor sections were significantly reduced in the pramipexole group (mean improvement 4.0 and 11.8, respectively) compared to the placebo group (2.0 and 5.6, $P < 0.001$). The magnitude of the response of pramipexole was larger than that of bromocriptine, but the study was not powered to detect differences between the two active treatment groups (Quality Score, 83%).

Wong and associates[24] enrolled 150 PD patients in a 15-week, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study. The populations was heterogeneous with both L-dopa–naïve (n = 43) and L-dopa–treated (n = 104) patients. The primary efficacy variable was the change from baseline in the sum of the UPDRS Part II (overall condition) and Part III (assessed during the *on* period). Secondary endpoints included UPDRS subscores, and the number of *off* hours as measured with diaries in patients receiving L-dopa. The mean daily dose of pramipexole used in this study was not reported. At week 15, UPDRS Parts II+III improved by 12.14 points on pramipexole and 2.45 on placebo ($P < 0.001$). For patients on L-dopa, the mean number of *off* hours improved on pramipexole, from baseline 7.07 to 6.15 hours/day at endpoint, whereas placebo-treated patients declined clinically from a baseline mean of 5.59 to 6.87 hours (Quality Score, 81%). Pramipexole's safety findings reported in these four new Level I trials were comparable to those already summarized in the previous MDS EBM report.[2]

Ropinirole (Four New Studies, No Change in Conclusions).

Brunt and coworkers[25] conducted a 6-month, randomized, parallel-group, bromocriptine-controlled (2:1 ratio), double-blind trial that enrolled 555 patients with PD. The population varied in their L-dopa daily doses, the presence of motor fluctuations and the use of dopamine agonists at study entry. The study was powered for safety (incidence of confusion and/or hallucinations). The efficacy outcome measure was complex and not validated, defining a positive patient response by ≥ 20% reduction in daily L-dopa dose plus any of the following: for patients on no prior treatment, a 20% reduction in UPDRS Motor score; for patients with motor fluctuations, a 20% reduction in *off* time; for patients already taking an agonist, an improvement on a CGI scale score. Safety and efficacy assessments showed no significant difference in the two treatment groups. Ropinirole and bromocriptine doses differed according to different patient subgroups, making the results even more confusing (Quality Score, 64%).

The 2 year L-dopa–controlled REAL-PET study[6] used putaminal [^{18}F]dopa uptake, a putative biomarker of disease progression, as a primary endpoint. As already described in the L-dopa section of this review, there was a lower reduction in ^{18}F-dopa uptake in the ropinirole group, but no definite conclusion on disease progression

can be drawn because of methodological issues. Secondary endpoints included UPDRS Motor score, a CGI assessment and incidence of dyskinesia (UPDRS Item 32). The mean UPDRS change from baseline favored L-dopa treatment (improvement of 5.6 vs. a decline of 0.7; 95% CI, 3.54–9.14). However, significantly fewer patients in the ropinirole group developed dyskinesias compared with the L-dopa group (3.4% vs. 26.7%; odds ratio [OR], 0.09; 95% CI, 0.02–0.29; $P < 0.001$; Quality Score, 74%).

Im and colleagues[26] reported a randomized, double-blind, parallel group, bromocriptine-controlled, 16-week trial in 76 L-dopa–treated PD patients with motor fluctuations. The primary efficacy variable was the number of responders, defined as patients who achieved at least a 20% reduction in L-dopa dose. Secondary endpoints were the numbers of patients with ≥20% improvement in UPDRS Motor examination, ≥20% improvement in *off* time assessed by diaries, and the number showing CGI improvement. Mean daily doses at endpoint were 7.9 mg of ropinirole and 15.4 mg of bromocriptine. The ropinirole group reduced L-dopa more frequently than the bromocriptine group (54% vs. 28%; OR, 3.0; 95% CI, 1.2–7.8; $P < 0.05$), but there were no significant differences on the secondary endpoints. This study raises several methodological issues, specifically the lack of validation and questionable relevancy of the outcome measure and the heterogeneity of the study population (Quality Score, 68%). Ropinirole safety findings reported in these four new Level I trials were comparable to those already summarized in the previous MDS EBM report.[2]

Cabergoline, Dihydroergocryptine, Lisuride (No New Studies, No New Conclusions)

Agonists Summary.

These collective results permit changes in conclusions for apomorphine and piribedil, and amplify but do not change former conclusions on the other agonists (see Table 5). For 'Efficacy', apomorphine, used as subcutaneous injections (and not by means of continuous pump) is now considered *Efficacious* for the treatment of Parkinsonism as an adjunct to L-dopa and *Efficacious* for the control of motor fluctuations. 'Safety Conclusions' remain unchanged, and the drug can be used with an *Acceptable Risk Without Special Monitoring*, but patients and caregivers should be referred to a specialty center for training on this relatively complex drug delivery system. Regarding 'Implications for Clinical Practice', apomorphine is now considered *Useful* for treating Parkinsonism and motor fluctuations. For piribedil, the new data change 'Efficacy' conclusions in that piribedil is now considered *Efficacious* for treating Parkinsonism as an adjunct to L-dopa. Based on the long use of this drug in several countries, and several Level III publications (see the original report), for 'Safety Conclusions', piribedil can be used with an *Acceptable Risk Without Specialized Monitoring*. For 'Clinical Practice Implications', piribedil is considered as *Useful* for this indication, but *Investigational* in other clinical settings. With regard to 'Safety', for all agonists in general, clinicians should be aware that recent pharmacoepidemiological data show that daytime sleepiness may reflect class-effects and, thereby, may be possible adverse events of any agonist.[27–31] This increased risk of somnolence appears to be greater when patients are treated with L-dopa plus an agonist than with L-dopa alone, but there is no clear evidence that one agonist is at greater risk than another.[30] Monitoring of driving for patients on any agonists is, therefore, a reasonable general management recommendation. Regarding valvular heart disorders with pergolide, and possibly other agonists, safety conclusions remain unchanged at this point, but this finding may change in the near future as the results of on-going pharmacoepidemiological trials should clarify soon what is the real implication of this side effect on clinical practice.

Amantadine (One New Study, No Change in the Conclusions) and Anticholinergics (No New Studies Relevant to Efficacy; One Relevant Study for Safety; No Changes in Conclusions)

Two new randomized clinical trials concerned amantadine use in controlling dyskinesia. Only one is reviewed, because the second[32] used an intravenous formulation of amantadine that is not clinically applicable. Thomas and coworkers[33] conducted a randomized, parallel, placebo-controlled trial of oral amantadine (300 mg/d) in advanced, L-dopa–treated PD patients with motor fluctuations and dyskinesias. Dyskinesias were evaluated by the UPDRS Part IV and blinded videotape-based ratings using the Dyskinesia Rating Scale. The primary rating tool was a simple binary clinical evaluation of dyskinesia severity as better than baseline or equal/worse, and the rating was repeated at time intervals to allow a survival analysis of improvement. Amantadine treatment was superior to placebo, with a mean positive duration effect of 4.9 versus 1.3 months ($P < 0.001$). Concomitantly, UPDRS Parts I–III scores decreased ($P < 0.001$) for the amantadine treated group and *on* time increased whereas *off* time decreased, although not significantly. Regarding safety, several subjects treated with amantadine experienced a rebound in dyskinesia

TABLE 5. *Conclusions on dopamine agonists*

Agonists	Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Bromocriptine					
Efficacy	Insufficient data	Likely efficacious	Efficacious	Likely efficacious	Likely efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Possibly useful	Clinically useful	Possibly useful	Possibly useful (F)
Pergolide					
Efficacy	Insufficient data	Efficacious	Efficacious	Insufficient data	Efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Clinically useful	Clinically useful	Investigational	Clinically useful (F)
Apomorphine					
Efficacy	Insufficient data	Insufficient data	Efficacious	Insufficient data	Efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Investigational	Clinically useful	Investigational	Clinically useful (F)
Piribedil					
Efficacy	Insufficient data	Insufficient data	Efficacious	Insufficient data	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Investigational	Clinically useful	Investigational	Investigational
Pramipexole					
Efficacy	Insufficient data	Efficacious	Efficacious	Efficacious	Efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Clinically useful	Clinically useful	Clinically useful	Clinically useful (F)
Ropinirole					
Efficacy	Insufficient data	Efficacious	Insufficient data	Efficacious	Efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Clinically useful	Possibly useful	Clinically useful	Clinically useful (F)
Cabergoline					
Efficacy	Insufficient data	Insufficient data	Efficacious	Efficacious	Likely efficacious (F)
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Investigational	Clinically useful	Clinically useful	Possibly useful (F)
Dihydroergocryptine					
Efficacy	Insufficient data	Efficacious	Insufficient data	Insufficient data	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Clinically useful	Investigational	Investigational	Investigational
Lisuride					
Efficacy	Insufficient data	Likely efficacious	Likely efficacious	Insufficient data	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice Implications	Investigational	Possibly useful	Possibly useful	Investigational	Investigational

Table data are shaded gray where present conclusions differ from those of the previous report (see Reference 2).
F, fluctuations.

severity after drug discontinuation, and 2 suffered from hyperthermia (Quality Score, 87%). Safety findings reported in this new Level I trial were comparable to those already summarized in the previous MDS EBM report.[2]

For anticholinergics, although no new efficacy studies were identified, a neuropathology report by Perry and associates[34] examined 120 cases of PD and quantified histologic markers for Alzheimer's disease according to the type and duration of anticholinergic exposure during life. Amyloid plaque densities were more than 2.5-fold higher in cases treated with long-term antimuscarinic medications compared to untreated or short-term treated cases ($P = 0.005$ and 0.00005, respectively). Neurofibrillary tangle densities were also highest when long-term anticholinergic drugs had been used compared to the untreated or short-term treatment groups ($P = 0.02$ and 0.05, respectively).

Amantadine and Anticholinergics Summary.

The new amantadine trial strengthens but does not change the original conclusions regarding efficacy (see Table 6). However, it provides brings a new perspective on the duration of the antidyskinetic effect of amantadine with an estimate of approximately 5 months. The anticholinergic study, considered as a serious alert, needs confirmation and does not dictate changes in conclusions.

Surgical Treatments

Whereas medication treatments for PD have been studied in the context of mild, moderate, and advanced

TABLE 6. *Conclusions on amantadine and anticholinergic agents*

Amantadine and anticholinergics	Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Amantadine					
Efficacy	Insufficient data	Likely efficacious	Likely efficacious	Insufficient data	Efficacious (D) Insufficient data (F)
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Clinically useful	Clinically useful	Investigational	Clinically useful (D)
Anticholinergics					
Efficacy	Insufficient data	Likely efficacious	Likely efficacious	Insufficient data	Insufficient data
Safety	Acceptable risk without specialized monitoring				
Practice implications	Investigational	Clinically useful	Clinically useful	Investigational	Investigational

Present conclusions show no change from the original (see Reference 2).
F, fluctuations; D, dyskinesias.

disease, surgery has been reserved only for patients with both severe motor impairment from PD and motor complications in the form of fluctuations and dyskinesias. In the 2001 report, the inclusion criteria for surgical interventions allowed studies with fewer than 20 subjects but required that postoperative evaluations occur at 3 months or longer. New Level I studies for unilateral pallidotomy, subthalamic nucleus (STN) stimulation, and fetal mesencephalic cell transplants permit modifications of conclusions for these procedures. Conclusions for all other procedures remain unchanged (see Table 7).

Unilateral Pallidotomy (Two New Studies, New Conclusions: *Efficacious* for Symptomatic Control of Parkinsonism; *Efficacious* for Control of Motor Fluctuations and Dyskinesias).

Vitek and colleagues[35] conducted a 36-patient randomized trial with blinded ratings comparing the effects of unilateral pallidotomy (n = 18) versus medical therapy (n = 18) over 6 months. With the total UPDRS as the primary outcome, they demonstrated that pallidotomy induced a 32% improvement compared to a 5% decline in the control group. Six-month group differences were statistically significant for the surgery group (mean baseline, 80.4 vs. 54.9; $P < 0.0001$) but not for the group receiving medical management (mean baseline, 76.8 vs. 76.6). Dyskinesias, measured objectively, and motor fluctuations, assessed by the UPDRS, significantly improved only in the surgery group; the study was not powered specifically to detect changes in these secondary indices (Quality Score, 82%).

A randomized observer-blind study by Esselink and associates[36] compared unilateral pallidotomy (n = 13) with chronic STN stimulation (n = 20) and used the change from baseline *off* UPDRS Motor score at 6 months after surgery as the primary measure of efficacy. Pallidotomy was associated with a median improved change score of 9.5 points (no statistical analysis provided), compared with 25 points with STN stimulation. The difference between the two surgeries was significantly different in favor of subthalamic stimulation ($P = 0.002$). The absence of statistical comparison between baseline and 6 months in the pallidotomy group for the outcome measures, including dyskinesias, precludes specific conclusions on this surgery from the study. The analysis was based on 13 patients in the pallidotomy group, rather than the original enrolled 14, because 1 patient committed suicide (Quality Score, 95%).

Other added safety information since the last report concerned primarily cognition studies and documented that global neuropsychological function is usually unaffected by unilateral pallidotomy, especially when the procedure is performed on the right side.[37,38] Other safety issues were similar to those covered in the earlier EBM critique.[2]

STN Deep Brain Stimulation (Two New Studies, New Conclusion: *Efficacious* for Symptomatic Control of Parkinsonism).

Katayama and coworkers[39] conducted blinded ratings of 14 PD subjects who had complications related to L-dopa therapy. The surgery was bilateral in 9 subjects and unilateral (4 right, 1 left) in the rest. The stimulator effects were determined 6 to 8 months after surgery, using a 2-day random-ordered protocol, 1 day with the stimulator on for12 hours and the other with the stimulator off for 12 hours. During the full-day evaluation periods, patients took their regular medications and the best clinical *on* UPDRS scores and worst clinical *on* UPRDS scores over 12 hours were compared in the two conditions. No single primary outcome was designated. The stimulator improved *off* UPDRS Motor scores by 27% ($P < 0.001$) and UPDRS ADL scores by 18% ($P < 0.002$). Motor fluctuations, as determined by percentage

TABLE 7. *Conclusions on surgical interventions*

Surgery	Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Unilateral pallidotomy					
Efficacy	Insufficient data	Insufficient data	Efficacious	Insufficient data	Likely efficacious (D,F)
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Clinically useful	Investigational	Clinically useful (D,F)
Pallidal stimulation					
Efficacy	Insufficient data	Insufficient data	Likely efficacious	Insufficient data	Insufficient data
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Possibly useful	Investigational	Investigational
Thalamotomy					
Efficacy	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Investigational	Investigational	Investigational
Thalamic stimulation					
Efficacy	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Investigational	Investigational	Investigational
Subthalamotomy					
Efficacy	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Investigational	Investigational	Investigational
Subthalamic nucleus stimulation					
Efficacy	Insufficient data	Insufficient data	Efficacious	Insufficient data	Insufficient data
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Clinically useful	Investigational	Investigational
Human fetal mesencephalic transplantation					
Efficacy	Insufficient data	Insufficient data	Non-efficacious	Insufficient data	Non-efficacious
Safety	Unacceptable risk				
Practice Implications	Investigational	Investigational	Investigational	Investigational	Investigational
Fetal porcine cell transplantation					
Efficacy	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Safety	Acceptable risk with specialized monitoring				
Practice Implications	Investigational	Investigational	Investigational	Investigational	Investigational

Treatments with new conclusions have gray backgrounds and those with no changes have white backgrounds.
D, dyskinesias; F, Fluctuations.

of time termed "immobile" improved by 33% ($P < 0.02$). L-Dopa was adjusted postoperatively, so that an evaluation of stimulator effects on dyskinesias could not be determined as a comparison to preoperative status. The most marked improvements in all domains occurred in the seven patients on low-dose L-dopa at study entry. The data extend efficacy observations on objective improvements to a full day; they do not directly document long-term maintained efficacy with continual stimulation (Quality Score, 73%).

Østergaard and colleagues[40] performed an STN study, but it is not included, because the preoperative evaluations were not randomized, and the postoperative order of examination, while blinded, was not specifically stated as randomized in order. This report is further compromised because the full cohort of 33 patients who received surgery was not reported, and 4 subjects in the study group had received prior surgery: unilateral thalamotomy, or unilateral thalamic deep brain stimulation.

Esselink and coworkers[36] compared chronic bilateral STN stimulation to unilateral pallidotomy in a 34-patient trial: 20 randomly assigned to STN chronic stimulation and 14 to pallidotomy (data analysis based on 13; see above). At 6 months, the UPDRS Motor assessment 12 hours after medications were withheld (primary outcome) was improved in both groups with a significantly enhanced improvement in favor of STN stimulation (median improvement, 25 vs. 9.5 points; $P = 0.002$). This study is notable because of its chronic treatment design, and comparisons of STN effects were made with the stimulator chronically on, just as the patients lived at home. However, the *on* data were obtained after giving patients suprathreshold doses of medications that they did not take outside of the prescribed experimental as-

sessments. These scores, showing improvement in both groups, but again favoring STN stimulation ($P = 0.02$) are more difficult to interpret in a clinical setting. Compared to preoperative status, STN-treated subjects reduced medications by 33% (L-dopa equivalents), precluding conclusions on dyskinesia improvements directly related to surgery (Quality Score, 95%).

Added safety information since the last report concerned primarily cognition with documentation that global neuropsychological global function is usually not adversely affected, although depression and even suicidal ideation can be seen postoperatively.[41,42] Electrode lead breakage, battery failure, and equipment malfunction continue to be issues of concern with deep brain stimulator technology and were covered in the original EBM critique.

Fetal Mesencephalic Cell Transplantation (One New Study, New Conclusion: *Non-efficacious* for Symptomatic Control of Parkinsonism).

Olanow and associates[43] conducted a 24-month, double-blind, placebo-surgery trial involving 34 subjects with advanced PD and motor complications. Subjects were randomly assigned to receive sham surgery (bilateral burr holes, n = 11), one fetal nigral graft bilaterally (n = 11), or four fetal nigral grafts bilaterally (n = 12). Immunosuppression was used for 6 months. The primary outcome measure was the change in first morning *off* UPDRS Motor score between baseline and final visit. At 2 years, there were no significant differences among the groups. Short-term efficacy at 6 and 9 months occurred in the surgical group ($P < 0.05$) but was not maintained. Stratification based on disease severity documented a treatment benefit of surgery in milder patients ($P < 0.006$) at the end of the study. In contrast to the failed clinical outcome, significant and dose-dependent improvements in fluorodopa uptake on PET scans occurred after transplantation. Adverse effects occurred more frequently in the transplantation subjects, and most importantly, 57% of the patients who received transplants develop dyskinesia in the *off* medication state. No placebo-treated subject developed this form of dyskinesia. This unusual form of dyskinesia, previously reported,[44] developed generally 6 to 12 months after surgery and predominantly affected the legs. In some cases, these dyskinesias were severely disabling and required another surgical intervention (Quality Score, 93%).

Neuropsychological safety issues related to mesencephalic transplants were studied and showed that cognitive performance is not adversely affected by this surgery.[45] Other safety issues were similar to those covered in the previous EBM critique.[2]

All Other Surgeries: Thalamotomy, Thalamic Stimulation, Pallidal Stimulation, Subthalamotomy, Porcine Fetal Transplantation (No New Studies, No Changes in Conclusions)

Surgery Summary.

With the Vitek study, for 'Efficacy Conclusions', unilateral pallidotomy is considered *Efficacious* for treatment of Parkinsonism and *Likely Efficacious* for both motor fluctuations and dyskinesias. These designations are changes from the prior report. For 'Safety Conclusions', with the continued follow-up reports, unilateral pallidotomy is considered to carry an *Acceptable Safety Risk with Special Monitoring Required* (unchanged). In 'Implications for Clinical Practice', unilateral pallidotomy is now considered *Useful* for the management of patients with advanced PD and motor complications who have not adequately responded to pharmacological management. With the addition of new Level I studies, for 'Efficacy Conclusions', STN deep brain stimulation is considered *Efficacious* for treatment of Parkinsonism. For both motor fluctuations and dyskinesias, there are still *Insufficient Data* in light of conflicting data on motor fluctuations and the confounding effects of medication dosage reduction on dyskinesia. For 'Safety Conclusions', with the continued follow-up reports, STN DBS is considered to be *Acceptable With Specialized Monitoring Required* (unchanged), and for 'Clinical Practice Implications', STN DBS is now considered *Useful* in patients with advanced PD and motor complications who have not responded adequately to pharmacological management. Finally, with regard to fetal mesencephalic transplants, for 'Efficacy Conclusions', surgery as performed in studies to date is considered *Non-efficacious* (changed from *Insufficient Data*) for treatment of Parkinsonism, motor fluctuations, and dyskinesias. It is important to emphasize that multiple important variables that likely impact on survival of fetal tissue and its ability to integrate into host tissue have not been studied in these few studies. Whereas the scientific basis of fetal and cellular transplantation has not been ended by these studies, the evidence strongly argues against continuing with treatments as studied to date. For 'Safety Conclusions', because of the new induction of dyskinesias, human fetal transplantation, as studied to date, is considered to carry an *Unacceptable Risk* (changed from *Acceptable Risk With Specialized Monitoring*), and for 'Clinical Practice Implications', fetal transplantation is considered *Investigational*, because the field remains open to a gamut of new techniques and genetic manipulations. Other conclusions remain unchanged.

DISCUSSION

This updated review incorporated new studies published between January 2001 and January 2004. Some of these new publications confirmed the original efficacy designations and others allowed rating reassignments to new categories. Apomorphine, piribedil, unilateral pallidotomy, and STN stimulation moved upward in efficacy ratings from *Likely Efficacious* to *Efficacious* as adjuncts to L-dopa in treating Parkinsonism. Apomorphine was also newly rated as *Efficacious* for the treatment for motor fluctuations and unilateral pallidotomy as *Likely Efficacious* for treating both dyskinesias and motor fluctuations. Rasagiline was newly rated *Efficacious* as monotherapy for the treatment of Parkinsonism. Equally important, new Level I data moved human fetal nigral transplants, as performed to date, from the ambiguous status of *Insufficient Data* to *Non-efficacious* for the treatment of Parkinsonism, motor fluctuations, and dyskinesias. New data on selegiline likewise allowed a new designation of *Non-efficacious* for the prevention of motor complications. In a field as active in clinical trials as PD, frequent updating of therapy-based reviews is essential. We consider a 3-year period a reasonable time frame for a publication and are working within the MDS to establish a Web-based mechanism to update in an ongoing manner in between publications.

EBM reviews are based on a systematic methodological approach that examines data sets in a uniform manner and prioritizes certain clinical design elements over others. Whereas this methodology allows consideration of all types of clinical data, most analyses based on this technique rely most heavily on the randomized (Level I) and nonrandomized but controlled (Level II) studies. Open-label observations, patient series, or case histories provide supporting data and safety insights but are otherwise less considered. In this update, the authors only reviewed new Level I data, as the trial designs for modern Parkinson's disease interventions regularly incorporate randomization and the authors agree with the categorical importance of this design element.

Implicit to its foundations in clinical trial methodology, EBM assessments use the designation *Insufficient Data* when the data themselves are conflicting or ambiguous and also when the study design is too weak to provide solid conclusions. Although we did not specify the primary reason for this designation for each entry, in most instances *Insufficient Data* related to poor study design at least in part. The science of clinical trial design has made significant progress over the past 30 years, so that the earlier medications including anticholinergics and amantadine were never studied with the rigor of the modern agonists. As young investigators interested in clinical trials enter the field of Movement Disorders, we consider the clinical conditions and treatments that intersect with *Insufficient Data* to be an open invitation for new research initiatives.

The authors have been impressed that colleagues often incorrectly equate EBM reviews with Practice Guidelines.[46] The two are quite different in their goals and process. Practice Guidelines are formulated to direct clinicians to specific treatments based on recommendations or algorithms for decision making. Data sources include the clinical trials that EBM reviews use, but, in addition, expert opinion, consensus panels, and other information that weigh heavily on the construction of directives. In fundamental contrast, systematic reviews provide a comparison among treatment options based on a standardized set of evaluation rules that anchor an analysis of otherwise diverse clinical trial data. The analysis is meant to place treatments into efficacy categories but not to rank them within that category. Systematic reviews are conceptualized to sit beside expert opinion, clinical experience, and other data sources as one of several tools for clinicians to use in treating their own patients by reaching their own decisions. No algorithm results from an EBM review, but instead a summary of the relative strength of data on efficacy, safety, and clinical usefulness for several treatment options. With EBM information categorized in a neutral context, treating clinicians are expected to exercise their own clinical judgment to effect integrative decision making and to develop a treatment plan that incorporates the patient's perceptions of impairment and disability.

Much closer in intent to our effort are the Cochrane reports[47] that also apply evidence-based methodology to provide reviews on numerous treatments, including some PD-related interventions. However, the Cochrane reports sometimes perform meta-analyses, which we have not applied and use more stringent entry criteria for study inclusion. We purposefully chose a broader approach to allow a wider scope and larger number of clinical papers for review, although, when evidence quality was weak, as reflected in low Quality Scores, we did not use them in our final conclusions. The authors of this current review participate in the Cochrane process with regard to PD treatments.

Acknowledgments: This study was reviewed and approved by the Scientific Issues Committee and International Executive Committee of the Movement Disorder Society.

REFERENCES

1. Sacket Dl, Straus S, Richardson S, Rosenber W, Haynes RB, editors. Evidence-based medicine: how to practice and teach EBM. 2nd ed. London: Churchill Livingstone; 2000.
2. Goetz CG, Koller WC, Poewe W, et al. Management of Parkinson's disease: an evidence-based review. Mov Disord 2002; 17(Suppl. 4)S1–S166.
3. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs. levodopa on Parkinson disease progression. JAMA 2002;287:1653–1661.
4. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. JAMA 2000;284:1931–1938.
5. Rakshi JS, Pavese N, Uema T, et al. A comparison of the progression of early Parkinson's disease in patients started on ropinirole or L-dopa: an 18F-dopa PET study. J Neural Transm 2002;109:1433–1443.
6. Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol 2003;54:93–101.
7. Djaldetti R, Inzelberg R, Giladi N, et al. Oral solution of levodopa ethylester for treatment of response fluctuations in patients with advanced Parkinson's disease. Mov Disord 2002; 17:297–302.
8. Myllyla VV, Kultalahti ER, Haapaniemi H, Leinonen M, FILOMEN Study Group. Twelve-month safety of entacapone in patients with Parkinson's disease. Eur J Neurol 2001;8:53–60.
9. Brooks DJ, Sagar H, UK-Irish Entacapone Study Group. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomized, placebo-controlled, double-blind, six month study. J Neurol Neurosurg Psychiatry 2003; 74:1071–1079.
10. Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M, Celomen Study Group. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). Acta Neurol Scand 2002; 105:245–255.
11. Fenelon G, Gimenez-Roldan S, Montastruc JL, et al. Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearin-off motor fluctuations. A randomized, double-blind, multicentre study. J Neural Transm 2003;110:239–251.
12. Shan DE, Lee SJ, Chao LY, Yeh SI. Gait analysis in advanced Parkinson's disease—effect of levodopa and tolcapone. Can J Neurol Sci 2001;28:70–75.
13. Koller W, Lees A, Doder M, Hely M, Tolcapone/Pergolide Study Group. Randomized trial of tolcapone versus pergolide as add-on to levodopa therapy in Parkinson's disease patients with motor fluctuations. Mov Disord 2001;16:858–866.
14. Caraceni T, Musicco M. Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomized multicenter study. Parkinsonism Relat Disord 2001;7:107–114.
15. Shoulson I, Oakes D, Fahn S, et al. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. Ann Neurol 2002;51:604–612.
16. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol 2002;59:1937–1943.
17. Mizuno Y, Yanagisawa N, Kuno S, et al. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. Mov Disord 2003;18:1149–1156.
18. Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y, on behalf of the Parkinson's disease research group on the United Kingdom. Ten-year follow-up of three different initial treatments in de-novo PD. A randomized trial. Neurology 2001;57:1687–1694.
19. Montastruc JL, Desboeuf K, Lapeyre-Mestre M, Senard JM, Rascol O, Brefel-Courbon C. Long-term mortality results on the randomized controlled study comparing bromocriptine to which levodopa was later added with levodopa alone in previously untreated patients with Parkinson's disease. Mov Disord 2001; 16:511–514.
20. Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004;363:1179–1183.
21. Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial on subcutaneously injected apomorphine for parkinsonian Off-state events. Arch Neurol 2001; 58:1385–1392.
22. Ziegler M, Castro-Caldas A, Del Signore S, Rascol O. Efficacy of piribedil as early combination to levodopa in patients with stable Parkinson's disease: a 6-month, randomized placebo-controlled study. Mov Disord 2003;18:418–425.
23. Pogarell O, Gasser T, Van Hilten JJ, et al. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomized, double-blind, placebo-controlled multicentre trial. J Neurol Neurosurg Psychiatry 2002;72:713–720.
24. Wong KS, Lu C-S, Shan D-E, et al. Efficacy, safety, and tolerability of pramipexole in untreated and levodopa-treated patients with Parkinson's disease. J Neurol Sci 2003;216: 81–87.
25. Brunt ER, Brooks DJ, Korczyn AD, Montastruc JL, Stocchi F, on behalf of the 043 study group. A six-month multicentre, double-blind, bromocriptine-controlled study of the safety and efficacy of ropinirole in the treatment of patients with Parkinson's disease not optimally controlled by L-dopa. J Neural Transm 2002;109:489–502.
26. Im JH, Ha JH, Cho IS, Lee MC. Ropinirole as an adjunct to levodopa in the treatment of Parkinson's disease. A 16-week bromocriptine controlled study. J Neurol 2003;250:90–96.
27. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian movement disorders group. JAMA 2002;287:455–463.
28. Hogl B, Seppi K, Brandauer E, et al. Increased daytime sleepiness in Parkinson's disease: a questionnaire survey. Mov Disord 2003; 18:319–323.
29. Paus S, Brecht HM, Koster J, Seeger G, Klockgether T, Wullner U. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. Mov Disord 2003;18:659–667.
30. Razmy A, Lang AE, Shapiro CM. Predictors of imparierd daytime sleep and wakefulness in patients with Parkinon disease treated with older (ergot) vs newer (nonergot) dopamine agonists. Arch Neurol 2004;61:97–102.
31. Etminan M, Samii A, Takkouche B, Rochon P. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease. A meta-analysis of randomised controlled trials. Drug Safety 2001;24:863–868.
32. Del Dotto PK Pavese N, Gambaccini G, et al. Intravenous amantadine improves levodopa-induced dyskinesias: an acute double-blind placebo-controlled study. Mov Disord 2001;16: 515–520.
33. Thomas A, Iacono D, Luciano AL, et al. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:141–143.
34. Perry EK, Kilford L, Lees AJ, et al. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. Ann Neurol 2003;54:235–238.
35. Vitek JL, Bakay RAE, Freeman A, et al. Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. Ann Neurol 2003;53:558–569.

36. Esselink RAJ, de Bie EMA, de Haan RJ, et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD. Neurology 2004;62:201–207.
37. Gironell A, Kulisevsky J, Rami L. Effects of pallidotomy and bilateral subthalamic stimulation on cognitive function in Parkinson's disease. J Neurol 2003;250:917–923.
38. Green J, McDonald WM, Vitek JL, et al. Neuropsychological and psychiatric sequelae of pallidotomy for PD. Neurology 2002;58: 858–865.
39. Katayama Y, Kasai M, Oshima H, et al. Subthalamic nucleus stimulation for Parkinson's disease: benefits observed in levodopa-intolerant patients. J Neurosurg 2001;95:213–221.
40. Østergaard K, Sunde N, Dupont E. Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. Mov Disord 2002;17: 693–700.
41. Funkiewicz A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834–839.
42. Doshi PK, Chhaya N, Bhatt MH. Depression leading to attempted suicide after bilateral subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 2002;17:1084–1085.
43. Olanow CW, Goetz CG, Kordower JH, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003;54:403–414.
44. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons on severe Parkinson's disease. N Engl J Med 2001;344:710–719.
45. Trott CT, Fahn S, Greene P, et al. Cognition following bilateral implants of embryonic dopamine neurons in PD. Neurology 2003; 60:1938–1943.
46. Olanow CW, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines from the American Academy of Neurology. Neurology 1988;50(Suppl. 3): S1–S57.
47. Katzenschlager R, Sampaio C, Costa J, et al. Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database Syst Rev 2003;2:CD003735.