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*Neurology* 2006;66;983-995; originally published online Apr 2, 2006;
DOI: 10.1212/01.wnl.0000215250.82576.87

**This information is current as of July 5, 2007**

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http://www.neurology.org/cgi/content/full/66/7/983

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AMERICAN ACADEMY OF NEUROLOGY

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Special Article

# Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review)

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

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**Abstract—***Objective:* To make evidence-based treatment recommendations for the medical and surgical treatment of patients with Parkinson disease (PD) with levodopa-induced motor fluctuations and dyskinesia. To that end, five questions were addressed. 1. Which medications reduce off time? 2. What is the relative efficacy of medications in reducing off time? 3. Which medications reduce dyskinesia? 4. Does deep brain stimulation (DBS) of the subthalamic nucleus (STN), globus pallidus interna (GPi), or ventral intermediate (VIM) nucleus of the thalamus reduce off time, dyskinesia, and antiparkinsonian medication usage and improve motor function? 5. Which factors predict improvement after DBS? *Methods:* A 10-member committee including movement disorder specialists and general neurologists evaluated the available evidence based on a structured literature review including MEDLINE, EMBASE, and Ovid databases from 1965 through June 2004. *Results, Conclusions, and Recommendations:* 1. Entacapone and rasagiline should be offered to reduce off time (Level A). Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B). Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C). 2. The available evidence does not establish superiority of one medicine over another in reducing off time (Level B). Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C). 3. Amantadine may be considered to reduce dyskinesia (Level C). 4. Deep brain stimulation of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C). There is insufficient evidence to support or refute the efficacy of DBS of the GPi or VIM nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function. 5. Preoperative response to levodopa predicts better outcome after DBS of the STN (Level B).

NEUROLOGY 2006;66:983–995

**Statement of purpose.** The Quality Standards Subcommittee (QSS) develops scientifically sound, clinically relevant practice parameters to aid in the practice of neurology. This article addresses medical and surgical treatments for the management of patients with Parkinson disease (PD) with levodopa-

**Editorial, see page 966**
**See also pages 968, 976, and 996**

*This article was previously published in electronic format as an Expedited E-Pub at www.neurology.org.*

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Quality Standards Subcommittee Members are listed in appendix E-4 on the *Neurology* Web site at www.neurology.org.
Approved by QSS July 30, 2005; Practice Committee December 15, 2005; Board of Directors February 23, 2006.
Endorsed by the National Parkinson Foundation and the Parkinson's Disease Foundation.
Disclosures are provided after the text.
Received August 16, 2005. Accepted in final form February 16, 2006.

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induced motor fluctuations and dyskinesia. These recommendations address the needs of specialists and nonspecialists caring for patients with PD.

**Background.** PD is a progressive neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity. Although initially effective, dopaminergic therapies are eventually complicated by motor fluctuations, including off time (periods of return of PD symptoms when medication effect wears off) and dyskinesia (drug-induced involuntary movements including chorea and dystonia) in most patients. These motor complications can impair quality of life and cause significant disability.[1] Risk factors for motor complications include younger age at onset of PD, disease severity, higher levodopa dosage, and longer disease duration.[2-4] These problems are often addressed with levodopa adjustments and the addition of adjunctive medications. The first part of this article addresses the effectiveness of adjunctive medications in this situation.

Motor fluctuations and dyskinesia can be resistant to medical therapy. This, along with advances in the understanding of basal ganglia circuitry, surgical techniques, neuroimaging, and intraoperative microelectrode recording, has led to a resurgence in surgical approaches for medically refractory disabilities. Initially, ablative procedures like thalamotomy and pallidotomy were used to treat PD symptoms. However, due to concerns about morbidity,[5] especially with bilateral procedures, deep brain stimulation (DBS) has become the most commonly performed surgery for PD in North America.

DBS is a stereotactic surgical procedure that uses an implanted electrode connected to an implantable pulse generator (IPG) that delivers electrical current to a targeted nucleus in the brain.[6] The three primary targets for DBS for PD are the ventral intermediate (VIM) nucleus of the thalamus, globus pallidus interna (GPi), and the subthalamic nucleus (STN). The IPG is programmed externally from several days to 4 to 6 weeks after implantation. Adjustable stimulation parameters include amplitude, frequency, and pulse width. The device is generally left on but patients can turn the device off when desired.

Although the criteria are evolving, currently patients with PD who are considered candidates for DBS include levodopa-responsive, non-demented, and neuropsychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor.

This practice parameter addresses five questions:

1. Which medications reduce off time?
2. What is the relative efficacy of medications in reducing off time?
3. Which medications reduce dyskinesia?
4. Does DBS of the STN, GPi, or VIM reduce off time, dyskinesia, and antiparkinsonian medication usage and improve motor function?
5. Which factors predict improvement after DBS?

The conclusions and recommendations addressing these questions are based only on the evidence available in the literature and are limited by the quality of the studies reviewed. An inherent problem with this process is that treatments may receive a recommendation lower than what may be expected based on clinical experience. This can be due to many factors including the possibility that older treatments may not have been studied as rigorously as newer therapies; published manuscripts may not have included sufficient details or used a study design that would eliminate potential bias; or a particular issue related to a specific treatment may not have been addressed in the literature.

**Description of the analytical process.** The QSS of the AAN identified an expert panel of experienced movement disorder specialists and general neurologists with methodologic expertise. For the literature review, a research librarian searched MEDLINE, EMBASE, and Ovid databases. This was supplemented by a secondary search using the bibliography of retrieved articles and knowledge from the expert panel. Panel members reviewed abstracts and titles for relevance. Then, at least two panel members reviewed articles meeting inclusion criteria. If a panelist was an author of one of the articles, at least two other panelists reviewed that article. Disagreements were arbitrated by an additional panel member. The risk of bias was determined using the classification of evidence for each study (appendix E-1 the *Neurology* Web site at www.neurology.org). The strength of the practice recommendations was linked directly to the level of evidence (appendix E-2). Conflicts of interest were disclosed. Support was provided by the AAN. Writing meetings were funded by the Michael J. Fox Foundation. Panelists were not compensated.

*Medical treatment.* For questions 1, 2, and 3, the authors used the following search terms: Parkinson disease, advanced Parkinson disease, dyskinesia, motor fluctuations, double masked trials, randomized trials, placebo controlled trials, clinical trials, medical treatment, human studies, adenosine A2A antagonists, amantadine, apomorphine, bromocriptine, cabergoline, controlled release carbidopa/levodopa, entacapone, pergolide, pramipexole, rasagiline, ropinirole, selegiline, tolcapone, clozapine, rotigotine (search restricted to English language and medications available in the United States or those having an approvable letter from the Food and Drug Administration). The initial search included articles from 1965 to June 2004 and a supplemental search was performed in 2005 to include the latest clinical trials.

The authors considered randomized masked trials that included at least 20 patients with motor fluctuations or dyskinesia followed for greater than 3

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months. If no articles met the 3-month criterion for a specific drug, the authors included articles with shorter durations of therapy and this led to a drop in class level.

The initial search identified 730 articles, of which 670 were excluded during the abstract review. An additional 34 articles were excluded during the article review, leaving 26 articles for consideration. Of the 704 articles eliminated, 172 were not related to the drugs examined, but instead looked at alternative agents, alternative modes of administration such as infusions, and a variety of surgical procedures. A total of 151 of the articles were reviews; 99 were studies of early PD or non-fluctuators; 75 were open label studies; 72 were about mechanisms of action, pharmacokinetics, or animal studies; 69 evaluated other uses of the drugs; 30 had fewer than 20 subjects; 17 were primarily about adverse effects; 11 had a study duration less than 3 months; and 8 were not peer reviewed. The supplemental search identified three additional articles. From each article the authors abstracted the following methodologic characteristics: trial design, method of allocation concealment, mechanism of masking, number of enrollees, comparative baseline characteristics of subjects, number of completers, trial duration, measure of "off" time or "on" time and dyskinesia, magnitude of response, adverse events, and levodopa dose change.

*Surgical treatment.* For questions 4 and 5, the authors used the following search terms: deep brain stimulation AND Parkinson disease; DBS AND Parkinson disease; subthalamic stimulation AND Parkinson disease; pallidal stimulation AND Parkinson disease; and thalamic stimulation AND Parkinson disease for all articles from 1965 through June 2004. All non-English language articles, review articles, and animal studies were excluded. A total of 478 articles resulted. The authors included studies of DBS for PD reporting postsurgical outcome in terms of motor improvement or reduction of motor complications that had a sample size of at least 20 subjects and a follow-up duration of at least 6 months post-DBS. Twenty articles met all inclusion criteria; 13 for subthalamic stimulation; 1 for subthalamic and pallidal stimulation; 2 for pallidal stimulation; and 4 for thalamic stimulation. A total of 458 articles were excluded for the following reasons: 200 had less than 20 patients in the study; 152 were not motor function outcome studies of DBS in PD; 41 were review articles; 26 were comments; 18 had less than 6 months follow-up; 9 were not from peer-reviewed sources; 4 were animal studies; 6 were redundant reports of included data; 1 did not differentiate results of PD vs essential tremor; and 1 did not use standard outcome measures for PD. The authors abstracted the following characteristics from the 20 articles meeting inclusion criteria: study design, patient selection criteria, follow-up duration, number, age, sex and disease duration of subjects, baseline Unified PD Rating Scale (UPDRS) activities of daily living (ADL) and motor scores in the medication on and medication off conditions at baseline and during follow-up evaluations in the stimulation on condition, specific measures of dyskinesia and motor fluctuations, adverse events, and medication reduction.

Brief summaries of the medical studies examining off time and the surgical studies can be found in tables 1 and 2, and complete evidence tables describing the methodologic details of the medical (table E-1) and surgical (table E-2) studies are available on the *Neurology* Web site.

**Results.** *Question 1: Which medications reduce off time?* Dopamine agonists. *Pergolide.* One Class I, 24-week, multicenter, placebo controlled, parallel group, double masked study compared 189 in the active group (mean dose 2.9 mg/day) and 187 in the control group.[7] More than 80% of the patients completed the study (84% on pergolide and 82% on placebo). The active group had a 32% decrease (1.8 hours) in off time compared to a 4% decrease (0.2 hours) in the control group ($p < 0.001$). There were also differences in level of improvement in UPDRS ADL and motor scores in the on state in favor of pergolide ($p < 0.001$). However, 62% of the active group had a new onset or worsening of dyskinesia, compared to only 25% of the placebo group. Levodopa dose decreased 24.7% in the pergolide group compared to 4.9% in the placebo group ($p = 0.001$).

*Pramipexole.* One Class I study[8] and one Class II study[9] compared pramipexole to placebo. The Class I multicenter, double masked, parallel group study randomized 360 patients (181 active, 179 control) for 32 weeks.[8] Eighty-three percent of the active group and 78% of the control group completed the study. Off time decreased by 31% in the active group (mean dose 3.4 mg/day) compared to 7% in the placebo group ($p = 0.0006$). UPDRS ADL in the on and off states, and motor examination in the on state all improved with pramipexole vs placebo ($p < 0.01$). Levodopa dose was reduced in the active group (27%) compared to the placebo group (5%) ($p = 0.0001$). There was a significant difference with regard to dyskinesia in the active group (61%) compared to the placebo group (40%).

In the Class II, multicenter, double masked, randomized, parallel group study, 79 patients received pramipexole (mean dose 3.4 mg/day) and 83 received placebo for 40 weeks.[9] There were 80% completers in the active group and 60% in the control group. The active group had a 15% (2.5 hour) decrease in off time vs a 3% reduction in the control group ($p = 0.007$). In the on state, the active group also experienced improvements in the UPDRS ADL and motor scores ($p < 0.0006$). Levodopa reduction was not reported. Dyskinesia was reported in 40% of pramipexole patients and 27% of controls.

*Ropinirole.* Two Class II studies compared the effect of ropinirole vs placebo on off time.[10,11] The first was a multicenter, randomized, parallel group, double masked, placebo controlled, 12-week study with 23 patients randomized to each group.[10] The


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***Table 1*** *Summary of medication studies examining off time changes*

| Ref | Drug | Class | N* | Age,† y | Disease duration,† y | Study duration, wk | Decrease off time active | Decrease off time placebo |
|---|---|---|---|---|---|---|---|---|
| Placebo-controlled studies | | | | | | | | |
| 7 | Pergolide | I | 189/187 | 62.5 | 11.4 | 24 | 32% (1.8 h)‡ | 4% (0.2 h) |
| 8 | Pramipexole | I | 181/179 | 63.3 | 9 | 32 | 31%‡ | 7% |
| 9 | Pramipexole | II | 79/83 | 62.9 | 6§ | 40 | 15% (2.5 h)‡ | 3% |
| 10 | Ropinirole | II | 23/23 | 62 | 8 | 12 | 23%‡ | 4% |
| 11 | Ropinirole | II | 95/54 | NR | 8.6 | 26 | 11.7%‡ | 5% |
| 12 | Apomorphine | II | 20/9 | 66 | 9.2 | 4 | 34% (2.0 h)‡§ | 0 |
| 9 | Bromocriptine | II | 84/83 | 61.5 | 7.2§ | 40 | 8% | 3% |
| 13 | Cabergoline | III | 19/18 | 60.8 | 13.6 | 24 | 40% (2.0 h)‡ | 18% (0.7 h) |
| 14 | Cabergoline | III | 17/10 | 67.5¶ | 12.3 | 24 | 59% (3.3 h)‡ | NS |
| 15 | Selegiline | III | 50/46 | 61.4 | 9.5 | 6 | NR | NR |
| 16 | Orally disintegrating selegiline | II | 94/46 | 66 | 6.3 | 12 | 32% (2.2 h)‡ | 9% (0.6 h) |
| 17 | Rasagiline (0.5 mg) | I | 164/159 | 62.6 | 9.3 | 26 | 23% (1.4 h)‡ | 15% (0.9 h) |
| 17 | Rasagiline (1.0 mg) | I | 149/159 | 62.9 | 8.8 | 26 | 29% (1.8 h)‡ | 15% (0.9 h) |
| 18 | Rasagiline | I | 231/229 | 63.9 | 8.7 | 18 | 21% (1.2 h)‡ | 7% (0.4 h) |
| 19 | Tolcapone (100 mg tid) | II | 69/66 | 63 | 11 | 12 | 32% (2.3 h) | 20% (1.4 h) |
| 19 | Tolcapone (200 mg tid) | II | 67/66 | 64 | 11 | 12 | 48% (3.2 h)‡ | 20% (1.4 h) |
| 20 | Tolcapone (100 mg tid) | II | 60/58 | 62 | 9 | 12 | 31.5%‡ | 11% |
| 20 | Tolcapone (200 mg tid) | II | 59/58 | 63 | 10 | 12 | 26.2% | 11% |
| 21 | Entacapone | I | 103/102 | 63.9 | 10.8 | 24 | NR | NR |
| 18 | Entacapone | I | 227/229 | 63 | 9.2 | 18 | 21% (1.2 h)‡ | 7% (0.4 h) |
| 22 | Entacapone | II | 197/104 | 60.7 | 8.3 | 24 | 25.8% (1.6 h)‡ | 13.4% (0.9 h) |
| 23 | Entacapone | II | 85/86 | 62.6 | 10.2 | 24 | 23.6% (1.3 h)‡ | 1.9% (0.1 h) |
| 24 | Entacapone | II | 99/63 | 63.5 | NR | 12 | 0.9 h | 0.4 h |
| Crossover studies (carbidopa/levodopa CR vs carbidopa/levodopa IR) | | | | | | | | |
| 26 | Carbidopa/levodopa CR/IR | III | 20 | 61.1 | 8.3 | 16 | NS | |
| 27 | Carbidopa/levodopa CR/IR | III | 21 | 67.2 | 10.2 | 24 | NS | |
| 28 | Carbidopa/levodopa CR/IR | III | 28 | NR | NR | 16 | NS | |
| 29 | Carbidopa/levodopa CR/IR | III | 24 | 66.2 | 9.3 | 16 | NS | |
| Comparator studies (not placebo-controlled) | | | | | | | | |
| 30 | Cabergoline [c]/bromocriptine [b] | II | 22/22 | 71 | 10 | 36 | 50% [c] | 31.3% [b] |
| 31 | Ropinirole [r]/bromocriptine [b] | II | 88/51 | 64 | 9 | 24 | 17.7% [r] | 4.8% [b] |
| 32 | Tolcapone [t]/entacapone [e] | II | 75/75 | NR | NR | 3 | NR | NR |
| 33 | Tolcapone [t]/pergolide [p] | III | 101/102 | 65 | 8 | 12 | 19% [t] | 20% [p] |

* Active/placebo.
† Data for active group, placebo not significantly different from active group.
‡ $p<0.05$.
§ Median values.
¶ Significantly older than placebo.

NR = not reported; NS = not significant; CR = controlled release; IR = immediate release.

ropinirole group had 87% completers and the control group had 65%. There was a greater reduction in off time per day (from 47% to 24%) in the active group (mean dose 6.8 mg/day) compared to controls (44% to 40%) ($p = 0.08$). Clinical Global Impression (CGI) favored ropinirole ($p = 0.004$). Levodopa dose change and dyskinesia were not reported.

The second multicenter, randomized, double masked, placebo controlled study randomized 95 subjects to ropinirole (maximum allowed dose 24 mg/day) and 54 to placebo for 26 weeks.[11] In the ropinirole group, 78% were completers, and in the placebo group, 65% were completers. Ropinirole decreased off time by 11.7% compared to 5.1% with placebo ($p = 0.04$). The ropinirole group had a 31% decrease in levodopa dose compared to 6% in the placebo group ($p = 0.001$). Dyskinesia occurred in 33.7% taking ropinirole and 13% taking placebo ($p = 0.006$).

*Apomorphine.* A single Class II study evaluated subcutaneously injected apomorphine (mean dose 5.4 mg/injection) in a double masked, parallel group, randomized study of 29 patients for 4 weeks (20 active, 9 placebo).[12] There were over 80% completers (85% active, 88% placebo). The active group experienced a 34% decrease (2 hours) in off time compared to 0% in the placebo group ($p = 0.02$). Dyskinesia occurred in 35% of the active group compared to 11% of the controls. UPDRS motor score in the off state improved more in the apomorphine group ($p = 0.001$).


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***Table 2*** *Summary of deep brain stimulation studies*

| Ref | Ther. Class | Prog. Class | Follow-up | Site | N | Age, y | PD duration | Baseline UPDRS motor* | Follow-up UPDRS motor† | Dyskinesia/ off time improvement | Meds reduction |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 36 | III | IV | 6 mo | B-STN | 96 | 59 | NA | 56% | 52% | Rush dyskinesia: 58%; Diary: dyskinesia reduced 23 to 7%; off time decreased 49 to 19% | 37% |
| 37 | III | IV | 1 y | B-STN | 26 | 59 | 15 | 54% | 64% (1 y) | UPDRS (item 32) dyskinesia 86%; UPDRS (item 39) off time 83% | 20% |
| 38 | III | IV | 1 y | B-STN | 33 | 58 | 12 | 40% (1 y) | 32% (1 y) | Diary: dyskinesia 18% to 4% (1 y), 19% to 11% (2 y) | 54% (1 y) |
| | | | 2 y | | 19 | | | 37% (2 y) | 28% (2 y) | Off time 44% to 20% (1 y), 43% to 17% (2 y) | 57% (2 y) |
| 39 | III | IV | 6 mo | B-STN | 20 | 61 | 12 | 59% | 49% | Dyskinesia UPDRS (item 32) 50%; dyskinesia UPDRS (item 33) 100% | 33% |
| 42 | IV | II | 6 mo | B-STN | 41 | 56 | 16 | 71% | 65% | Duration fluctuations 87%; duration dyskinesia 69%; UPDRS IV 78% | 68% |
| 45 | IV | II | 2 y | B-STN | 25 | 57 | 13 | 55% | 48% (1 y) | Dyskinesia Rating Scale 48% (1 y), 50% (2.5 y) | 38% (1 y) |
| | | | | | | | | | 41% (2.5 y) | UPDRS (#33) 83% (1 y), 82% (2.5 y); UDPRS (#32) 58% (1 y), 80% (2.5 y) | 36% (2.5 y) |
| 40 | IV | IV | 1 y | B-STN | 22 | 57 | 15 | 51% (1 y) | 63% (1 y) | Dyskinesia significantly reduced | 32% (1, 2 y) |
| | | | 2 y | | 9 | | | 51% (2 y) | 48% (2 y) | Data not shown in manuscript | |
| 41 | IV | IV | 6 mo | B-STN | 38 | 56 | 13 | 43% | 44% (6 mo) | Off time reduced 35% (10–60%) | 53% |
| | | | 1 y | | | | | | 48% (1 y) | Dyskinesia 72% (6 mo, 1 y) | |
| 43 | IV | IV | 6 mo | B-STN | 23 | 58 | NA | NA | 53% (6 mo) | Dyskinesia 77% (6 mo) 60% (1 y) | 56% (6 mo) |
| | | | 1 y | | 14 | | | | 61% (1 y) | Off time 71% | 53% (1 y) |
| 44 | IV | IV | 2 y | B-STN | 48 | 60 | 15 | 57.70% | 51% (6 mo) | UPDRS (#32) 77% (6 mo), 83% (1 y), 73% (2 y) | 49% (6 mo) |
| | | | | | | | | | 57% (1 y) | UPDRS (#33) 92% (6 mo,1 y, 2 y) | 42% (1 y) |
| | | | | | | | | | 57% (2 y) | | 68% (2 y) |
| 46 | IV | IV | 5 y | B-STN | 42 | 55 | 15 | 74.30% | 66% (1 y) | UPDRS (#32) Dyskinesia 71% (1, 3, 5 y) | 59% (1 y) |
| | | | | | | | | | 59% (3 y) | UPDRS (#33) 63% (1 y), 68% (3 y), 50% (5 y) | 63% (3 y) |
| | | | | | | | | | 54% (5 y) | | 63% (5 y) |
| 47 | IV | IV | 1 y | B-STN | 25 | 57 | 14 | 59.40% | 50% | UPDRS (#32) dyskinesia 80% (1 y); UPDRS (#33) dyskinesia 86% (1 y); UPDRS (#39) off duration 95% (1 y) | 66% (1 y) |
| 48 | IV | IV | 30 mo | B-STN | 24 | 58 | 14 | 65% | 38% | UPDRS IV (item 39) 16%; dyskinesia 69% (1 y) 71% (30 mo); fluctuations 52% (1 y) 50% (30 mo) | 39% (1 y) 30% (30 mo) |
| 49 | IV | IV | 4 y | B-STN | 20 | 61 | NA | 56% | 43% | NA | 47% (4 y) |
| 36 | III | IV | 6 mo | B-GPi | 36 | 56 | NA | 53% | 33% | Rush dyskinesia: 67%; Diary: dyskinesia reduced 35 to 12%; off time reduced 37 to 24% | 3% more |
| 51 | IV | IV | 33 mo | U-GPi | 26 | 56 | 13 | 60% | -8% | Dyskinesia: 28% (UPDRS IVA); off time: 3.5% worsening (UPDRS IVB) | 53% more |
| 50 | IV | IV | 6 mo | GPi | 30 | 58 | 8 | 32% | 49% (6 mo) | UPDRS (#32–35) dyskinesia | NA |
| | | | 1 y | U-10 | | | | (total UPDRS) | 46% (1 y) | 93% (6 mo) | |
| | | | | B-20 | | | | | (total UPDRS) | | |
| 52 | IV | IV | 6 mo | TS | 80 | NA | NA | NA | NA | NA | 49% (3 mo) |
| | | | | | | | | | | | 15% (6 mo) |
| 53 | IV | IV | 1 y | U-TS | 24 | 65 | NA | NA | NA | NA | NA |
| 54 | IV | IV | 21 mo | U-TS | 18 | 66 | 10 | NA | 29% | NA | NA |
| 55 | IV | IV | 1 y | TS | 73 | 62 | 10 | NA | 31% | NA | None |
| | | | | U-56 | | | | | | | |
| | | | | B-16 | | | | | | | |

* % Improvement baseline meds OFF vs meds ON.
† % Improvement follow-up meds OFF/Stim ON vs baseline meds OFF.

Ther = therapeutic; Prog = prognostic; PD = Parkinson disease; UPDRS = Unified PD Rating Scale; STN = subthalamic nucleus; B-STN = bilateral STN; Gpi = globus pallidus interna; B-GPi = bilateral GPi; U-GPi = unilateral GPI; NA = not available; TS = thalamus; U-TS = unilateral TS.



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*Bromocriptine.* In a single Class II multicenter, randomized, double masked study, bromocriptine was compared to pramipexole and placebo for 40 weeks.[9] Eighty-four patients received bromocriptine (mean dose 22.6 mg/day) and 83 received placebo. Eighty percent of the bromocriptine patients completed compared to 60% of the placebo group. There was an 8% decrease in off time for bromocriptine compared to 3% in placebo, which was not different ($p = 0.2$). Maximum improvement occurred at 8 weeks. Bromocriptine therapy led to an improvement in the primary end points, UPDRS ADL and motor scores, compared to placebo ($p < 0.02$). Change in levodopa dose was not reported. Dyskinesia occurred in 45% of bromocriptine patients and 27% of controls.

*Cabergoline.* Two Class III studies evaluated whether cabergoline can reduce off time without a significant increase in dyskinesia.[13,14] In a Class III, single center, 24-week placebo controlled study of 37 patients (19 active, 18 placebo), the active group (cabergoline mean dose 5.4 mg/day) had a 40% decrease in off time (2 hours/day) compared to 18% (0.7 hours/day) for the placebo group ($p < 0.05$).[13] However, there were confounding differences at baseline; the active group had an off time duration of 5 hours compared to only 4 hours for the placebo group. Fewer than 80% of the patients completed the study (58% active, 39% placebo), and there was no information provided on allocation concealment. Levodopa dose decreased 8% in the cabergoline group and 5% in the placebo group. Neither group had worsening of dyskinesia. CGI was improved in the cabergoline group ($p < 0.05$).

A Class III, single center, 24-week, double masked, parallel group study compared 17 patients (mean age 67.5 years) on cabergoline (mean dose 4.9 mg/day) to 10 patients (mean age 57.9 years) on placebo.[14] No information on allocation concealment was provided, and there were less than 80% completers (76% active, 70% placebo). Neither group had a change in dyskinesia. The active group had a 30% (2.7 hours) increase in on time and a 59% decrease (3.3 hours) in off time. No information was provided for the placebo group. UPDRS motor scores improved ($p = 0.006$). Levodopa dose decreased by 28% with cabergoline and 10% with placebo ($p = 0.004$).

Dopamine agonists adverse effects. The adverse effects associated with dopamine agonists are similar for all the agents. In the clinical trials reviewed, the following side effects were reported in the accompanying ranges in the actively treated groups: nausea 18 to 36%; symptomatic orthostatic hypotension 5 to 48% (highest with cabergoline and pramipexole); dizziness 11 to 37%; somnolence 10 to 35% (highest with apomorphine); and hallucinations 10 to 19%. Two studies reported pedal edema, cabergoline 8% and apomorphine 10%. Two studies reported confusion, pramipexole 14% and cabergoline 16%. Rare cases of cardiac valvular fibrosis have been reported with pergolide although this was not reported in the clinical trials. Screening for valvular disease is recommended with pergolide use. Similarly, problems with impulse control have also been recently reported but not in the clinical trials.

MAO B inhibitors. *Selegiline.* One Class III multicenter, double masked, parallel group study randomized 50 patients to selegiline (mean dose 10 mg/day) and 46 to placebo for 6 weeks.[15] There were greater than 80% completers (100% active, 93% controls). Fifty-eight percent of the selegiline group had improved "mean hourly overall symptom control" scores compared to 26% of the placebo group ($p = 0.002$). CGI change also favored selegiline ($p < 0.001$). Dyskinesia initially worsened in 60% of the selegiline patients and 30% of the placebo patients.

*Orally disintegrating selegiline.* One Class II, 12-week, multicenter, randomized, parallel group, double masked study randomized 94 patients to orally disintegrating selegiline (mean dose 2.5 mg/day) and 46 to placebo.[16] Information on allocation concealment was not provided. Off time was reduced by 32% (2.2 hours) in the active group vs 9% (0.6 hours) in the placebo group ($p = 0.001$). Hours on were increased 20% (1.8 hours) for the active group and 5% (0.4 hours) for the control group ($p = 0.006$). Dyskinesia did not significantly worsen with active treatment and was not reported in the placebo group. There was no report on change in levodopa dose.

*Rasagiline.* Two Class I, double masked, placebo controlled, parallel group studies compared rasagiline with placebo. In the Parkinson's Rasagiline: Efficacy & Safety in the Treatment of OFF (PRESTO) study, rasagiline 1.0 mg/day or rasagiline 0.5 mg/day was compared with placebo for 26 weeks.[17] There were 87.5% completers. The total daily off time decreased by 29% (1.8 hours) for rasagiline 1 mg/day and 23% (1.4 hours) for rasagiline 0.5 mg/day, which were both more than the decrease of 15% (0.9 hours) with placebo ($p < 0.0001$ for 1.0 mg/day; $p = 0.02$ for 0.5 mg/day). Compared to placebo, global impression, UPDRS ADL off, and UPDRS motor scores also improved significantly. Significant increases in on time corresponded to decreases in off time. However, for the 1.0 mg group, 32% of the increase in on time included troublesome dyskinesia ($p = 0.048$).

In the Lasting effect in Adjunct therapy with Rasagiline Given Once daily (LARGO) study,[18] rasagiline 1.0 mg/day was compared to entacapone 200 mg with each dose of levodopa (up to eight per day) and placebo in a double dummy paradigm (each drug compared to placebo; not directly compared to each other). A total of 687 patients were randomized: 231 to rasagiline, 227 to entacapone, and 229 to placebo. There were 87% completers (90% rasagiline, 87% entacapone, and 85% placebo). The total daily off time decreased by 21% (1.18 hours) for rasagiline 1.0 mg/day and 21% (1.2 hours) for entacapone, both of which were more than the decrease of 7% (0.4 hours) with placebo ($p \leq 0.0001$ for both rasagiline and entacapone). Compared to placebo, global impression, UPDRS ADL off, and UPDRS motor score on


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also improved significantly. Significant increases in on time corresponded to decreases in off time. There was no change in on time with troublesome dyskinesia and the percent of subjects with dyskinesia as an adverse effect was similar for all three groups.

*MAO-B inhibitor adverse effects.* Adverse effects with selegiline in the reviewed study[16] included nausea 20%, symptomatic orthostatic hypotension 12%, hallucinations and confusion 6% each. There was no mention of insomnia. In the article on orally disintegrating selegiline, 6% reported dizziness and 4% reported hallucinations. The incidence of other adverse events was not disclosed. In PRESTO,[17] rasagiline was associated with weight loss in 2.4 to 9.4%, vomiting in 3.7 to 6.7%, anorexia in 1.8 to 5.4%, balance difficulties in 3.4 to 5.5%, and three cases of melanoma (0.6%). In LARGO[18] the primary side effects were postural hypotension (2%), nausea (3%), peripheral edema (2%), depression (3%), dizziness (3%), hallucinations (2%), dyskinesia (5%), and sleep disorders (3%) but none were significantly more common than in controls.

COMT inhibitors. *Tolcapone.* Two Class II studies evaluated tolcapone vs placebo.[19,20] The first was a double masked, randomized, placebo controlled, multicenter 12-week trial with three treatment groups; tolcapone 100 mg TID, tolcapone 200 mg TID, and placebo.[19] There were 136 active and 66 placebo patients. No concealment allocation information was provided. Tolcapone 100 mg TID decreased off time 32% (2.3 hours), tolcapone 200 mg TID decreased off time 48% (3.2 hours), and placebo decreased off time 20% (1.4 hours) ($p < 0.01$ for the tolcapone 200 mg TID group). At both tolcapone doses, a significant improvement in investigator global score occurred, as well as a significant decrease in levodopa dose (≤200 mg) and number of levodopa doses per day (decreased by approximately one). Dyskinesia increased in the first 30 days but was treated effectively with reductions in levodopa dose.

The second Class II study was multicenter, double masked, and placebo controlled with follow-up ranging from 3 to 12 months.[20] Patients were randomized to one of three groups: tolcapone 100 mg TID (n = 60), tolcapone 200 mg TID (n = 59), and placebo (n = 58). There were 81% completers in the active groups and 93% in the control group. Off time decreased by 26.2% on tolcapone 200 mg TID, 31.5% on tolcapone 100 mg TID, and 10.5% on placebo ($p < 0.01$). There was a corresponding increase in on time by 20.6% in the 200 mg TID group and 21.3% in the 100 mg TID group. Levodopa doses dropped 16% for the tolcapone 100 mg TID group and 18% in the tolcapone 200 TID group compared to 4% for the placebo group. Dyskinesia developed or worsened in 37% at 100 mg TID of tolcapone, 52.5% at 200 mg TID of tolcapone, and in 21% of the placebo group.

*Entacapone.* Two Class I[18,21] and three Class II studies[22-24] evaluated entacapone vs placebo. In one Class I double masked, parallel group, multicenter trial, 103 patients received entacapone (200 mg with each dose of levodopa) and 102 received placebo for 24 weeks.[21] On time increased by 5% in the entacapone group. Patients who had the smallest percent of on time at baseline (<55%) had the largest increase in on time with entacapone. Dyskinesia developed in 53% of the entacapone patients vs 32% of the placebo patients ($p = 0.002$). Masking may have been compromised due to urine discoloration by entacapone. The other Class I study was the LARGO study.[18] In this study, rasagiline 1 mg/day was compared to placebo and entacapone 200 mg with each dose of levodopa (up to eight per day) was also compared to placebo in a double dummy paradigm. The active groups were compared to placebo, not each other. A total of 687 patients were randomized: 231 to rasagiline, 227 to entacapone, and 229 to placebo. There were 87% completers (90% rasagiline, 87% entacapone, and 85% placebo). The total daily off time decreased by 21% (1.2 hours) for entacapone, which was more than the decrease of 7% (0.4 hours) with placebo ($p < 0.0001$). Compared to placebo, global impression, UPDRS ADL off, and UPDRS motor score on also improved significantly. Significant increases in on time corresponded to decreases in off time. There was no change in on time with troublesome dyskinesia and the percent of subjects with dyskinesia as an adverse effect was similar for all three groups.

In a Class II multicenter, parallel group, randomized, placebo controlled double masked study, 197 patients received entacapone (200 mg/dose) and 104 received placebo in addition to their daily dose of levodopa.[22] Only 78% of patients randomized completed the trial. Off time decreased by 25.8% (1.6 hours) with entacapone compared to 13.4% (0.9 hours) with placebo. Thirty-four percent of patients reported dyskinesia as an adverse event on entacapone compared to 26% on placebo.

A Class II, multicenter, parallel group, randomized, double masked study evaluated 171 patients on entacapone 200 mg/dose (n = 85) or placebo (n = 86) for 6 months.[23] Allocation concealment was not described. There were 90% completers in both groups. Patients taking entacapone had a decrease in off time that was 22% more than the decrease with placebo ($p < 0.001$) and a concomitant increase in on time of 13% ($p < 0.001$). Worsening of dyskinesia was more common in the entacapone group (8.2%) than the placebo group (1.2%) ($p < 0.05$).

A Class II, multicenter, double masked, placebo controlled study of 162 patients randomized 3:2 to entacapone 200 mg/dose or placebo failed to show a benefit in favor of entacapone.[24] Allocation concealment was not described. Seventy-seven percent completed the 3-month study. Patients on entacapone had more dyskinesia (31%) than those on placebo (13%).

*COMT inhibitor adverse effects.* The adverse effects associated with tolcapone and entacapone were similar but more frequent with tolcapone in the stud-


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ies reported; however, it is important to stress that these studies cannot be directly compared. Diarrhea occurred in 20 to 34% of tolcapone treated patients in the reviewed trials and 8 to 20% with entacapone. Other side effects included nausea in 28 to 50% with tolcapone and 10 to 20% with entacapone; somnolence in 16 to 32% with tolcapone and 4% with entacapone; and hallucinations in 24% with tolcapone and 4 to 9% with entacapone. Symptomatic orthostasis was reported with tolcapone in 24% of patients in one study. Finally, an elevation of liver enzymes ALT and AST occurred in 1% of patients taking tolcapone 100 mg TID and 3% of patients taking tolcapone 200 mg TID. Rare cases of fatal hepatotoxicity have been reported with tolcapone leading to a recommendation of more stringent liver function monitoring.[25] Tolcapone should only be used in PD patients taking levodopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapy. If the patient does not have a substantial clinical benefit within 3 weeks of initiation of tolcapone, they should be withdrawn from the drug. In appropriate candidates for tolcapone, liver function monitoring should be done at baseline and then periodically (i.e., every 2–4 weeks) for the first 6 months and thereafter as clinically necessary.

Sustained release carbidopa/levodopa. Four Class III single center, double masked, crossover studies examining 97 total patients failed to demonstrate any difference in off time with sustained release carbidopa/levodopa compared to the immediate release preparation.[26-29] Baseline characteristics and allocation concealment were not described for any of the studies. The daily dose of levodopa was higher with the sustained release preparation, but there was a significant decrease in the number of doses per day with sustained release. Dyskinesia was only described in one study,[27] which was similar in the sustained release and immediate release groups. The adverse effects of both drugs were the same.

Conclusions. Entacapone (two Class I studies) and rasagiline (two Class I studies) are established as effective in reducing off time.

Pergolide (one Class I study), pramipexole (one Class I and one Class II study), ropinirole (two Class II studies), and tolcapone (two Class II studies) are probably effective in reducing off time.

Apomorphine subcutaneously injected (one Class II study), cabergoline (two Class III studies), and selegiline (one Class II study, one Class III study) are possibly effective in reducing off time.

Based on four Class III studies, sustained release carbidopa/levodopa does not decrease off time compared to immediate release. The doses of sustained release carbidopa/levodopa were higher, but given less frequently. Based on one Class II study, bromocriptine does not decrease off time compared to placebo.

Recommendations. For patients with PD with motor fluctuations the available evidence suggests the following (see appendix E-3):

- Entacapone and rasagiline should be offered to reduce off time (Level A).
- Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B). Tolcapone (hepatotoxicity) and pergolide (valvular fibrosis) should be used with caution and require monitoring.
- Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level c).
- Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C).

*Question 2: What is the relative efficacy of medications in reducing off time?* There was one Class I study,[18] four Class II studies,[9,30-32] and one Class III study[33] that compared the efficacy of antiparkinsonian medications in reducing off time. In one Class I study, there was no significant difference between rasagiline 1 mg/day and entacapone 200 mg with each levodopa dose in reducing off time (reduction of 0.8 hours relative to placebo for both; not powered to compare rasagiline to entacapone directly). There was no difference in dyskinesia or other adverse events.

In one Class II study, there was no significant difference between pramipexole mean dose 3.4 mg/day and bromocriptine mean dose 22.6 mg/day in the reduction in off time (15% vs 8%).[9] The study was not powered to show a difference between the two active groups. There were no differences in adverse events in the two groups.

In another Class II study, there was no statistical difference between reduction in off time with cabergoline mean dose 3.2 mg/day compared to bromocriptine 22.1 mg/day (50% vs 31.3%).[30]

In a Class II study comparing ropinirole mean dose 10 mg/day with bromocriptine mean dose 18 mg/day, ropinirole reduced off time by 17.7% compared to 4.8% with bromocriptine.[31] Adverse events were similar, except ropinirole caused more nausea and bromocriptine caused more hallucinations.

A three-week Class II study compared tolcapone 100 mg TID and entacapone 200 mg/dose.[32] Increase in on time showed a trend but was not statistically different between the two groups (tolcapone 1.3 hours vs entacapone 0.6 hours). Adverse events were similar.

In a Class III study, there was no significant difference in change in off time between tolcapone 100 to 200 mg TID and pergolide mean dose 2.2 mg/day (17.9% vs 18.2%).[33] Adverse events leading to withdrawal from the study were more common with pergolide (15% vs 5%).

Conclusions. Six studies (one Class I, four Class II, one Class III study) compared the efficacy of antiparkinsonian medications in reducing off time: rasagiline was similar to entacapone; bromocriptine was similar to pramipexole; tolcapone was similar to per-


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golide; cabergoline was similar to bromocriptine; tolcapone was similar to entacapone; and ropinirole was possibly superior to bromocriptine. Many of these studies were not powered to demonstrate superiority of one drug over another. Other than comparisons of ropinirole and bromocriptine, there is insufficient evidence to conclude which one agent is superior to another in reducing off time.

Recommendations. Ropinirole may be chosen over bromocriptine for reducing off time (Level C). Otherwise, there is insufficient evidence to recommend one agent over another (Level U).

*Question 3: Which medications reduce dyskinesia?* Two studies, one Class II and one Class III, evaluated the efficacy of medications in reducing dyskinesia.[34,35]

A Class II single center, double masked, placebo controlled, randomized, crossover trial enrolled 24 subjects for 3 weeks of treatment with amantadine (100 mg BID) and placebo.[34] Ninety-two percent of the subjects completed the trial. Total dyskinesia score (Goetz scale) decreased 24% after amantadine ($p = 0.004$). In addition, there was a 17% decrease in maximal dyskinesia score ($p = 0.02$) and a significant decrease in percentage of time with dyskinesia (UPDRS part IVa) ($p = 0.02$) on amantadine compared to placebo. UPDRS motor off state score improved ($p = 0.04$) and the on state score was unchanged. No adverse effects were reported in this study.

A Class III double masked, placebo controlled, parallel group study evaluated the effect of clozapine on the treatment of levodopa-induced dyskinesia in patients with severe PD for 10 weeks.[35] There were 76% completers. Clozapine treatment (mean dose 39.4 mg/day) resulted in a decrease in hours on with dyskinesia per day of 1.7, while hours on with dyskinesia increased in the placebo group by 0.7 hours (overall 2.4 hours difference between groups). Onset of change was noted at 4 weeks. Duration of on and off time and UPDRS motor scores were not different between groups. The most common adverse effects reported in this study were somnolence (100%), hypersalivation (38%), and asthenia (62%).

Studies of other drugs, including bupidine, dextromethorphan, idazoxan, istradefylline, memantine, nabilone, quetiapine, remacemide, riluzole, sarizotan, and talampanel did not meet the inclusion criteria.

Conclusions. Amantadine is possibly effective in reducing dyskinesia (one Class II study).

There is insufficient evidence to support or refute the effectiveness of clozapine in reducing dyskinesia (single Class III study).

Recommendations. Amantadine may be considered for patients with PD with motor fluctuations in reducing dyskinesia (Level C).

There is insufficient evidence to support or refute the efficacy of clozapine in reducing dyskinesia (Level U). Clozapine's potential toxicity including agranulocytosis, seizures, myocarditis, and orthostatic hypotension with or without syncope, and required white blood cell count monitoring must be considered.

**Surgical therapy.** *Question 4: For patients with PD, does DBS of the STN, GPi, or VIM reduce off time, dyskinesia, and antiparkinsonian medication usage, and improve motor function?* Patients undergoing DBS surgery are evaluated with the UPDRS ADL and motor sections before surgery in the medication off and medication on states to determine maximum improvement with medication. The improvement with DBS, except for the possibility of increased tremor control, is generally equivalent to the best improvement seen with medications; however, this benefit persists for a longer amount of time resulting in a decrease in off time. Follow-up evaluations are generally performed in the medication off and on states with the stimulators turned on. The baseline medication off scores are then compared to the follow-up medication off/stimulation on scores to determine the effect of stimulation. In order to reach an evidence class of III, an objective measure of symptoms must be used such as timed tapping or walking tests, patient symptom diaries, or patient self report questionnaires. The effect of stimulation on dopaminergic medication use is examined by converting daily dosages of these medications, with a formula which varies slightly across sites, to a single value referred to as the levodopa equivalence dose.

Subthalamic nucleus stimulation. Fourteen articles met inclusion criteria for STN stimulation. There were 4 Class III studies[36-39] and 10 Class IV studies.[40-49] All studies examined bilateral DBS of the STN. Only the Class III studies are discussed in detail. Details of the Class IV studies can be found in the evidence tables (see table 2 and table E-2).

A Class III, 6-month, prospective, multicenter trial examined 102 PD patients with 96 patients receiving bilateral implants (mean age 59.0 ± 9.6 years) and 91 patients completing a 6-month follow-up.[36] At 6 months, off medication with stimulation on, there was a mean improvement of 52.4% in UPDRS motor scores ($p < 0.001$) and a 43.7% improvement in UPDRS ADL scores compared to the baseline off medication state ($p < 0.001$). Patient diaries indicated an increase in on time without dyskinesia from 27% to 74% of the waking day ($p < 0.001$), a decrease in on time with dyskinesia from 23% to 7%, and a decrease in off time from 49% to 19% ($p < 0.001$). The Rush Dyskinesia scale improved 58% ($p < 0.001$) and there was a decrease in daily levodopa equivalence dose of 37.3% ($p < 0.001$). Adverse events included infections in 3.9% of patients, intracranial hemorrhage leading to hemiparesis in 2.9%, seizures in 2.9%, increased dyskinesia in 2.0%, diplopia in 2.0%, lead migrations in 2.9%, device infections in 2.9%, improper lead placement in 2.0%, and brachial plexus injury, dysarthria, headache, paresthesia, confusion, paralysis, pulmonary embolus, abnormal healing, seroma, device erosion,


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broken lead, and device with intermittent function each in 1.0% of the patients.

A second Class III study of 26 PD patients (mean age 59 ± 8 years) one year after DBS of the STN reported similar results.[37] There was a 66.3% improvement in UPDRS ADL scores ($p < 0.0001$) and a 64.3% improvement in UPDRS motor scores with stimulation in the medication off condition compared to baseline ($p < 0.0001$). Timed walking improved 37.6% ($p < 0.001$) and number of steps to walk 4.5 meters improved 46.6% ($p < 0.003$). Similarly, tapping scores increased by 45.1% ($p < 0.0001$). There was also an 86% improvement in dyskinesia (UPDRS item 32; $p < 0.0001$) and an 83% improvement in motor fluctuations (UPDRS item 39; $p < 0.0001$). Levodopa equivalence dose was decreased by 19.5% ($p < 0.001$). Adverse events included worsening of dysarthria in 15.4% of patients; depression in 7.7%; memory worsening in 7.7%; misplaced leads in 7.7%; scalp infection requiring system removal leading to the development of meningitis in 3.8%; seizures, hallucinations, confusion, dysphagia, eyelid apraxia, and lead fracture each in 3.8%.

A Class III study of 33 PD patients with a mean age of 58.5 ranging from 35 to 75 years 1 year after DBS of the STN also showed improvements in motor function.[38] UPDRS ADL (32.3%; $p < 0.001$) and motor (38.1%; $p < 0.003$) scores in the medication-off/stimulation on condition were significantly improved compared to baseline medication off scores. Finger tapping scores increased by 45.3% ($p < 0.001$) in the right hand and by 36.2% ($p < 0.002$) in the left hand. Patient diaries showed an increase in daily on time without dyskinesia from 38% at baseline to 76% at 1 year ($p < 0.002$). On time with dyskinesia was reduced from 18% to 4% and off time was also reduced from 44% to 20%. Levodopa equivalence dose was decreased by 44.2% ($p < 0.004$). Similar improvements were maintained in 19 patients 24 months after surgery. Surgical adverse events included transient confusion in 14.3% of patients, seizures in 8.6%, infection in 8.6%, visual disturbances in 2.9%, and hemiballismus in 2.9%. Stimulation related events included dysarthria in 28.6%, gait problems in 8.6%, paresthesia in 5.7%, depression in 2.9%, and muscle spasms in 2.9%. Adverse events related to the devices included lead replacements due to lack of benefit or misplacement in 25.7% of patients, IPG malfunctions in 22.9%, lead revisions in 20%, extension fractures in 5.7%, lead fracture in 2.9%, and extension erosion in 2.9%.

The final Class III study compared patients randomized to pallidotomy or DBS of the STN.[39] For purposes of this article, only the results of the 20 DBS patients (mean age 61, ranging from 55 to 66 years) are discussed ($p$ values not included). The median change in UPDRS ADL scores in the medication off and stimulation on condition compared to baseline medication off was 46.3%, and for UPDRS motor scores was 48.5%. The duration of dyskinesia decreased by 50% (UPDRS item 32) and the severity of dyskinesia decreased 100% (UPDRS item 33). Patients also completed the PD Quality of Life questionnaire that showed a median improvement of 23.2%. Levodopa equivalence dose was reduced by 33%. Adverse events included emotional lability in 30.0% of patients; increased drooling in 10.0%; postural instability in 10.0%; severe cognitive deterioration in 5.0%; CSF leakage requiring drainage in 5.0%; mild dysphasia, dysarthria, and dysphagia in 5.0%; transient confusion in 5.0%; extension strain in the neck (discomfort due to extension wire pulling with or without neck movement) in 5.0%; and displaced electrodes in 10%.

All 10 Class IV studies reported results similar to the Class III studies. All studies showed significant improvements in motor function and significant reductions in motor fluctuations, dyskinesia, and antiparkinsonian medication.

Globus pallidus stimulation. Three articles met inclusion criteria for GPi stimulation. There was one Class III study[36] and two Class IV studies.[50,51] Only the Class III study is discussed in detail; however, the details of the Class IV studies are available in the evidence tables (see table 2 and table E-2). The Class III study[36] was a 6-month, prospective, multicenter trial of 41 PD patients, 38 of whom received DBS (mean age 55.7 ± 9.8 years), with 36 patients completing the 6-month follow-up. At 6 months, there was a 33.3% improvement in UPDRS motor scores ($p < 0.001$) and a 35.8% improvement in UPDRS ADL scores ($p < 0.001$) with stimulation on compared to the baseline medication off condition. Patient diaries indicated an increase in on time without dyskinesia from 28% to 64% of the waking day ($p < 0.001$), a decrease in on time with dyskinesia from 35% to 12%, and a decrease in off time from 37% to 24% ($p < 0.01$). The Rush Dyskinesia scale showed an improvement of 67% ($p < 0.01$). There was no change in daily levodopa equivalence dose. Adverse events included intracranial hemorrhage in 9.8% of patients (7.3% leading to hemiparesis); increased dyskinesia in 7.3%; dystonia in 4.9%; lead migrations in 4.9%; and dysarthria, seizure, infection, broken lead, seroma, and abdominal pain each in 2.4%.

One Class IV study[50] of 20 patients receiving bilateral and 10 patients receiving unilateral DBS of the GPi (mean age 57.7, range 42 to 77 years) had results similar to the Class III study with a significant improvement >40% in UPDRS off medication with stimulation on at 6 and 12 months post surgery ($p < 0.005$) and a 92.9% reduction in dyskinesia at 6 months $p < 0.05$). The second Class IV study[49] included 26 PD patients (mean age 56.2 ± 8.6 years) with unilateral DBS of the GPi after 32.7 months of follow-up. In contrast to the other two studies, at long-term follow-up, UPDRS medication off and stimulation on motor scores worsened by 8.3%, UPDRS motor fluctuations worsened by 3.5%, and medication usage increased by 53.8%. On the other


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hand, dyskinesia scores were improved by 28% at long-term follow-up (no $p$ values included).

Thalamic stimulation. Four articles met inclusion criteria for thalamic stimulation.[52-55] All four articles were Class IV. Due to the low quality of evidence, thalamic stimulation is not discussed.

Adverse events. Given the importance of understanding the risk/benefit ratio for DBS surgery, four additional articles focusing specifically on adverse events from large series of patients with DBS are discussed.[56-59] The results from these studies are combined to include 360 total patients undergoing DBS, of which 288 were PD patients. Adverse events are categorized as surgical (during or within 1 month of surgery), hardware related, and stimulation related. Of the 360 patients undergoing DBS, death resulted in two patients due to pulmonary embolism and aspiration pneumonia (0.6%) and 2.8% had permanent neurologic sequelae. Other surgical complications not resulting in permanent neurologic sequelae included infection in 5.6% of patients, hemorrhage in 3.1%, confusion/disorientation in 2.8%, seizures in 1.1%, pulmonary embolism in 0.6%, CSF leak in 0.6%, peripheral nerve injury in 0.6%, and venous infarction in 0.3%. Complications related to the DBS hardware included lead replacement due to fracture, migration, or malfunction in 5% of patients; lead reposition due to misplacement in 2.8%; extension wire replacement due to fracture or erosion in 4.4%; IPG replacement due to malfunction in 4.2%; IPG repositioning for cosmetic purposes or due to skin growth in 1.7%; and allergic reaction to the hardware in 0.6%. Stimulation-related adverse effects are generally mild and can be resolved with reprogramming of the stimulation parameters. The most common stimulation adverse effects are paresthesia, dysarthria, eyelid opening apraxia, hemiballismus, dizziness, dyskinesia, and facial contractions.

Conclusions. Based on four Class III studies, DBS of the STN is possibly effective in improving motor function and reducing motor fluctuations, dyskinesia, and antiparkinsonian medication usage in PD patients. Adverse events may limit application of this therapy.

Based on one Class III study and two Class IV studies, data are insufficient to determine if DBS of the GPi is effective in reducing motor fluctuations, dyskinesia, and antiparkinsonian medications or in improving motor function.

There is insufficient evidence to support or refute the efficacy of DBS of the VIM nucleus of the thalamus in reducing motor fluctuations, dyskinesia, and medication usage or to determine if DBS of the VIM improves motor function.

Recommendations. DBS of the STN may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C). Patients need to be counseled regarding the risks and benefits of this procedure.

There is insufficient evidence to make any recommendations about the effectiveness of DBS of the GPi or VIM nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients (Level U).

*Question 5: Which factors predict improvement after DBS?* Of the 14 articles that met inclusion criteria for DBS of the STN, there were two prognostic Class II studies[42,45] and 12 Class IV studies.[36-41,43,44,46-49] Only the Class II studies are discussed in detail. Although these studies were rated Class IV relative to Question 4 regarding efficacy, they earned grades of Class II relative to prognosis for Question 5. Efficacy in these two studies was similar to the Class III studies reported above.

One Class II study was designed to examine factors predictive of outcome after DBS of the STN in 41 PD patients (mean age 56.4 $\pm$ 8.6).[42] Regression analyses indicated that age ($p < 0.005$) and disease duration ($p < 0.007$) had a relationship with outcome. Therefore, patients were stratified by mean age, examining those 56 and older separately from those younger than 56 years. It was reported that the younger group had greater improvements in medication off UPDRS ADL (70.6% vs 53.3%; $p < 0.05$) and UPDRS motor (70.6% vs 60.0%; $p < 0.05$) scores with stimulation compared to baseline. Similarly, the group was stratified by mean disease duration and those with disease duration less than 16 years had greater improvements than those with disease duration 16 years or greater in medication off UPDRS ADL (64.5% vs 57.0%; $p < 0.05$) and UPDRS motor (67.6% vs 61.6%; $p < 0.05$) scores with stimulation compared to baseline. Levodopa responsiveness, defined as low residual motor disability on drug compared to the off state, correlated strongly with benefit from STN DBS (correlation coefficient 0.74). In addition to age and disease duration, it was concluded that levodopa responsiveness is the strongest predictor of outcome ($p < 0.002$).

The second Class II study[45] included 25 patients with a mean age of 57.2 years, ranging from 34 to 76 years at the time of DBS implantation. The study examined age, sex, disease duration, baseline drug usage, baseline dyskinesia, age at onset, and baseline levodopa responsiveness by stratifying each variable at the median. Levodopa responsiveness was the only factor that was shown to be related to postsurgical outcome ($p < 0.004$). The smaller size of this study reduced the ability to detect the association between age and disease duration and outcome.

There were no studies of GPi or VIM DBS examining predictive factors.

Conclusions. Based upon two Class II studies, preoperative response to levodopa is probably predictive of postsurgical improvement. Based on one Class II study, younger age and shorter disease duration (less than 16 years) are possibly predictive of greater improvement after DBS of the STN.

Data are insufficient to reach a conclusion on predictive factors influencing improvement after DBS of the GPi and VIM DBS.



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Recommendations. Preoperative response to levodopa should be considered as a factor predictive of outcome after DBS of the STN (Level B).

Age and duration of PD may be considered as factors predictive of outcome after DBS of the STN. Younger patients with shorter disease durations may possibly have improvement greater than that of older patients with longer disease durations (Level C).

There is insufficient evidence to make any recommendations about factors predictive of improvement after DBS of the GPi or VIM nucleus of the thalamus in PD patients (Level U).

**Recommendations for future research.** *Medical treatment.* Comparative, randomized, double masked, controlled trials are needed to determine which drugs are the most effective in reducing off time and dyskinesia in patients with moderate to advanced PD. Uniform and more specific inclusion criteria need to be reported in these series. Outcome measures should also be standardized to include a specific diary form for measuring on/off/dyskinesia. Non-motor fluctuations, PD-specific quality of life measures, and neuropsychiatric features require greater assessment and reporting. Additional novel drug classes need further investigation.

*Surgical treatment.* Further research in DBS of the STN, GPi, and VIM nucleus of the thalamus should include objective clinical measures such as finger tapping, walking times, patient diaries, or patient global assessments and include the effect of DBS on disability status. Raters should be masked to whether surgery was performed for evaluations of motor function. Currently, most DBS series include a homogeneous young, fluctuating population, based on the clinical impression that this group most robustly responds to DBS. Additional studies should systematically examine which factors are predictive of a positive outcome and evaluate the optimal timing for surgery. Long duration prospective trials of DBS vs optimal medical management would provide tremendous clinical guidance. A large multicenter, randomized, double masked trial examining the long-term effects of DBS of the GPi and the STN compared to optimal medical management is currently underway and is anticipated to provide a stronger level of evidence for the effects of DBS vs optimal medical management. Research to determine cost-benefit analysis over the longer term is necessary. In addition, research to document regional disparity in access is needed.

**Disclaimer.** This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

**Disclosure.** R. Pahwa has received research grant support or participated in clinical trials for GSK, Novartis, BI, Medtronic, and Teva, is a consultant for GSK, Teva, Novartis, BI, Medtronic, and Valeant and is a speaker for GSK, Novartis and Medtronic; S.A. Factor has received research grant support from Teva, is a consultant for Valeant and GSK and is a speaker for Novartis and BI; K.E. Lyons has received research grant support from GSK and has been a consultant for Teva, GSK, Novartis and Medtronic; W.G. Ondo has received research grant support or participated in clinical trials for GSK and Novartis and is a speaker for GSK, BI and Novartis; J. Miyasaki has received research grant support from BI and Elan, has received educational grant support from Teva and is a consultant for BI; W.J. Weiner has received research grant support from Teva and BI, is a consultant for Teva, and a speaker for BI, G. Gronseth, H. Bronte-Stewart, M. Hallett and J. Stevens have no conflicts to declare.


### Acknowledgment

The authors thank Nancy King and Wendy Edlund for administrative support and Andrew Wilner, MD, for help with manuscript preparation.


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# Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology

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*Neurology* 2006;66;983-995; originally published online Apr 2, 2006;
DOI: 10.1212/01.wnl.0000215250.82576.87

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