

# Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review

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

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**Abstract**—In 1993, the last AAN Practice Parameter on medical treatment of Parkinson's disease (PD) concluded that levodopa was the most effective drug for management of this disorder. Since then, a number of new compounds including non-ergot dopamine agonists (DA) and sustained-release levodopa have been released and studied. Thus, the issue of treatment in de novo PD patients warrants reexamination. Specific questions include: 1) does selegiline offer neuroprotection; 2) what is the best agent with which to initiate symptomatic treatment in de novo PD; and 3) is there a benefit of sustained release levodopa over immediate-release levodopa? Using evidence-based principles, a literature review using MEDLINE, EMBASE, and the Cochrane Library was performed to identify all human trials in de novo PD between 1966 and 1999. Only articles that fulfilled class I or class II evidence were included. Based on this review, the authors conclude: 1) Selegiline has very mild symptomatic benefit (level A, class II evidence) with no evidence for neuroprotective benefit (level U, class II evidence). 2) For PD patients requiring initiation of symptomatic therapy, either levodopa or a DA can be used (level A, class I and class II evidence). Levodopa provides superior motor benefit but is associated with a higher risk of dyskinesia. 3) No evidence was found that initiating treatment with sustained-release levodopa provides an advantage over immediate-release levodopa (level B, class II evidence).

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**Mission statement.** *The Quality Standards Subcommittee of the American Academy of Neurology is charged with developing practice parameters for neurologists for diagnostic procedures, treatment modalities, and clinical disorders. The selection of topics for which practice parameters are used is based on prevalence, frequency of use, economic impact, membership involvement, controversy, urgency, external constraints, and resources required.*

Parkinson's disease (PD) is a common neurodegenerative disorder with an estimated prevalence of 100 to 200/100,000 population. As it is a progressive disorder that results in significant disability 10 to 15 years after onset, the financial and social burden of this disease is considerable,<sup>1</sup> particularly with our aging population. The worldwide cost of medications alone is estimated to be US \$11 billion per year, with costs increasing three- to fivefold for patients with advanced disease.<sup>2,3</sup>

Ideally, if a drug were available, initial treatment of PD should slow disease progression. Once symptomatic benefit is required, treatment should reduce disability without inducing complications over the long term. Based on these goals, there are several controversial questions regarding initial PD treatment. These include: Does selegiline have neuroprotective benefit in the treatment of early PD? What is the best agent to initiate specific dopaminergic therapy in early PD? Finally, is there a benefit of sustained-release levodopa over immediate-release levodopa in the treatment of early PD?

The 1993 AAN Practice Parameter examined anticholinergics, amantadine, selegiline, dopamine agonists, and levodopa in the treatment of PD.<sup>4</sup> The conclusions were that:

1. Levodopa is usually the most effective on average of all the drugs for symptoms of PD, especially for bradykinesia or rigidity (class I, II, III) (table 1).
2. Anticholinergic agents are commonly used as ini-

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**Table 1** Levels of evidence employed in 1993

Class I	Evidence provided by one or more well-designed, randomized, controlled clinical trials.
Class II	Evidence provided by one or more well-designed clinical studies such as case control, cohort studies, etc.
Class III	Evidence provided by expert opinion, nonrandomized historical controls or case reports of one or more.

tial therapy, especially in cases where tremor is predominant, but there is evidence that anticholinergic agents are better than levodopa for tremor (class II).

3. Amantadine has a modest effect on all features of the disease and has a low adverse effect profile (class II).
4. Dopamine agonists are effective for all features of the disease, but are not generally as effective as levodopa and are more expensive than levodopa (class I, II).
5. Selegiline. Class I evidence suggests a mild therapeutic and partial protective effect from selegiline, but confirmation of the neuroprotective effect is needed. Selegiline also has antidepressant activity that offers modest direct symptomatic benefit for PD (Evidence not classified in statement).

Recent publications have compared levodopa directly to dopamine agonists (pramipexole, ropinirole and cabergoline)<sup>5-7</sup> in treatment of de novo (previously untreated) patients with PD. These studies were a result of concern that early use of levodopa might predispose patients to develop long-term motor complications<sup>8</sup> such as wearing off, dyskinesia, dystonia, and on-off phenomenon. Some studies have reported incidence of these complications as high as 80% in young patients and 44% in older patients after 5 years of levodopa treatment.<sup>9</sup> The frequency of dyskinesias alone is reported to range between 30 and 80% after 5 to 7 years of levodopa use. Dyskinesias may become severe with pronounced interference in the performance of activities of daily living. Hence, quality of life can be negatively and significantly affected by dyskinesias. Increasing problems with motor fluctuations also leads to use of several different medications in combination, typically at higher doses.<sup>3,10,11</sup>

Ideally, patients should not have to choose between accepting the inevitability of dyskinesias or unacceptable levels of disability. The goal of treatment should be to obtain an optimal reduction of parkinsonism with a minimal risk of long-term side effects. In an effort to decrease the risk of motor complications, attention has turned to initial use of dopamine agonists as monotherapy. Historically, dopamine agonist monotherapy has been thought to be poorly tolerated with decreased efficacy and a delay in onset of symptomatic benefit in comparison with levodopa.<sup>12-15</sup> This may not be the case with newer agonists. In addition, one of the theoretical benefits

of dopamine agonists over levodopa is a longer half-life resulting in less pulsatile stimulation of dopamine receptors. This may reduce the risk of the development of dyskinesias and motor fluctuations.<sup>16,17</sup>

The common occurrence of the wearing-off phenomenon (end of dose bradykinesia) with immediate-release levodopa led to the development of sustained-release levodopa.<sup>16,17</sup> Whether motor complications are influenced by initial symptomatic treatment of PD with sustained-release levodopa versus immediate-release levodopa was investigated. Evidence comparing these two levodopa preparations is evaluated.

**Literature review.** To prepare this report, experienced neurologists with special expertise in PD were appointed by the Quality Standards Subcommittee (QSS). The English literature between 1966 and 2000 was searched using MEDLINE, EMBASE, and the Cochrane Library. The key words used were: early or de novo Parkinson's disease, human trials, double-blind method. Since the effectiveness of levodopa and dopamine agonists compared with placebo in the treatment of early PD is established, we focused on studies comparing dopamine agonists with levodopa. Articles were identified using the generic term dopamine agonist or specific drug names (bromocriptine, cabergoline, pergolide, lisuride, pramipexole, ropinirole). Similarly, for controlled-release versus regular or immediate-release levodopa, comparator only studies were used. In examining the neuroprotective effects of selegiline, only studies in de novo patients were evaluated. Given the controversy generated by the report of Lees et al.<sup>18</sup> that mortality was increased in patients with PD taking selegiline, studies utilizing selegiline in patients already receiving symptomatic therapy were included to address the safety of selegiline in this patient population.

The results of the literature search were as follows: 38 articles for selegiline were identified, two of which addressed the issue of neuroprotection. Articles were rejected for the following reasons: 13 utilized selegiline as adjunctive treatment, 5 examined symptomatic benefit only, 5 examined nonmotoric effects of selegiline, 3 were repeat publications, 3 were interim reports, 3 were commentaries on ongoing research, and 1 was a review, not a meta-analysis. Three articles addressing safety of selegiline in PD were reviewed. Seventy-eight articles for dopamine agonists used as monotherapy in de novo patients were identified; only three were long-term studies (2 years or longer) fulfilling AAN criteria for level I or II evidence (criteria defined in table 2). Articles were rejected for the following reasons: 36 utilized the dopamine agonist as adjunctive treatment, 19 did not use a levodopa (active) control, 5 utilized nonmotor endpoints, 5 provided level IV evidence, 4 were open-label studies, 3 were interim reports with subsequent publication of the complete study, 2 were repeat publications, 1 was a review article, not a meta-analysis, and 1 was a report of human toxicity. Only one article was found that examined immediate-

**Table 2** Current levels of evidence classification

Rating of recommendation	Translation of evidence to recommendations	Rating of therapeutic article
A = Established as effective, ineffective or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
B = Probably effective, ineffective or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a through d.
C = Possibly effective, ineffective or harmful for the given condition in the specified population	Level C rating requires at least two convincing and consistent class III studies	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
U = Data inadequate or conflicting; given current knowledge, treatment is unproven		Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

release versus sustained-release levodopa in a trial fulfilling AAN criteria for level II evidence.

**Selegiline.** *What is the role of selegiline in the treatment of early PD?* A neuroprotective benefit of selegiline through decreased free radical production was proposed<sup>19</sup> and resulted in the DATATOP (Doprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) clinical trial. An interim analysis of the DATATOP trial demonstrated that selegiline reduced the risk of developing disability requiring levodopa therapy by 50%.<sup>20</sup> The authors concluded that this was possibly consistent with a neuroprotective effect. Further follow-up of the patient cohort revealed a symptomatic benefit of selegiline<sup>21</sup> with a 17.2% absolute reduction in the risk of requiring levodopa by selegiline compared with placebo. Even patients who did not experience an initial improvement in the Unified Parkinson Disease Rating Scale (UPDRS) when selegiline was started had a decreased likelihood of reaching the endpoint of requiring levodopa. These results were reported as hazard ratios and were significant. UPDRS scores had a slower rate of worsening in the selegiline group compared with placebo. In a second study examining this issue, Palhagen et al.<sup>22</sup> found a 4-month delay to requiring levodopa in those randomized to selegiline. The rate of decline of the motor UPDRS scores was

significantly slower at 6 months. Additionally, the rate of decline of motor UPDRS scores from baseline to the end of the washout was significantly slower for the selegiline-treated patients. Since both groups<sup>20,22</sup> found an initial decline in functional disability during the 2-month washout period, it must be concluded that symptomatic benefit at least partially explained the reduced risk of requiring levodopa. CSF homovanillic acid levels continued to manifest changes induced by selegiline 2 months after the last administration of the drug.<sup>23</sup> Although these differences were not significant, it has been argued that a 2-month washout period was insufficient to completely exclude symptomatic benefit as the sole basis for the differences in selegiline versus placebo groups seen in DATATOP. In addition, if selegiline had neuroprotective effects, those taking selegiline for a longer period of time would be expected to show less evidence of clinical progression compared with those starting it later in the course of the disease. Once levodopa was initiated, motor complications would be expected to be less frequent in those who had received selegiline than in those who had not. Neither of these expectations was realized, further supporting the idea that the symptomatic effects of selegiline accounted for the delay in the need for levodopa therapy.<sup>24,25</sup> Both the DATATOP<sup>20</sup> and Palhagen et

al.<sup>22</sup> studies provided class II evidence that neuroprotective benefits were not seen with selegiline.

One study raised the issue of the safety of selegiline. Lees et al.<sup>18</sup> reported a significant excess mortality in patients receiving selegiline with levodopa (76/271) compared with those receiving levodopa alone (44/249). Concerns about this study include: the high percentage of patients withdrawn from their original treatment assignment (>50), the re-randomization of patients unable to tolerate the trial drug or gain useful functional improvement to a different arm of the trial, the inclusion of these “randomized” patients in the intention-to-treat analysis, questions about the equivalency of patient groups (specifically comorbid conditions), the predominant death certificate diagnosis of cause of death being PD in patients with relatively brief disease duration, and the difficulty reconciling the findings of this study with numerous other reports that have failed to demonstrate an increase in mortality with selegiline. A meta-analysis of prospective trials with long-term follow-up including patients with similar exposure to selegiline as in the UK Parkinson Disease Research Group study was performed.<sup>26</sup> There was no difference in mortality between selegiline and nonselegiline treatment groups. Analysis of levodopa plus selegiline versus levodopa alone did not reveal a difference in mortality rates. The Parkinson Study Group (PSG) reported that there was no difference in mortality in the 800 original DATATOP subjects who had been assigned to deprenyl, tocopherol, or combined treatments after an average follow-up of 8.2 years. The mortality rate observed in these patients was very similar to that expected in the age- and sex-matched US population.<sup>27</sup>

**Conclusions.** Selegiline has mild symptomatic benefit (class II). There is no convincing clinical evidence for neuroprotective benefit with selegiline (class II). There is no convincing evidence for increased mortality with selegiline whether it is given in combination with levodopa or as monotherapy (class II).

### **Recommendations for patients with PD who require symptomatic treatment.**

- Initial symptomatic treatment of patients with PD with selegiline in order to confer mild, symptomatic benefit prior to the institution of dopaminergic therapy may be considered (level A, class II evidence).
- There is insufficient evidence to recommend the use of selegiline to confer neuroprotection in patients with PD (level U).

**Initiating dopaminergic treatment.** *When symptomatic therapy is required does levodopa or a dopamine agonist offer best control of motor symptoms?* Once functional disability in PD requires treatment with a dopaminergic agent, the choice of levodopa versus a dopamine agonist has been arbitrary. Decades of debate concerning this issue did not clarify the choice

because the clinical trials conducted in those years were inadequate to answer the question.<sup>28,29</sup> In this evidenced based-review, only one article provided class I evidence comparing levodopa against pramipexole,<sup>7</sup> while two articles providing class II evidence compared a dopamine agonist (cabergoline 1, ropinirole 1)<sup>5,6</sup> versus levodopa as early monotherapy. All three of these studies compared the effect of a single agonist versus levodopa in the treatment of PD patients who were not receiving dopamine agonist or levodopa therapy. Each study was designed to allow the addition of open-label levodopa to “rescue” patients who were not doing well motorically. Although each study was designed to evaluate long-term motor complications associated with dopaminergic therapy, they also evaluated basic parameters of PD including motor response and effect on activities of daily living (ADL). The definition of motor complications and the assessment of those complications differed in each study. All dopamine agonists and levodopa demonstrated efficacy in the relief of motor symptoms.

The study of cabergoline versus levodopa by Rinne et al.<sup>5</sup> found that the motor portion of the UPDRS (part III) decreased by 40 to 50% with both drugs during the first year of therapy. Levodopa appeared to be better than cabergoline for improvement in both part II (ADL) and part III (motor) of the UPDRS,<sup>30</sup> but the publication does not report a statistical comparison of these data. After 4 years in the clinical trial, levodopa subjects still showed an average of 30% improvement in motor disability (part III), while patients treated with cabergoline showed a 22 to 23% improvement.<sup>5</sup> The same pattern was seen after 1 year and 4 years of treatment with regard to improvement in ADLs, again without reports of statistical comparison.

The study of ropinirole versus levodopa by Rascol et al.<sup>6</sup> found that for patients who completed the study (5 years), levodopa treatment resulted in a significantly greater increase in motor improvement than did ropinirole treatment (part III UPDRS, levodopa 4.8 point improvement, ropinirole 0.8 point improvement,  $p = 0.008$ ). They also reported that there was no significant difference between the treatment groups at 5 years with regard to score on the ADL portion of the UPDRS (part II, UPDRS, + 1.6 points for ropinirole, 0.0 point change for LD,  $p = 0.08$ ). These results suggest that for the course of the study, levodopa produced more motor improvement than ropinirole.

The study of pramipexole versus levodopa by the PSG<sup>7</sup> was assessed as providing class I evidence due to its lower dropout rate (13.9% compared with 48.9% withdrawal rate in the ropinirole study and insufficient reporting of withdrawals and losses to follow-up in the cabergoline study). The pramipexole study found that after 23.5 months of treatment, levodopa resulted in a significantly greater improvement than pramipexole in both the motor and ADL portions of the UPDRS (motor, levodopa 7.3 points, pramipexole 3.4 points  $p < 0.001$ ; ADL, levodopa 2.2 points, pramipexole 1.1 points,  $p = 0.001$ ). It should

**Table 3** Levodopa versus dopamine agonists as monotherapy

Study	Parkinson Study Group <sup>7</sup>		Rinne et al. <sup>5</sup>		Rascol et al. <sup>6</sup>	
Level of evidence	Class I		Class II		Class II	
Agonist	Pramipexole		Cabergoline		Ropinirole	
No. of patients	301		412		268	
Study duration, y	2		3–5		5	
Efficacy	<u>Motor</u> *	<u>ADL</u> *	<u>Motor</u> †		<u>Motor</u> *	<u>ADL</u> *
LD	7.3	2.2	30		4.8	0
Agonist	3.4	1.1	22		0.8	1.6
Motor complications, %	<u>All motor</u>	<u>Dyskinesias</u>	<u>All motor</u>	<u>Dyskinesias</u>	<u>Wearing off</u>	<u>Dyskinesias</u>
LD	51	31	34	14	34	45
Agonist	28	10	22	6	23	20
Patients remaining on agonist alone, %	32		35		16	

\* Change in UPDRS scores from baseline (absolute values).

† Percent improvement in UPDRS scores from baseline.

ADL = activities of daily living; UPDRS = Unified PD Rating Scale.

be noted that in both the ropinirole and pramipexole studies,<sup>6,7</sup> investigators were allowed to add open-label levodopa in the agonist-treated patients if there was insufficient symptomatic benefit from the agonist alone.

**Conclusions.** Levodopa, cabergoline, ropinirole, and pramipexole are effective in ameliorating motor and ADL disability in patients with PD who require dopaminergic therapy.

Levodopa is more effective than cabergoline, ropinirole, and pramipexole in treating the motor and ADL features of PD.

**Initiating dopaminergic treatment.** *When symptomatic therapy is required, does levodopa or a dopamine agonist offer the most favorable long-term complication profile?* All three studies<sup>5-7</sup> demonstrated that levodopa, cabergoline, ropinirole, or pramipexole have efficacy in alleviating motor symptoms of PD (table 3). All three of these studies defined motor complications differently. The cabergoline study used a checklist of symptoms suggesting motor fluctuations to determine the endpoint. The study staff documenting the checklist findings was not specified. The motor fluctuation abnormalities had to be present on two subsequent study visits to be considered present. Motor fluctuations in this study included wearing off, dyskinesias, and random freezing (which were also evaluated in the ropinirole and pramipexole studies). However, the motor complications checklist in the cabergoline study also included nocturnal akinesia, early morning akinesia, “off” period freezing, early morning dystonia, dose-related “off” period dystonia, and dose-related “on” period dystonia. These latter items were not evaluated in the ropinirole or pramipexole studies. The cabergoline study found an absolute risk reduction of 12% for the development of “motor complications” during the study comparing this

agonist (with or without levodopa rescue) to levodopa.<sup>5</sup> The motor complication endpoint was reached in 22% of patients treated with cabergoline versus 34% treated with levodopa ( $p < 0.02$ ). A subanalysis of the two most frequent motor complications (daily wearing off and peak dose dyskinesia) utilizing a Cox model revealed borderline significant difference between cabergoline and levodopa treatment for end of dose failures and a significant difference in favor of cabergoline for dyskinesias without or with levodopa. The median duration of treatment was 3.7 years. At the time of reporting, 35% of patients could be satisfactorily managed on cabergoline monotherapy. Patients included in this analysis were treated for at least 3 years and up to 5 years. Adverse events were higher in the cabergoline group (75.8%) versus levodopa (65.7%), with nausea being the most common in both.<sup>30</sup>

In the study of ropinirole versus levodopa,<sup>6</sup> the primary endpoint was dyskinesias rather than other types of motor complications. The absolute risk reduction for dyskinesias after 5 years of treatment was 26% for the ropinirole group (monotherapy or with the later addition of levodopa adjunctive therapy). If only disabling dyskinesias were considered, the absolute risk reduction was 14% in the ropinirole group (number needed to treat with 95% CI is 7 [4 to 16]). Seven patients would need to start on a dopamine agonist first strategy instead of a levodopa first strategy to prevent one additional patient from developing dyskinesias. In this study, dyskinesias were assessed using part IV of the UPDRS scale that is obtained by patient interview.

Adverse events were similar in the levodopa and ropinirole monotherapy groups, with the two most common reasons for dropping out of the study being nausea and hallucinations. The incidence of hallucinations was higher in the ropinirole group (31/179, 17%) than in the levodopa group (5/89, 6%), as was

the incidence of edema of the legs (ropinirole 25/179, 14%; versus levodopa 5/89, 6%) and somnolence (49/179, 27%; versus levodopa 17/89, 19%). However, dropout rates due to adverse events were no different in the two treatment groups. Retention of subjects in the 5-year study was 47.5% for the ropinirole group and 50.6% for the levodopa group. Among patients who completed the study and were originally randomized to ropinirole monotherapy, 16% were maintained on ropinirole monotherapy for 5 years (based on intention-to-treat analysis). A lower percentage of the levodopa group required the addition of adjunctive open-label levodopa (35.6% versus 51% taking ropinirole). The results demonstrate that initiation of treatment with ropinirole and the later addition of levodopa as necessary resulted in a significantly lower incidence of dyskinesia compared with levodopa alone.

The PSG study of pramipexole versus levodopa monotherapy in PD demonstrated similar findings.<sup>7</sup> Motor complications, defined as dyskinesias, wearing off, and on-off motor fluctuations, were significantly less common in the pramipexole group (28%) versus levodopa-treated patients (51%) at the end of 23.5 months. Motor complication also occurred less frequently in the pramipexole-treatment group in each of the four 6-month study periods. Most of the motor endpoints occurred after the addition of supplemental levodopa in both treatment groups. Thirty-two percent of the originally randomized group of pramipexole monotherapy patients were maintained on monotherapy until the end of the study (48/151). This study also examined the impact of treatment on the quality of life of patients using the PD Quality of Life Scale (PDQUALIF) and the EuroQol. During the first 78 weeks of the trial, there was no difference in quality of life measures for either treatment group. At 102 weeks, a significant group difference in the PDQUALIF score in favor of the levodopa group was detected. This was also seen in the visual analog component of the EuroQol during the same time frame. Motor endpoints (wearing off, dyskinesias, or on-off fluctuations) in this study were prespecified and defined. One blinded investigator at each site made the judgment as to the occurrence of a dopaminergic complication.

Significantly more patients in the pramipexole group experienced somnolence ( $p = 0.003$ ), hallucinations ( $p = 0.03$ ), and both generalized ( $p = 0.01$ ) and peripheral edema ( $p = 0.002$ ) compared with those in the levodopa group. The group difference in somnolence and hallucinations emerged during the dose escalation phase of the trial and the edema difference emerged during the maintenance phase of the trial.

As noted in the 1993 practice parameter on this subject, treatment with dopamine agonists is more costly than the use of levodopa. This remains true.

**Conclusions.** Cabergoline, ropinirole, and pramipexole treatment of PD patients requiring dopaminergic therapy results in fewer motor complications

(wearing off, dyskinesias, on-off motor fluctuations) than levodopa treatment after 2.5 years of follow-up.

Cabergoline, ropinirole, and pramipexole treatment of PD patients requiring dopaminergic therapy is associated with more frequent adverse events including hallucinations, somnolence, and edema than levodopa therapy.

**Recommendations.** In patients with PD who require the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. The choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each individual patient with PD (level A, class I and class II evidence).

*Sustained-release versus immediate release levodopa: When initiating levodopa therapy, which formulation should be used—immediate-release or sustained-release levodopa?* Only one study compared sustained-release and immediate-release formulations of levodopa in a prospective, randomized, double-blind manner.<sup>31</sup> The 5-year study (“CR First”) had an overall low rate of dyskinesias (20.6% immediate-release Sinemet (DuPont Pharmaceuticals, Wilmington, DE) versus 21.6% in the Sinemet CR group). The diagnostic criteria used to define the presence of dyskinesias and motor fluctuations included review of patient diaries and observations of investigators in the clinic recorded on a standard questionnaire. The only difference detected between the treatment groups was a greater improvement in activities of daily living scores in the Sinemet CR group (mean change for immediate release +0.2 compared to -0.8 in the Sinemet CR group,  $p = 0.031$ ). The results of this study do not demonstrate sufficient differences to recommend controlled-release levodopa over immediate-release levodopa when initiating levodopa treatment. The study design initiated treatment with twice-daily dosing, thereby resulting in pulsatile stimulation from both formulations. Therefore, the lack of difference in the treatment groups may reflect poor study design rather than lack of superior efficacy.

**Conclusions.** When initiating therapy with levodopa, there is no difference in the rate of motor complications between immediate-release levodopa and sustained-release levodopa.

**Recommendations.** For patients with PD in whom levodopa treatment is being instituted, either an immediate-release or sustained-release preparation may be considered (level B, class II evidence).

**Future research needs.** Since there is a significant difference in the incidence of dyskinesias between levodopa monotherapy and dopamine agonist monotherapy, the relative impact of dyskinesias versus motor impairment on quality of life in PD needs to be determined. The relative importance of relief of motor symptoms compared with the impact on quality of life that dyskinesias produce would assist the neurologist in deciding which agent to utilize.

Although this parameter examined levodopa monotherapy compared with dopamine agonist monotherapy, the potential utility of combination therapy or the early addition of agonist before motor complications arise is not known. Large groups of patients in such trials would be required to enable valid conclusions to be drawn.

All the comparative trials of levodopa versus a dopamine agonist have examined levodopa monotherapy, agonist monotherapy, and agonist monotherapy plus rescue levodopa. No study has yet examined with as much detail levodopa monotherapy plus agonist rescue if motor complications appear. This would help determine if there is any long-term difference in motor performance and/or motor complications related to the initial choice of therapy in patients with PD.

Investigations of whether the early onset of mild dyskinesia or motor fluctuations predict a different outcome in patients with PD for greater than 5 years are 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.

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### Appendix

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