

# International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease

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**ABSTRACT: Objective:** The objective of this review was to update evidence-based medicine recommendations for treating motor symptoms of Parkinson's disease (PD).

**Background:** The Movement Disorder Society Evidence-Based Medicine Committee recommendations for treatments of PD were first published in 2002 and updated in 2011, and we continued the review to December 31, 2016.

**Methods:** Level I studies of interventions for motor symptoms were reviewed. Criteria for inclusion and quality scoring were as previously reported. Five clinical indications were considered, and conclusions regarding the implications for clinical practice are reported.

**Results:** A total of 143 new studies qualified. There are no clinically useful interventions to prevent/delay disease progression. For monotherapy of early PD, nonergot dopamine agonists, oral levodopa preparations, selegiline, and rasagiline are clinically useful. For adjunct therapy in early/stable PD, nonergot dopamine agonists, rasagiline, and zonisamide are clinically useful. For adjunct therapy in optimized PD for general or specific motor symptoms including gait, rivastigmine is possibly useful and physiotherapy is clinically useful; exercise-based movement strategy training and formalized

patterned exercises are possibly useful. There are no new studies and no changes in the conclusions for the prevention/delay of motor complications. For treating motor fluctuations, most nonergot dopamine agonists, pergolide, levodopa ER, levodopa intestinal infusion, entacapone, opicapone, rasagiline, zonisamide, safinamide, and bilateral STN and GPi DBS are clinically useful. For dyskinesia, amantadine, clozapine, and bilateral STN DBS and GPi DBS are clinically useful.

**Conclusions:** The options for treating PD symptoms continues to expand. These recommendations allow the treating physician to determine which intervention to recommend to an individual patient. © 2018 International Parkinson and Movement Disorder Society

**Key Words:** Parkinson's disease; evidence-based medicine; randomized controlled trial; 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; complementary therapies

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The number of interventions for treating motor symptoms in PD continues to expand. Evidence-based medicine (EBM) recommendations are designed to assist a treating physician in deciding which intervention to use in an individual PD patient. The International Parkinson and Movement Disorder Society (MDS) EBM Committee has published recommendations on treating PD symptoms since 2002.<sup>1,2</sup> These recommendations have also been used to develop regional or national guidelines, reflecting local availability of interventions.<sup>3-8</sup>

## Methods

The previous MDS EBM publication<sup>9</sup> reviewed studies from January 2004 to December 2010 and updated earlier EBM reviews.<sup>1,2</sup> We have continued the process and included new studies published up to December 31, 2016 (summary updates were posted on the MDS website).<sup>10</sup> Studies were also included if “in press” or in “early view status” at the time of the literature search. If new therapeutics not previously reviewed in prior EBM publications were identified, further searches were made retrospectively to include all appropriate studies.

The methodology has been refined since the original review,<sup>1</sup> where studies with less than level I data were also included. The subsequent EBM reviews have used a standard method using literature searches performed using electronic databases (Medline, Cochrane Library) and systematic checking of references from review articles and other reports. Inclusion criteria included pharmacological, surgical, and other therapies commercially available in at least 1 country, assessed using level I, randomized controlled trial (RCT) methodology and where motor symptoms were the primary endpoint measured with an established rating scale or well-described outcome. The included studies had to have a minimum of 20 patients who were treated for a minimum of 4 weeks.

Each study was rated by at least 2 committee members using the Rating Scale for Quality of Evidence<sup>11</sup> that assigns a percentage rating to the study based on the number of applicable quality criteria fulfilled. Thus, for a study to be designated high quality, it must achieve a quality score of 75% or greater. Each intervention was then assigned an efficacy conclusion—efficacious, likely efficacious, unlikely efficacious, nonefficacious, or insufficient evidence—according to the level of evidence (Supplementary Table e1). Safety was assessed and assigned as one of the following: acceptable risk with no specialized monitoring, acceptable risk with specialized monitoring, unacceptable, or insufficient evidence. The overall implications for clinical practice were then assessed and classed as clinically useful, possibly useful, unlikely useful, not useful, or investigational. In this article, we use the terms *negative* and *positive* when

referring to adequately powered trials designed to test a well-specified statistical hypothesis; we understand “positive” to signify a trial where the primary endpoint was met at the defined level of significance and “negative” to signify a trial that failed to meet the pre-defined primary endpoint.

Interventions were considered for the following 5 clinical indications:

1. Prevention/delay of disease progression
2. Symptomatic monotherapy
3. Symptomatic adjunct therapy to levodopa:
  - a. in early or stable PD
  - b. in PD patients optimized on treatment for specific or general motor symptoms
4. Prevention/delay of motor complications (motor fluctuations and dyskinesia)
5. Treatment of motor complications (motor fluctuations and dyskinesia).

## Results and Conclusions

A total of 143 new studies were reviewed (77 articles were excluded after careful review). The article is organized according to the 5 clinical indications and further subdivided into types of intervention. The efficacy; safety conclusions, and the implications for clinical practice are summarized in Tables 1 to 5. In all tables, interventions where new studies have been published since January 2011 or prior to this date in the case of newly identified interventions not previously reviewed are indicated in bold, and changes in conclusions are italicized. Individual trial details and quality scores appear in the Supporting Information as Tables e2S to e11.

### Treatments that Prevent/Delay Disease Progression in PD

#### ***New Conclusions***

A total of 11 new studies were assessed. The descriptions of the trials and the quality scores are summarized in Supporting Information Table e2. Table 1 outlines the intervention, efficacy and safety conclusions, and implications for clinical practice. Unless otherwise stated, the safety conclusion is “acceptable risk without specialized monitoring.”

**Dopamine Agonists.** One new high-quality but negative study<sup>12</sup> evaluated the dopamine agonist (DA) pramipexole. There were no new studies evaluating pergolide. However, safety issues (including cardiac fibrosis) related to ergot DAs mean that the safety conclusion remains “acceptable risk with specialized monitoring,” and the implication for practice changes to “not useful.”

**Monoamine Oxidase B Inhibitors (MAO-B Inhibitors).** There were no new studies evaluating selegiline or rasagiline, and the conclusions remain unchanged,

TABLE 1. Treatments that prevent/delay disease progression

Intervention	Drug	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Dopamine agonists	Ropinirole	Insufficient evidence	Acceptable risk with specialized monitoring	Investigational <i>Not useful</i> <i>Not useful</i>
	<b>Pramipexole</b>	<i>Nonefficacious</i>		
	Pergolide	Unlikely efficacious		
Levodopa/peripheral decarboxylase inhibitor	Standard IR formulation	Insufficient evidence		Investigational
MAO-B inhibitors	Selegiline	Insufficient evidence		Investigational
	Rasagiline	Insufficient evidence		Investigational
Supplements	<b>Coenzyme Q<sub>10</sub></b>	<i>Nonefficacious</i>		<i>Not useful</i>
	<b>Creatine</b>	<i>Nonefficacious</i>		<i>Not useful</i>
	<b>Vitamin D</b>	<i>Insufficient evidence</i>		<i>Investigational</i>
	<b>Exercise</b>	<i>Insufficient evidence</i>		<i>Investigational</i>

MAO-B, monoamine oxidase B.

**Bolded** text indicates interventions where **new studies** have been published since January 2011, or prior to this date in the case of newly identified interventions not previously reviewed; *Italicized* indicates *changes in conclusions* since last publication.

<sup>a</sup>Unless otherwise stated, the conclusion for safety is acceptable risk without specialized monitoring.

that is, insufficient evidence and investigational. The 3-year, open-label, follow-up (but with a delay after the end of the original trial) of the early use of rasagiline trial (ADAGIO)<sup>13</sup> had no new safety data; thus the safety conclusion remains unchanged.

**Supplements.** Studies evaluating a number of supplements that had not been included in the earlier EBM publications were reviewed. Coenzyme Q<sub>10</sub> was evaluated in four studies using a variety of doses. There were 2 negative high-quality studies,<sup>14,15</sup> 1 overall negative low-quality study,<sup>16</sup> and 1 low-quality study<sup>17</sup> that was possibly positive; thus the efficacy conclusion is “nonefficacious” and the practice implication is that coenzyme Q<sub>10</sub> is “not useful.”

**Creatine.** Creatine has been evaluated in 1 high-quality study<sup>18</sup> and 1 low-quality study<sup>19</sup> with negative outcomes; the efficacy conclusion is “nonefficacious”, and the practice implication is “not useful.” One new study using vitamin D had unclear conclusions<sup>20</sup>; thus the efficacy conclusion is “insufficient evidence” and the practice implication is “investigational.” There are no safety concerns with any of the aforementioned supplements.

**Exercise.** Two new studies evaluated exercise as an intervention for disease progression in early PD.<sup>21,22</sup> Both studies were low quality, and the efficacy conclusion is thus “insufficient evidence” and the practice implication is “investigational.” There are no safety concerns with these reported exercise programs.

## Treatments for Symptomatic Monotherapy

### **New Conclusions for Symptomatic Monotherapy of PD**

A total of 8 new studies were evaluated (see Table 2). Study descriptions and quality scores are in Supporting Information Table e3.

**Dopamine Agonists.** New positive studies evaluated pramipexole immediate release (IR)<sup>23</sup> and pramipexole extended release (ER),<sup>24</sup> and the practice implication remains “clinically useful.” An extension study using pramipexole ER<sup>25</sup> reported no new safety concerns. A total of 2 new positive studies evaluating rotigotine<sup>26,27</sup> also confirmed the practice implication of “clinically useful.” There are no new safety concerns with any of these drug preparations.

**Levodopa Preparations.** Levodopa IR was compared to MAO-B inhibitors (as a group) or DAs (as a group; PD MED).<sup>28</sup> All 3 groups were effective; thus levodopa IR remains “clinically useful” as monotherapy. The new ER preparation of levodopa (IPX066; levodopa ER) was evaluated<sup>29</sup> and was efficacious with a practice implication of “clinically useful.” No safety concerns were noted.

**Other Pharmacological Targets.** The adenosine A<sub>2A</sub> antagonist istradefylline is commercially available in Japan for adjunct therapy (see the Treatments for Motor Complications [Fluctuations and Dyskinesia] section) and was thus included in this review; 1 high-quality RCT in early PD<sup>30</sup> did not show efficacy and thus the practice implication is that it is clinically “not useful.”

## Symptomatic Adjunct Therapy

### **Results**

Interventions for adjunct therapy for motor symptoms of PD were subdivided into adjunct for earlier or stable PD patients, whereas a second category reviewed adjunct therapies for general or specific motor PD symptoms, including tremor, gait and balance, and speech, in PD patients optimized on treatment (see Tables 3a and 3b).

**TABLE 2.** Treatments for symptomatic monotherapy

Intervention	Drug	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Dopamine agonists Nonergot	Pramipexole IR	Efficacious		Clinically useful
	Pramipexole ER	Efficacious		Clinically useful
	Rotigotine	Efficacious		Clinically useful
	Piribedil	Efficacious		Clinically useful
	Ropinirole IR	Efficacious		Clinically useful
	Ropinirole PR	Likely efficacious		Possibly useful
Ergot	Cabergoline	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	DHEC	Efficacious		Clinically useful
	Pergolide	Efficacious		Clinically useful
	Bromocriptine	Likely efficacious		Possibly useful
Levodopa/peripheral decarboxylase inhibitor	Standard (IR) formulation	Efficacious		Clinically useful
	Controlled release (CR)	Efficacious		Clinically useful
	Extended release	<i>Efficacious</i>		<i>Clinically useful</i>
MAO-B inhibitors	Selegiline	Efficacious		Clinically useful
	Rasagiline	Efficacious		Clinically useful
Others	Anticholinergics	Likely efficacious		Clinically useful
	Amantadine	Likely efficacious		Possibly useful
Adenosine A <sub>2A</sub> antagonist	Istradefylline	<i>Nonefficacious</i>		<i>Not Useful</i>

DHEC, dihydroergocryptine; MAO-B, monoamine oxidase B; IR, immediate release; PR, prolonged release; ER, extended release; CR, controlled release; s.c., subcutaneous.  
**Bolded** text indicates interventions where **new studies** have been published since January 2011, or prior to this date in the case of newly identified interventions not previously reviewed; *Italicized* indicates *changes in conclusions* since last publication.  
<sup>a</sup>Unless otherwise stated, the conclusion for safety is acceptable risk without specialized monitoring.

**New Conclusions for Symptomatic Adjunct Therapy to Levodopa in Early or Stable PD Patients**

A total of 4 new studies were evaluated. See the Supporting Information for study descriptions and quality scores (Supporting Information Table e4).

**Dopamine Agonists.** Pramipexole ER was evaluated in 1 new high-quality positive study in a mixed

population of PD that included stable patients without fluctuations but “undertreated” with levodopa,<sup>31</sup> with the practice implication of “clinically useful.”

**COMT Inhibitors.** There were no new studies using COMT-inhibitors in nonfluctuating PD patients. As a result of issues related to safety (potential for liver toxicity), the practice implication for tolcapone has been revised to “unlikely useful.”

**TABLE 3a.** Treatments for symptomatic adjunct therapy in early or stable PD patients

Class	Intervention	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Dopamine agonists Nonergot	Piribedil	Efficacious		Clinically useful
	Pramipexole IR	Efficacious		Clinically useful
	Pramipexole ER	<i>Efficacious</i>		<i>Clinically useful</i>
	Ropinirole IR	Efficacious		Clinically useful
Ergot	Rotigotine	Efficacious		Clinically useful
	Bromocriptine	Likely efficacious	Acceptable risk with specialized monitoring	Possibly useful
COMT inhibitors	Entacapone	Nonefficacious		
	Tolcapone	Efficacious	Acceptable risk with specialized monitoring	<i>Unlikely useful</i>
MAO-B inhibitors	Selegiline	Insufficient evidence		
	Rasagiline	Efficacious		Clinically useful
MAO-B inhibitor plus Channel blockers	Zonisamide	Efficacious		Clinically useful
	Safinamide	<i>Nonefficacious</i>		<i>Not useful</i>
Others	Anticholinergics	Likely efficacious		Clinically useful
	Amantadine	Likely efficacious		Possibly useful
Surgery	Bilateral STN DBS	<i>Insufficient evidence</i>	Acceptable risk with specialized monitoring	<i>Investigational</i>

COMT, catechol-O-methyl transferase; MAO-B, monoamine oxidase B; IR, immediate release; ER, extended release.  
**Bolded** text indicates interventions where **new studies** have been published since January 2011, or prior to this date in the case of newly identified interventions not previously reviewed; *Italicized* indicates *changes in conclusions* since last publication.  
<sup>a</sup>Unless otherwise stated, the conclusion for safety is acceptable risk without specialized monitoring.

**TABLE 3b.** Adjunct therapies for specific or general motor symptoms in PD patients optimized on treatment

Symptom	Intervention	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Drugs for gait and balance	Donepezil	<i>Insufficient evidence</i>		<i>Investigational</i>
	Rivastigmine	<i>Likely efficacious</i>		<i>Possibly useful</i>
	Methylphenidate	<i>Insufficient evidence</i>		<i>Investigational</i>
	Memantine	<i>Insufficient evidence</i>		<i>Investigational</i>
	Cannabidiol	<i>Insufficient evidence</i>		<i>Investigational</i>
Interventions for general motor symptoms	Bee venom	<i>Nonefficacious</i>		<i>Not useful</i>
	Physiotherapy	<i>Likely efficacious</i>		<i>Clinically useful</i>
	Movement strategy–exercise based	<i>Insufficient evidence</i>		<i>Possibly useful</i>
	Movement strategy–technology based	<i>Insufficient evidence</i>		<i>Investigational</i>
	Formalized patterned exercises	<i>Insufficient evidence</i>		<i>Possibly useful</i>
	Speech therapy	Insufficient evidence for speech <i>Insufficient evidence for swallowing problems</i>		Possibly useful (overall)
	Occupational therapy	<i>Insufficient evidence</i>		Possibly useful
	Acupuncture	Insufficient evidence		Investigational
	Repetitive Transcranial Magnetic Stimulation (rTMS)	<i>Insufficient evidence</i>		<i>Investigational</i>
	tDirect Current Stimulation (tDCS)	<i>Insufficient evidence</i>		<i>Investigational</i>
Interventions for tremor	Unilateral thalamotomy	Likely efficacious	Acceptable risk with specialized monitoring	Possibly useful
	Thalamic stimulation (uni or bilateral)	Likely efficacious		Possibly useful

**MAOB Inhibitors.** Rasagiline was evaluated in 1 high-quality positive study as an adjunct to DA in early PD<sup>32</sup> with the practice implication remaining “clinically useful.”

There was 1 new study evaluating the mixed MAOB inhibitor and channel blocker with glutamate release inhibition, safinamide as an adjunct to DAs in early PD.<sup>33</sup> The conclusion is “nonefficacious” and “not useful” in PD without motor fluctuations. There are no safety concerns.

**Early Bilateral Subthalamic Nucleus Deep Brain Stimulation.** Early PD patients without motor complications with less than 4 years of disease duration were treated with bilateral subthalamic nucleus

(STN) deep brain stimulation (DBS) in 1 new study.<sup>34</sup> The primary outcome was safety, and as such the efficacy conclusion for early PD is “insufficient evidence” and the practice implication is that early STN DBS is “investigational.” The safety conclusion is “acceptable risk with specialized monitoring.”

#### **New Conclusions for Adjunct Therapies for Specific or General Motor Symptoms in PD Patients Optimized on Treatment**

**Pharmacological Interventions.** A total of 6 studies were evaluated (Supporting Information Table e5).

**TABLE 4.** Treatments to prevent/delay motor fluctuations (F) or dyskinesia (D)

Class	Intervention	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Dopamine agonists	Pramipexole IR	Efficacious (F, D)		Clinically useful (F, D)
	Ropinirole IR	Efficacious (D) <i>Insufficient evidence</i> (F)		Clinically useful (D) Investigational (F)
Ergot	Cabergoline	Efficacious (F,D)	Acceptable risk with specialized monitoring	Clinically useful (F,D)
	Bromocriptine	Likely efficacious (D) <i>Insufficient evidence</i> (F)		Possibly useful (D) Investigational (F)
	Pergolide	Likely efficacious (D) <i>Insufficient evidence</i> (F)		Possibly useful (D) Investigational (F)
COMT inhibitors	Entacapone	Nonefficacious (F,D)		Not useful (F,D)
MAO-B inhibitors	Selegiline	Nonefficacious (D) <i>Insufficient evidence</i> (F)		Not useful (D) Investigational (F)

COMT, catechol-O-methyl transferase; MAO-B, monoamine oxidase B; IR, immediate release.

**Bolded** text indicates interventions where **new studies** have been published since January 2011, or prior to this date in the case of newly identified interventions not previously reviewed; *Italicized* indicates *changes in conclusions* since last publication.

<sup>a</sup>Unless otherwise stated, the conclusion for safety is acceptable risk without specialized monitoring.



**TABLE 5a.** Treatments for motor fluctuations

Class	Intervention	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Dopamine agonists Nonergot	Pramipexole IR	Efficacious		Clinically useful
	Pramipexole ER	<i>Efficacious</i>		<i>Clinically useful</i>
	Ropinirole	Efficacious		Clinically useful
	Ropinirole PR	Efficacious		Clinically useful
	Rotigotine	Efficacious		Clinically useful
	Apomorphine	Efficacious		Clinically useful
	Intermittent s.c. Apomorphine infusion	Likely efficacious	Acceptable risk with specialized monitoring	Possibly Useful
	Piribedil	Insufficient evidence		Investigational
Ergot	Pergolide	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Bromocriptine	Likely efficacious		Possibly useful
	Cabergoline	Likely efficacious		Possibly useful
	DHEC	Insufficient evidence		Investigational
Levodopa/peripheral decarboxylase inhibitor	Standard formulation	Efficacious		Clinically useful
	Controlled release	Insufficient evidence		Investigational
	Rapid onset	Insufficient evidence		Investigational
	Extended release	<i>Efficacious</i>		<i>Clinically useful</i>
	Intestinal Infusion	<i>Efficacious</i>	<i>Acceptable risk with specialized monitoring</i>	<i>Clinically useful</i>
COMT inhibitors	Entacapone	Efficacious		Clinically useful
	Tolcapone	Efficacious	Acceptable risk with specialized monitoring	Possibly useful
MAO-B inhibitors	Opicapone	<i>Efficacious</i>		<i>Clinically useful</i>
	Rasagiline	Efficacious		Clinically useful
	Selegiline	Insufficient evidence		Investigational
	Oral disintegrating selegiline	Insufficient evidence		Investigational
MAO-B inhibitor plus Channel blockers	Zonisamide	<i>Efficacious</i>		<i>Clinically useful</i>
	<i>Safinamide</i>	<i>Efficacious</i>		<i>Clinically useful</i>
Others	<i>Istradefylline</i>	<i>Likely efficacious</i>		<i>Possibly useful</i>
	Amantadine	Insufficient evidence		Investigational
Surgery	Bilateral STN DBS	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Bilateral GPi DBS	Efficacious		Clinically useful
	Unilateral pallidotomy	Efficacious		Clinically useful
	Unilateral thalamotomy	Insufficient evidence		Investigational
	Thalamic stimulation (uni or bilateral)	Insufficient evidence		Investigational
	Subthalamotomy	Insufficient evidence		Investigational
	Human fetal transplantation	Nonefficacious	Unacceptable risk	Investigational

DHEC, dihydroergocryptine; MAO-B, monoamine oxidase B; IR, immediate release; PR, prolonged release; ER, extended release; CR, controlled release; s.c., subcutaneous.

**Bolded** text indicates interventions where **new studies** have been published since January 2011, or prior to this date in the case of newly identified interventions not previously reviewed; *Italicized* indicates *changes in conclusions* since last publication.

<sup>a</sup>Unless otherwise stated, the conclusion for safety is acceptable risk without specialized monitoring.

Donepezil was assessed in 1 positive study<sup>35</sup> with a reduction in the number of falls, but because of the lower quality of the evidence, the efficacy conclusion is “insufficient evidence” and the practice implication is “investigational” for gait problems.

Rivastigmine was assessed in a high-quality study<sup>36</sup> with a positive primary outcome of improved step-time variability and a secondary outcome of falls reduction, but because of the unclear clinical importance of the primary measure, the efficacy conclusion is “likely efficacious” with the practice implication is “possibly useful.” There are no safety concerns.

Methylphenidate was assessed in 2 studies, but as a result of conflicting data (1 positive, but in a highly

selected cohort of post-STN-DBS patients,<sup>37</sup> and 1 negative study),<sup>38</sup> there is “insufficient evidence.” There are no safety concerns, and the implications for clinical practice are “investigational” for PD patients with gait problems.

Memantine was evaluated in 1 low-quality study<sup>39</sup>; there was no effect on gait (stride length), and the efficacy conclusion is “insufficient evidence” with a clinical practice implication of “investigational” for treating gait disorders in PD. There are no safety concerns.

Cannabidiol had no significant effects on any of the outcome measures in 1 low-quality study<sup>40</sup>; thus the efficacy outcome is “insufficient evidence,” and

TABLE 5b. Treatments for dyskinesia

Class	Intervention	Efficacy conclusions	Safety <sup>a</sup>	Implications for clinical practice
Dopamine agonists Levodopa/peripheral decarboxylase inhibitor Others	Pramipexole	Insufficient evidence		Investigational
	Intestinal infusion	Likely efficacious	Acceptable risk with specialized monitoring	<i>Clinically useful</i>
	Amantadine Clozapine	Efficacious Efficacious	Acceptable risk with specialized monitoring	Clinically useful Clinically useful
Surgery	Zonisamide	Insufficient evidence		Investigational
	Levetiracetam	<i>Insufficient evidence</i>		<i>Investigational</i>
	Bilateral STN DBS	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Bilateral GPI DBS	Efficacious		Clinically useful
	Unilateral pallidotomy	Efficacious		Clinically useful
	Unilateral thalamotomy	Insufficient evidence		Investigational
	Thalamic stimulation (uni or bilateral) Subthalamotomy	Insufficient evidence Insufficient evidence		Investigational Investigational
Human fetal transplantation	Nonefficacious	Unacceptable risk	Investigational	
Nonpharmacological	Physical therapy	<i>Insufficient evidence</i>		<i>Investigational</i>

because of the single study with a short duration and small sample size, the implication for clinical practice is “investigational.”

**Non-Pharmacological Interventions.** A range of activity-related interventions were evaluated in 64 new studies. In keeping with the prior review, the following 3 groups have been delineated to categorize the methods of intervention: (1) physiotherapy, (2) movement strategy training that is subdivided into (2a) exercise-based and (2b) technology-based falls prevention, and (3) formalized patterned exercises.

1. **Physiotherapy studies.** A total of 31 new studies were reviewed (Supporting Information Table e6). These included a range of physiotherapy techniques including treadmill, aerobic, strengthening, and stretching exercises. The results are summarized in order of quality with statistical significance versus active comparator, followed by both interventions showing positive outcomes versus baseline.

High-quality studies with positive outcomes versus active comparator included studies comparing 2 interventions i.e. multidisciplinary in-patient physiotherapy (PT) versus “regular” PT,<sup>41</sup> treadmill versus stretching,<sup>42</sup> and progressive resistance exercising versus modified fitness<sup>43</sup> and were significantly positive when compared with baseline and the other intervention. Lower quality studies, but with an overall positive outcome of first intervention versus active comparator, included intensive inpatient PT versus home-based PT,<sup>44</sup> partially weighted treadmill versus conventional gait training,<sup>45</sup> hydrotherapy versus land based,<sup>46</sup> individual versus group-based PT,<sup>47</sup> and balance training versus resistance training.<sup>48</sup> The remaining lower quality studies compared 2 interventions (a mixture of treadmill-based exercises and aerobics and resistance/strengthening exercises; water-based physiotherapy or usual physical activity), and both interventions were

generally positive with improvements when compared with baseline in both groups but not compared to each other.<sup>49-65</sup> Studies in which there was no active intervention or unclear final statistical analysis were all low quality, and therefore the interpretation of outcomes was limited.<sup>66-69</sup>

Overall, although the 3 high-quality level I studies that compared 2 interventions had 1 positive outcome in 1 type of PT compared to another, none had a best medical therapy/control group; thus the overall conclusion is “likely efficacious.” Because of the generally overall positive outcomes in all PT studies, the conclusion for clinical practice is “clinically useful.”

2a. **Movement strategy training—exercise based.** A total of 11 new studies were reviewed (Supporting Information Table e7). This group included exercise-based techniques such as cueing (with some use of treadmill) as a means of reducing falls in PD. There was 1 high-quality study using balance and strength training “minimally supervised” exercises versus “usual-care,” but was negative for falls prevention.<sup>70</sup>

Lower quality studies, but with overall positive outcome of first intervention versus active comparator on reducing falls included a “highly challenging balance program,”<sup>71</sup> balance training with dual tasking training versus arm exercises,<sup>72</sup> and a “global postural education” method versus no intervention.<sup>58</sup> Lower quality studies with overall positive outcomes with both interventions included PT plus mental imagery or relaxation<sup>73</sup> and visual step training with cues versus leg strength exercise.<sup>74</sup>

Interventions that evaluated change in spinal posture directly as a primary outcome included low-quality studies that were either positive for 1 intervention including “perceptive rehabilitation” versus conventional rehabilitation<sup>75</sup> or both interventions, static and dynamic balance training with/without attentional-

focus training,<sup>76</sup> or postural rehabilitation with/without back taping for posture.<sup>77</sup>

Overall, these movement strategy training studies using exercise techniques had mixed outcomes, with 1 high-quality negative study and 1 lower quality positive study, leading to an overall efficacy conclusion of “insufficient evidence” for exercise strategies (noting the variable interventions). However, as the majority of studies were generally positive, the implication for clinical practice is “possibly useful”.

**2b. Movement strategy training—technology-based interventions.** A total of 12 new studies were reviewed (Supporting Information Table e7). A range of technology-based interventions were used for movement strategy training. One high-quality study evaluated virtual reality combined with treadmill training that reduced falls when compared with treadmill alone.<sup>78</sup> A lower quality study using a gamepad with avatar was positive compared to physiotherapy.<sup>79</sup> A lower quality study evaluating a home virtual reality device versus home conventional balance exercises was positive in both groups.<sup>80</sup> In contrast, 2 high-quality studies were negative; 1 using an avatar versus conventional balance training for balance<sup>81</sup> and 1 evaluating robotic gait training versus balance training.<sup>82,83</sup>

Other technologies that were evaluated included the use of a Nintendo Wii versus balance exercises,<sup>84</sup> smartphone biofeedback<sup>85</sup> and a gamepad—“dancing software,”<sup>86</sup> vibratory devices added to shoes<sup>87</sup> with overall positive outcomes in both groups, but all were lower quality studies. Studies in which there was no active intervention and where participants received the usual medical therapy as a comparator or where there was unclear final statistical analysis were all low-quality, and therefore the interpretations of outcome conclusions were limited.<sup>88,89</sup>

Overall, because of the conflicting outcomes (even allowing for variable techniques), there is “insufficient evidence” for technology-based movement strategies, and the implication for clinical practice is “investigational.”

**3. Formalized patterned exercise studies.** A total of 9 new studies were reviewed (Supporting Information Table e8). Tai chi has been evaluated in 2 high-quality studies with conflicting results.<sup>90,91</sup> A low-quality study evaluated tai chi versus qi-gong with negative outcomes in both groups.<sup>92</sup> Two positive but low-quality studies reported by the same group evaluated power yoga.<sup>93,94</sup> Dance has also been used as an intervention, and although outcomes are positive compared to the active comparator for a variety of dance modalities including tango and Irish dancing, the studies are low quality.<sup>95-98</sup> One low-quality study evaluating tango versus normal exercise was negative.<sup>99</sup> Studies evaluating formalized patterned exercises had variable outcomes, and the efficacy conclusion is thus

“insufficient evidence”; however, the implication for clinical practice is “possibly useful.”

Overall, there are no safety concerns with the aforementioned interventions, and the conclusions for all interventions above are “acceptable risk without specialized monitoring.” However, increased falls as a result of participation was noted in some studies (Supporting Information Tables e6-e8), and caution may be needed with some at risk individuals with certain physical therapy interventions. Further work is needed to clarify this.

**Other Nonpharmacological Interventions.** A total of 9 new studies were reviewed (Supporting Information Table e9).

Occupational therapy was evaluated in 2 new high-quality but conflicting outcome studies; thus 1 showed positive outcomes at 3 months but not at 6 months,<sup>100</sup> and another was negative at 3 months.<sup>101</sup> The efficacy conclusion is “insufficient evidence,” but the implication for clinical practice remains as “possibly useful.”

One new low-quality study using video-assisted swallowing therapy for swallowing issues in PD was positive versus conventional therapy.<sup>102</sup> There were no new studies for speech issues. The overall efficacy conclusion remains “insufficient evidence,” and the implication for clinical practice remains as “possibly useful.”

Repetitive transcranial magnetic stimulation (rTMS) was evaluated in 3 new studies for PD motor symptoms. Two were positive versus sham,<sup>103,104</sup> whereas 1 was positive in all interventions including sham.<sup>105</sup> All were low quality, and because of the conflicting data the efficacy outcome is “insufficient evidence,” and the implication for clinical practice is “investigational.”

Transcranial direct current stimulation (tDCS) was evaluated in 1 low-quality trial for PD motor symptoms.<sup>106</sup> Both groups (receiving active tDCS and sham tDCS) were positive when compared with baseline without a significant difference between them. Thus the conclusion is “insufficient evidence,” and the implication for clinical practice is “investigational.”

One new study<sup>107</sup> was reviewed but because of the low-quality score and the additional use of bee venom as an intervention, the efficacy conclusion remains as “insufficient evidence” and “investigational” for clinical practice. Bee venom alone versus placebo was evaluated in 1 new high-quality negative study.<sup>108</sup> Thus the designation is “nonefficacious” and clinically “not useful.”

There are no safety concerns with the aforementioned interventions, and the conclusions for all interventions are “acceptable risk without specialized monitoring.”

### Treatments to Prevent/Delay Motor Fluctuations or Dyskinesia

There were no new studies (Table 4).



### **Conclusions for New Treatments to Prevent/Delay Motor Fluctuations or Dyskinesia**

The previous conclusions remain unchanged.

#### **Treatments for Motor Complications (Fluctuations and Dyskinesia)**

##### **New Conclusions for Treatments for Motor Fluctuations**

A total of 36 new studies were reviewed (Supporting Information Table e10).

**Dopamine Agonists.** High-quality studies reported positive outcomes for pramipexole ER,<sup>31,109</sup> pramipexole IR, ropinirole IR, rotigotine,<sup>110</sup> and ropinirole PR<sup>111</sup> with conclusions of “efficacious” and “clinically useful” for all. Ropinirole PR<sup>112</sup> and rotigotine<sup>27,113</sup> (see earlier) were evaluated in open-label extension studies of prior double-blind RCTs; the quality of these studies was not scored, but they were considered for new safety issues, of which none were reported.

**Levodopa Preparations.** Two new high-quality positive studies evaluated the new levodopa preparation, levodopa ER. One study compared levodopa ER to levodopa/carbidopa IR,<sup>114</sup> whereas the second compared levodopa ER to levodopa/carbidopa IR/entacapone;<sup>115</sup> both improved OFF time, and the conclusions are thus “efficacious” and “clinically useful.” There are no safety concerns.

One new high-quality study evaluated levodopa-carbidopa intestinal gel infusion,<sup>116</sup> which is “efficacious” and with the new implication that it is “clinically useful.” Because of the possibility of device-related complications, the safety conclusion is changed to “acceptable risk with specialized monitoring.”

**COMT Inhibitors.** A total of 3 high-quality positive studies,<sup>117-119</sup> evaluated entacapone, with the conclusions remaining as “efficacious” and “clinically useful.” There were no new safety concerns. There were no new studies evaluating tolcapone, and the conclusion remains unchanged. Opicapone, a new COMT inhibitor, was evaluated in 2 high-quality positive efficacy studies<sup>119,120</sup> and 1 high-quality pharmacokinetic study but with motor outcomes.<sup>121</sup> The conclusion is thus “efficacious,” and the implication for clinical practice is “clinically useful” for treating motor fluctuations. There were no safety concerns.

**MAO-B Inhibitors.** One new study evaluated rasagiline,<sup>122</sup> and the outcome was “efficacious”; thus the practice implication remains as “clinically useful.” No new studies were published using selegiline, and the conclusions remain the same. There are no new safety concerns. Zonisamide, a mixed MAO-B inhibitor; channel blocker, and glutamate release inhibitor, was evaluated in 1 new high-quality study<sup>123</sup>; the efficacy conclusion was changed to “efficacious,” and the new practice implication is “clinically useful.”

There are no new safety concerns. Safinamide was evaluated in 2 high-quality studies<sup>124,125</sup> (1 with an 18-month placebo-controlled extension),<sup>126</sup> leading to the conclusion of “efficacious” and the practice implication of “clinically useful.” There were no safety concerns.

**Adenosine A2A Antagonist.** Istradefylline was evaluated in 7 high-quality studies, with 6 positive<sup>127-131</sup> (and a 12-month extension<sup>132</sup>) and 1 negative<sup>133</sup>; 1 positive, lower quality study compared to rTMS.<sup>134</sup> Because of the conflicting evidence but generally positive outcomes, the efficacy conclusion is “likely efficacious,” and the implication for clinical practice is “possibly useful.” There are no safety concerns.

**Surgery.** STN DBS for motor fluctuations was evaluated in new high-quality positive studies.<sup>135,136</sup> There were 2 extension studies reported from prior RCTs that were not rated but included for safety outcomes that are unchanged; a 3-year extension<sup>137</sup> of the study by Odekerken et al.<sup>136</sup> and a 3-year extension of a study by Follett et al.<sup>138,139</sup> One new study evaluated STN DBS for early PD with motor fluctuations (average disease duration 7.5 years) and was positive versus medical therapy.<sup>140</sup> A lower quality positive study evaluated STN and GPi DBS for gait and balance outcomes.<sup>141</sup> Thus, overall the conclusions remain as “efficacious” for motor fluctuations and “clinically useful.” GPi DBS was evaluated in 1 new study versus STN DBS,<sup>136</sup> and the previous conclusions of “efficacious” and “clinically useful” are unchanged. There were no new studies using other techniques.

The safety conclusions for all surgical interventions remain as having an “acceptable risk with specialized monitoring.”

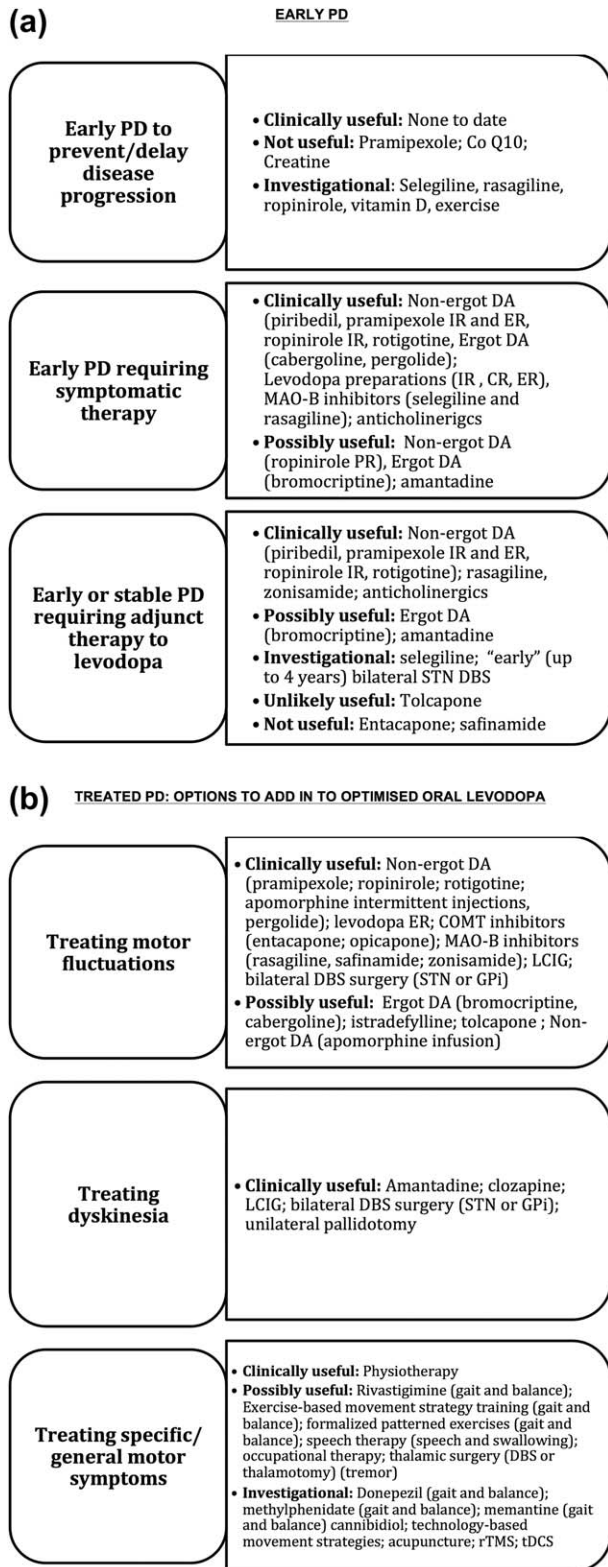
##### **New Conclusions for Treatments for Dyskinesia**

New studies were reviewed (Supporting Information Table e11).

**Dopamine Agonists.** One new study evaluated pramipexole as a treatment for dyskinesia<sup>142</sup>; although positive outcome, the lower quality meant “insufficient evidence” and “investigational” conclusions for clinical practice.

**Levodopa Preparations.** Levodopa-carbidopa gel infusion was evaluated in 1 new positive study<sup>116</sup> (see also the Motor Fluctuations section); the conclusion is “likely efficacious” as dyskinesia disability was not the primary endpoint; however, the implication for clinical practice is that levodopa-carbidopa gel infusion is “clinically useful” for overall motor response complications. Safety concerns are as described previously.

**NMDA Antagonist.** There were 3 new high-quality positive studies using amantadine.<sup>143-145</sup> There was no change in the conclusions of “efficacious” and “clinically useful.” There are no new safety issues.



**FIG. 1.** Evidence-based medicine review of treatment options for motor symptoms of PD. Boxes to the left define the type of patient (a) early PD (upper figure) and (b) treated PD optimized on levodopa (lower figure). Boxes to the right summarize the EBM conclusions for interventions (see text for definitions).

**Sv2a Agonist/Channel Blocker.** Levetiracetam, a clinically available antiepileptic drug, was evaluated for dyskinesia, and positive results were reported in 1 lower quality study<sup>146</sup> and negative results in 1 high-quality study.<sup>147</sup> Thus because of the conflicting evidence, the efficacy conclusion is “insufficient evidence” and “investigational” in clinical practice. There are no safety concerns.

**Surgery.** STN DBS and GPi DBS were evaluated in new studies as described in the Motor Fluctuations section and are both efficacious for dyskinesia, and the implication for clinical practice remains as “clinically useful.” There are no new safety concerns and the conclusion remains unchanged as “acceptable risk with specialized monitoring.”

**Physical Therapy.** Physical therapy was evaluated using intensive inpatient compared with home exercises in 1 positive low-quality study<sup>186</sup>; the efficacy conclusion is “insufficient evidence,” and its implication for clinical practice is “investigational.”

## Discussion

Many new options exist for treating motor symptoms of PD. The decision as to which intervention to use in an individual PD patient can be helped by using EBM recommendations (Fig. 1). However, EBM is just one strategy that is used to treat an individual patient, and other factors include local availability of the drug/intervention, cost, and other patient-/medical-related factors such as side effects and tolerability as well as the patient’s preference.

Figure 1 outlines the approach to a patient with PD using the current EBM findings for each stage and motor symptom.

### Treatments That May Delay/Prevent Disease Progression

To date, no intervention has shown efficacy or is designated as being useful in clinical practice as a means of preventing or slowing PD disease progression. Prior studies using ropinirole were inconclusive<sup>9</sup> because of study design issues. However, the recent high-quality study<sup>12</sup> using pramipexole was negative. The endpoint measured was the effect on total UPDRS score, and a delayed-start design was used to reduce the confounding effects of symptomatic benefits of pramipexole. As such, the practice implication is “not useful” in contrast to the “investigational” conclusion for ropinirole.

Dietary/nutritional supplements, including coenzyme Q<sub>10</sub>, creatine, and vitamin D remain popular among PD patients because of widespread availability, ease of use, and good tolerability, but the EBM review shows that there is no evidence of clinical benefit. The scientific rationale for each is beyond the scope of this

review, but generally relates to mitochondrial and cellular functions preventing dopamine cell death. Physical exercise has also recently been investigated as a method of disease modification in PD, as preclinical studies suggest dopamine cell loss is reduced with exercise.<sup>148</sup> Suggested mechanisms include production of growth factors with an effect in the brain induced by exercise, corroborated in some animal models. However, the studies evaluating physical exercise were low quality, and the results were mixed, and as such the clinical practice implication is “investigational.”

Ongoing issues with measuring disease progression in PD have meant that drawing efficacy conclusions remains challenging with current study designs. The use of clinical rating scales to evaluate PD severity as an ancillary measure of disease progression is fraught with issues including confounding changes as a result of symptomatic therapies, and lack of sufficient sensitivity to detect subtle clinical changes.<sup>149</sup> Other issues that may lead to negative outcomes are a lack of stratification for PD disease subtypes. It is apparent that PD is heterogeneous with certain subtypes (including genetic phenotypes) having a better response to medications and better long-term outcomes.<sup>150,151</sup> Moreover, to date all of these interventions have been performed in patients with early PD as defined by the presence of classical motor features. Studying interventions in the prodromal phase of disease could offer a window of opportunity in which these interventions might be effective assuming less-advanced pathology and greater potential to intervene at critical points of molecular pathogenesis.<sup>152</sup> Overall, the area of slowing and preventing disease progression in PD remains a large unmet need.

### Treatments for Symptomatic Monotherapy (Including Strategies to Delay/Prevent Motor Complications)

There are a number of factors that need to be considered when deciding which intervention to offer an early PD patient requiring treatment for motor symptoms. These include the level of disability the patient is experiencing, the relative efficacy of the therapy, potential side effects, and the need to prevent the development of long-term motor complications (see Table 4).

There are several options for monotherapy in early PD. Both levodopa and all DAs (where evaluated) significantly improve motor symptoms when compared with placebo, and the new studies add to the evidence of “possibly” or “clinically useful” from the previous EBM review.<sup>9</sup> The relative efficacy of the different DAs appears to be similar. The choice of DA may thus depend on the duration of action (e.g., shorter duration with IR vs longer acting ER), which may be important in certain clinical outcomes, for example,

rapid reversal of symptoms, or compliance. One shortcoming of the current EBM review methodology is a lack of comparison statistics, for example, meta-analysis to determine relative efficacy of interventions when direct comparator randomized controlled trials are unavailable.

The major issue with DAs (at all disease stages) remains side effects. The ergot DA-related side effects (including fibrosis/restrictive heart valve changes) have reduced the use in most areas of the world. Overall, nonergot DAs have similar profile of side effects (sleepiness, postural hypotension, peripheral edema, and neuropsychiatric issues). Rotigotine has additional side effects related to the transdermal administration. In clinical practice, a significant side effect is the high risk of impulse control disorders (ICDs) with DAs compared to levodopa. Although lower rates of ICDs associated with long-acting or transdermal DAs have been reported, to date there has been no interventional study evaluating the relative risk of ICDs between the DAs, and this remains an important area of research.<sup>153,154</sup>

The clinical equipoise has consistently been whether a patient with early PD should be started on levodopa or a “levodopa-sparing” option such as a DA or an MAO-B inhibitor to delay the emergence of motor fluctuations and dyskinesia. There are no new studies specifically addressing this outcome, and thus previous MDS EBM conclusions remain unchanged. For interventions preventing/delaying the onset of motor fluctuations, pramipexole and cabergoline is “clinically useful,” and for delaying dyskinesia compared to levodopa as initial treatment, pramipexole, ropinirole, and ropinirole PR are “clinically useful,” cabergoline, bromocriptine, and pergolide are “possibly useful,” but their use is limited because of their ergot properties. Of importance, these studies showed superior benefit of levodopa over DAs in improving motor scores and, where assessed, quality of life, and significantly more nonmotor side effects have been reported with DAs.<sup>155</sup> In addition, in longer term follow-up, the available evidence suggests that there is no clinically relevant difference on motor function, troublesome motor complications, or mortality according to the choice of initial therapy. Moreover, one study<sup>156</sup> showed that in clinical practice it is possible to start treatment with levodopa when needed and still apply “levodopa-sparing” strategies later by adding a DA in an attempt to reduce the development of dyskinesia.

MAO-B inhibitors (selegiline and rasagiline) improve motor symptoms in early PD, but the effect size has been smaller than with levodopa and DAs. Indeed, the PD MED study<sup>28</sup> suggested some superiority of levodopa over “levodopa-sparing” strategies (DA or MAO-B inhibitors), with a slight but significantly better motor response and quality of life at 3



years. In terms of relative tolerability of MAOB inhibitors, there was slightly less dyskinesia than in the levodopa group. However, the evidence for delaying motor fluctuations with rasagiline or selegiline remains “investigational” for delaying fluctuations; selegiline is “not useful” for delaying dyskinesia.

An alternative “levodopa-sparing” strategy has been to target nondopaminergic pathways to improve symptoms, potentially without dopamine-related side effects. Amantadine, which has anti-glutamatergic (and dopaminergic) properties, has been investigated as early monotherapy, and older studies led to a classification of amantadine as “likely efficacious” and “possibly useful” for the treatment of motor symptoms. The adenosine system is implicated in basal ganglia function, and several adenosine  $A_{2A}$  receptor antagonists are in development for PD.<sup>157</sup> Istradefylline is clinically available in Japan as an adjunct to levodopa. However, the lack of efficacy as monotherapy suggests that targeting the adenosine system alone may not be sufficient for treating PD motor symptoms. It remains unknown whether this is a class effect or specific to istradefylline as other adenosine  $A_{2A}$  receptor antagonists are in development.

Overall, the choice of treatment in early disease thus depends on the need for relief from motor symptoms and tolerability/side effects both over the short and long term. Factors to be taken into account include the higher risk of motor complications in younger onset patients and personal circumstances. These may include the need for rapid improvement, for example, for reasons of employment (which would favor initial levodopa) or the predominant need or desire to delay dyskinesia for as long as possible (which favors levodopa-sparing initial treatments).

## Treatments for Adjunct Therapy

### ***Symptomatic Adjunct Therapy in Early or Stable PD Patients***

In early PD patients on levodopa, it may be desirable to add nonlevodopa agents instead of increasing levodopa when a greater treatment effect is needed as the disease progresses, particularly in younger patients where a treatment goal may be to delay the development of motor complications. Adding a DA (pramipexole IR or ER, ropinirole IR, rotigotine, or piribedil) is “efficacious” in improving motor symptoms and “clinically useful.” However, there is no evidence of clinical superiority in terms of tolerability or short- and long-term benefits of one DA over the other, including delaying or preventing motor fluctuations (as discussed previously). Deciding which DA to add is thus based on local availability and cost, and the decision whether to switch to a different DA later depends on individual tolerability/efficacy.

For PD patients on DA monotherapy with symptoms, then alternative adjuncts instead of levodopa may be appealing to prevent development of motor complications. Thus, rasagiline is “efficacious” and “clinically useful” as an adjunct to DA,<sup>32</sup> whereas the new mixed MAO-B/glutamate release inhibitor safinamide was “not useful” in early PD patients.<sup>33</sup>

The early use of COMT-I in nonfluctuating patients has also been investigated as a means of providing more continuous dopaminergic stimulation to potentially prevent the development of motor complications. Tolcapone was previously evaluated in predominantly nonfluctuating patients and is classified as “efficacious,”<sup>158</sup> although its clinical use is greatly limited because of potential liver toxicity and it is not recommended in patients without motor fluctuations and thus has been redesignated as “unlikely useful.” However, the early use of entacapone in nonfluctuating PD patients resulted in increased motor complications,<sup>159</sup> and thus it remains “not useful.” To date, the new COMT-I opicapone has not been evaluated in nonfluctuating PD patients.

Surgery remains an option for treating motor symptoms of advanced PD and is reviewed later. The use of STN DBS for early PD without motor fluctuations or dyskinesia<sup>34</sup> remains “investigational,” with a clear need to balance risks versus benefits in this mildly symptomatic population.

### ***Symptomatic Adjunct Therapy to Levodopa for Specific or General Motor Symptoms in PD, Optimized on Treatment***

Gait and balance are often levodopa-resistant symptoms because of the involvement of nondopaminergic pathways. Thus, cholinesterase inhibitors (donepezil and rivastigmine) have been evaluated to reduce falls because of pathology in brain stem centers involved in gait and balance resulting in cholinergic dysfunction.<sup>35,36</sup> However, there is conflicting evidence of benefit to date, and further studies are required. Likewise, adrenergic and glutamatergic involvement in gait have also been targeted using methylphenidate and memantine, respectively, but without evidence of benefit for treating gait disorders.

For younger patients, anticholinergics are an option and remain “clinically useful.” They may have a somewhat better effect on tremor than on other parkinsonian motor signs and may also be considered as part of a levodopa-sparing combination of drugs (although no evidence exists for an effect on the time to development of motor complications). Their use should generally be limited to young and cognitively intact patients because of their unfavorable neuropsychiatric adverse effect profile and the long-term risk of memory impairment.



Nonpharmacological interventions are expanding as adjuncts to medical therapy for a range of PD motor symptoms, including a focus on gait and balance. The largest number of new RCTs are exercise-based therapies, with 64 new studies since 2011. Despite an increase, the overall quality of studies remains lower than pharmacological and surgical trials. This is partly because of the factors inherent in the design, for example, nonblinding of patients, the nature of the comparison groups used (usually 2 “active” groups but different interventions, and often not a third, best medical therapy/control group), and the lack of clinically relevant or important measures as a primary outcome, for example, stride-length measurements are used rather than a motor rating or number of falls. In several studies, the generalization of the intervention to falls prevention in PD is unclear as only a proportion of the participants had documented falls at baseline. This may be a result of recruitment bias in favor of more active patients. Indeed, although there were no overall safety concerns, increased falls as a result of participation was noted in some studies, and caution may be needed with some at risk individuals with certain PT interventions. Further work is needed to clarify this. Another challenge with the use of EBM reviews is also the inherent bias in evidence conclusions because of the relative lack/lower rate of publication of negative studies. However, several studies were of high enough quality to allow upgrading prior conclusions, although the overall interpretation of the studies is challenging because of the variability in interventions between studies.

Physiotherapy-based exercises including treadmill, aerobic, and strengthening/balance exercises continue to be the most common intervention in PD. In general, these strategies improve PD motor symptoms when compared with baseline. Many factors remain unknown as to the best format of physiotherapy to use in PD, including the frequency, intensity, duration, and setting (such as home vs group based).<sup>160</sup> Determining the relative benefit of one type of exercise therapy over another remains a challenge. The majority of studies reviewed evaluated two active types of exercise, and in most cases both interventions were positive compared to baseline measures. This suggests that any active physiotherapy intervention can be beneficial for PD. Several meta-analyses of different physiotherapy techniques have been performed to attempt to answer these questions, however, the conclusions are inconclusive.<sup>160-164</sup> Despite these caveats, physiotherapy remains a “clinically useful” strategy for PD patients.

Movement strategy techniques, primarily for falls prevention, were divided into 2 subtypes. The first, exercise-based included primarily physiotherapy (treadmill etc.) techniques and variable cueing techniques (including visual; mental imagery or tactile

sensory cues), and as such there was some overlap with studies in physiotherapy. These newer studies evaluated aspects related to how to use the intervention, for example, frequency of intervention/need for supervision and overall were “possibly useful” for falls prevention. Newer studies are beginning to be reported which incorporate technology-based interventions including virtual reality/avatars and biofeedback methods. Evidence to date is limited and practical issues are a factor, including limited availability and need for specialist expertise and thus the implication for clinical practice is that such technology is “investigational.” This is a large area of study, and many new technological interventions are being developed.<sup>165</sup> A recent Cochrane review<sup>166</sup> on virtual reality concluded that the evidence is low for improving PD motor symptoms, with similar effects to physiotherapy in gait and balance, and confirms the need for further studies.

Formalized patterned exercises, including dance and Tai Chi, are increasingly popular with PD patients, and despite insufficient evidence this category of intervention is considered “possibly useful” in clinical practice. However, to date there is conflicting evidence of benefit because of the variable outcomes. The ongoing challenge with such studies is having an appropriate control group, although comparing 2 types of the same modality, for example, comparing 2 different types of dance and so on, may improve quality ratings and study validity.

Speech therapy is a component of managing PD in most clinical practices. Despite the importance of bulbar dysfunction in PD, no new studies evaluating speech therapy for speech in PD have been published since the previous review. The 2011 EBM review included the Lee Silverman Voice Training technique, which is commonly used in clinical practice, and the conclusion remains “possibly useful.” A new study examining visual input to help improve swallowing issues reported positive outcome but this was a lower quality study, and therefore further studies are required. Occupational therapy likewise is used in day-to-day clinical practice in PD and has been designated as “possibly useful.” High-quality efficacy evidence is lacking partly because of the challenges related to study designs using occupational therapy.

The use of external stimulation devices continues to be explored in PD. rTMS has been evaluated for motor symptoms of PD. However, because of the variability in the sites of rTMS application (e.g., primary motor cortex or supplementary motor area), frequency (low 0.2Hz, or high 5Hz), and duration of stimulation (every 3 days to every 7 days), and the conflicting results of the studies, there is “insufficient evidence” for rTMS at the current time. A recent review suggested an overall moderate effect size of rTMS but

also highlighted the issue of variability in technique.<sup>167</sup> tDCS is another technique that has been used to treat PD motor symptoms. Several studies have been reported, but only 1 was included that fulfilled inclusion criteria; the main reasons for exclusion were small numbers of patients or short duration of intervention. Two recent reviews also reported inconclusive outcomes for use in PD.<sup>168,169</sup>

So-called “alternative therapies” remain an area of investigation. Acupuncture has been evaluated for treating motor symptoms in PD, but the low quality of studies means that acupuncture remains “investigational.” The use of bee venom has also been reported; this high-quality study was negative. Cannabis-based therapies are increasingly explored by patients for both motor and nonmotor symptoms with, to date, few RCTs fulfilling the EBM criteria for inclusion. There is a clear need for high-quality RCTs to evaluate efficacy and, just as important, safety in PD.

Tremor is the only cardinal motor feature of PD that may respond better to surgery than to sufficient doses of levodopa. STN DBS and GPi DBS are “efficacious” for tremor, and in the majority of cases, these are the preferred targets, but targeting the thalamus (DBS or thalamotomy) for tremor-dominant PD remains “possibly useful” (used in clinical practice in patients where DBS of other targets may pose a greater surgical risk). Gamma knife thalamotomy and new techniques such as focused ultrasound, although available in some regions, were not included as, to date, no published studies fulfilled the inclusion criteria.

### Treatments for Motor Fluctuations

There are many options available for treating motor fluctuations in PD. In daily clinical practice, adjusting the timing of levodopa preparations to a shorter time interval and improving absorption, for example, by taking levodopa on an empty stomach and by improving gastrointestinal transit by treating constipation are all partly effective methods. Alternative levodopa preparations include levodopa ER (IPX066), which is clinically useful although relative efficacy compared to other dopaminergic options remains unknown. The clinical challenge as to which agent to then use, or add in, requires evaluating side effect profiles and individual patient characteristics as well as cost and availability. In clinical practice there is a hierarchical use of interventions according to safety risks. Thus, earlier in the course of developing motor fluctuations, the first-line treatments are usually oral (or transdermal) agents (dopaminergics, enzyme inhibitors or nondopaminergics), followed by parenteral and surgical techniques for more advanced patients. All widely clinically available nonergot oral and transdermal dopamine agonists are “clinically useful” for reducing motor fluctuations. To date, there is no evidence of clinical

superiority of one DA over another. Longer term follow-up studies, more than 1 year with rotigotine<sup>113</sup> and 2 years with ropinirole PR,<sup>170</sup> suggest maintained benefit (not included in recommendations, as these were not newly randomized studies). Long-term comparative side effects between nonergot DAs, including risk of ICDs, is as yet unclear.

Enhancing levodopa duration of action with enzyme inhibition using COMT and/or MAO-B inhibition remains an effective approach for reducing motor fluctuations. The COMT-inhibitors entacapone and opicapone are “clinically useful,” without the safety issue of liver function monitoring required with tolcapone. The MAO-B inhibitor rasagiline remains “clinically useful.” As a result of prior low-quality studies, the conclusion for selegiline remains “investigational.” There are no new studies since the previous EBM review<sup>9</sup> to determine the relative efficacy of COMT inhibitors compared to MAO-B inhibitors. A study previously discussed in the 2011 EBM review<sup>9</sup> found comparable effects of entacapone and rasagiline in reducing OFF time.<sup>171</sup> Mixed MAO-B inhibition with glutamate release inhibition using the new agent safinamide is “clinically useful.” A similar agent, zonisamide, also “clinically useful” and has been approved in Japan. The relative efficacy of these 2 drugs compared to other add-on therapies remains unclear. Adenosine A2A antagonism is a novel target for treating motor fluctuations. Istradefylline is approved in Japan and has been assessed in several studies with mixed outcomes, but overall the efficacy appears to be positive.

For more advanced suitable PD patients, injection/infusion therapies or surgery are options for bothersome motor fluctuations (and to reduce dyskinesia). Intermittent injections of the DA apomorphine are “clinically useful” for motor fluctuations, particularly for OFF periods that require rapid reversal. Subcutaneous apomorphine continuous infusion is widely used in clinical practice in patients with motor complications, but to date a double-blind RCT has been published in abstract form only.<sup>172</sup> Percutaneous infusion of levodopa (levodopa-carbidopa intestinal gel) is clinically useful for certain patients with severe motor fluctuations, although it requires appropriate clinical support, restricting use to specialized centers. DBS targeting the STN or GPi remains clinically useful for carefully selected PD patients and is again restricted to specialized centers. There are no RCTs directly comparing device-aided therapies, but expert consensus opinions discussing the pros and cons of each approach have been published.<sup>173</sup> Other targets such as the pedunculopontine nucleus have been suggested as options for deep brain stimulation particularly for gait and balance symptoms; however, to date no trials have been published that fulfil EBM inclusion criteria

## Treatments for Dyskinesia

Overall, there are few clinically available interventions specifically for dyskinesia. In clinical practice, strategies include optimizing oral levodopa doses if possible but with the risk of worsening motor symptoms. In advanced PD, levodopa-carbidopa intestinal gel can reduce OFF time and improve ON time without bothersome dyskinesia.<sup>116</sup> The mechanism is likely a combination of both reducing oral levodopa dosing as well as a direct effect on dopamine receptors with a continuous-stimulation approach rather than the intermittent pulsatile dopaminergic stimulation of oral IR levodopa.<sup>174</sup> Similarly, surgery using bilateral STN DBS with a reduction in oral levodopa is also efficacious at reducing dyskinesia. GPi DBS appears to reduce dyskinesia because of a direct stimulation effect, as the daily dose of levodopa remains unchanged.<sup>136</sup>

Nondopaminergic targets for reducing dyskinesia have been an area of research for many years.<sup>175</sup> Currently, the most effective target appears to be the glutamate-N-Methyl-D-aspartate (NMDA) receptor antagonist, amantadine, which remains clinically useful for treating dyskinesia in PD. There are long-acting preparations in development, but these were not approved within the review dates.<sup>176</sup> To date, however, few other nondopaminergic targets have shown significant efficacy and become clinically available. “Indication-switching” or “drug repurposing” studies have used clinically available drugs from other fields, for example, epilepsy, to test hypotheses. Thus, studies evaluating the antiepileptic agent levetiracetam, which targets Synaptic vesicle glycoprotein 2A (SV2A) channels, have shown some potential in preclinical studies, but so far 2 RCTs have yielded conflicting outcomes. The atypical neuroleptic clozapine, targeting 5-Hydroxytryptamine (5HT) receptors, is efficacious according to 1 study, but this agent has safety concerns requiring blood count monitoring. ■

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## Supporting Data

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