

# Advanced Strategies for Treatment of Parkinson's Disease: The Role of Early Treatment

Michael W. Jann, PharmD

**P**arkinson's disease (PD) is a progressive neurodegenerative disease associated with motor dysfunction characterized by bradykinesia, and at least 1 of the following: resting tremor, muscle rigidity, and postural instability.<sup>1</sup> Levodopa has been considered the standard therapy for PD due to its ability to control the symptoms of motor dysfunction.<sup>2</sup> Levodopa is converted in the neuron by striatal enzymes to dopamine to increase brain dopamine levels and treat motor symptoms. Carbidopa inhibits the peripheral plasma breakdown of levodopa to enhance delivery to the brain.<sup>3</sup> After initially experiencing benefit with levodopa, with continued treatment, patients may develop dyskinesia and other motor complications, as well as nonmotor adverse effects.<sup>2</sup> Additionally, the beneficial effects of levodopa wear off over time and its effectiveness gradually diminishes. The complications and wearing-off of levodopa effectiveness will be experienced by as many as 50% of patients within 5 years of initiating therapy.<sup>3</sup> A recent study found that early treatment was cost-effective when patients with PD were treated with a dopamine agonist or monoamine oxidase type B (MAO-B) inhibitor (from a United Kingdom payer perspective).<sup>4</sup> Exacerbation of both motor and nonmotor complications of PD may lead to hospitalization, which is considered a major direct cost factor associated with PD. Parkinson's disease-related loss of productivity accounts for 30% to 40% of major direct costs. In improving both economic and health-related patient outcomes in PD, it is worthwhile to examine the impact of early diagnosis and treatment.<sup>5,6</sup>

From an economic perspective, a study showed that preventing levodopa-induced complications and delaying the initiation of levodopa therapy may be an effective strategy.<sup>4</sup> In this Markov model economic evaluation, data from 2 trials of dopamine agonists (rasagiline, pramipexole) in early PD were examined for effectiveness (time to levodopa and time to levodopa-induced dyskinesia), cost, and quality-adjusted life-years (QALYs). Rasagiline was found to reduce costs by 18% per patient over 5 years and demonstrated a 25% prolongation of time to levodopa and a 10% delay in onset of dyskinesia. Rasagiline also demonstrated a 5% gain in QALYs relative to pramipexole.<sup>4</sup> Despite this apparent benefit of utilizing dopamine agonists in early PD to delay the need for levodopa, there is still much controversy regarding when and how to diagnose PD, as well as when to

## Abstract

Parkinson's disease (PD) is associated with significant patient disability and costs to the healthcare system. It is questioned whether early treatment may improve outcomes and delay disability. Early treatment relies on early diagnosis, which can be difficult to achieve because the diagnosis of PD is based on motor symptoms, is clinical in nature, and is complicated by potential presentation of nonmotor symptoms prior to motor symptoms. Economic analyses demonstrate that treatments other than levodopa may be cost-effective. The lack of correlation between Unified PD Rating Scale (UPDRS) outcomes and imaging studies of dopamine uptake may reflect the inappropriate selection of study end points, since activities of daily living scores may be more applicable than motor function scores. Levodopa, the standard therapy for motor control of PD and one of the most effective options, is associated with complications (a wearing-off effect) when used long term. Other therapies, including dopamine agonists and monoamine oxidase type-B (MAO-B) inhibitors, may limit the rate of dyskinesia relative to levodopa-based regimens. It appears that early treatment with the MAO-B inhibitor rasagiline (1 mg), as compared with late treatment, delays the onset of worsened UPDRS score, especially the nonmotor activities of daily living subscore.

*(Am J Manag Care. 2011;17:S315-S321)*

For author information and disclosures, see end of text.

## Reports

initiate treatment. The next section will provide a brief overview of early diagnosis.

### Early Diagnosis

Parkinson's disease is challenging to diagnose, since there are no well-established biomarkers to determine if the disease is present.<sup>7</sup> From a diagnostic standpoint, there are 3 basic aspects to the disease: pathology, impairment, and disability. Pathology changes reflect alterations in dopaminergic and other transmitters, both nigrostriatal and throughout the brain. Impairment involves motor, cognitive, and autonomic dysfunction of PD. Disability reflects the changes in the motor and cognitive domains, and their impact on the patient. Symptom severity may be measured by tools such as the Unified PD Rating Scale (UPDRS), which measures motor dysfunction, or the Nonmotor Symptoms Scale (NMSS), which rates the frequency and severity of nonmotor effects of PD.<sup>17</sup> The most frequently used scale in evaluating early treatment of PD is the total UPDRS scale, which also has subscales that score motor function, mentation, and activities of daily living.

From a diagnostic perspective, PD may present in a manner similar to dystonic tremor, drug-induced parkinsonism, vascular parkinsonism, multisystem atrophy, progressive supranuclear palsy, or corticobasal degeneration. There is no reliable diagnostic test for PD, so the diagnosis is clinical in nature and is made by identification of bradykinesia and at least 1 of the following: resting tremor, muscle rigidity, and postural instability. Confirmation of a PD diagnosis also involves exclusion of other disease and presence of at least 3 positive criteria, which include: unilateral onset, resting tremor, progressive disorder, persistent asymmetry affecting side of onset most prominently, excellent response to levodopa, severe levodopa-induced chorea, levodopa response for 5 years or more, or clinical course of 10 years or more.<sup>18</sup> Interestingly, the nonmotor factors associated with PD may be present for up to 10 years before the diagnosis is made.<sup>9</sup>

Brain imaging techniques are used as an adjunct in establishing and monitoring brain pathology. Single photon emission computed tomography (SPECT), using a dopamine transporter radiolabelled ligand, is used to establish alterations in uptake of dopamine, but cannot differentiate PD from multisystem atrophy, progressive supranuclear palsy, and corticobasal degeneration. Magnetic resonance imaging (MRI) may be used to differentiate PD through various techniques, but its use is not widely accepted. Similarly, transcranial sonography and positron emission tomography (PET) are other options, with the latter scan being very expensive and limited in availability.<sup>7</sup>

Based on the aforementioned challenges in diagnosis of PD, early identification of this disease remains challenging. It is quite possible that by the time motor symptoms of PD develop to the extent that a diagnosis can be considered, the nonmotor symptoms may have been present for years. In this context, there is debate regarding whether treatment should be initiated immediately or delayed until greater motor functional disability presents.<sup>10</sup> At the core of the debate is the question of whether it is worthwhile to begin levodopa (which is limited by eventual wearing-off effects) early in the disease process, before significant disability develops. Also being questioned is the effect of early initiation of a therapy other than levodopa on disease progression.<sup>11</sup> The remainder of this article will examine the evidence surrounding early treatment of PD.

### Early Treatment

Landmark randomized trials of early treatment in PD are summarized in the [Table](#).<sup>11-19</sup> Where possible, studies that included imaging biomarkers and clinical outcomes were included in order to determine disease progression and correlation of clinical and pathological findings. Studies where dopamine agonists were compared with levodopa to determine disease progression and the preferred initial treatment were also included. Finally, studies of MAO-B inhibitors versus placebo were included in order to determine the presence of an early treatment effect. The following sections summarize these results with respect to clinical and radiological outcomes.

### Levodopa-Based Regimens

The Parkinson's Study Group examined carbidopa-levodopa at various daily doses (compared with placebo) in a 40-week, randomized, double-blind, placebo-controlled trial (Earlier versus Later Levodopa Therapy in PD; ELLDOPA) of 361 patients.<sup>11</sup> Patients were diagnosed within 2 years of randomization and judged unlikely to require medication for symptoms of PD for at least 9 months. The evaluation was completed at 42 weeks (after a 2-week washout) and the total UPDRS scale was used to evaluate the primary end point. In the carbidopa-levodopa group, the UPDRS score improved in a dose-related fashion ([Figure 1](#)) and the improvement was retained for the duration of the study (although follow-up time was relatively short). In sharp contrast, the SPECT [<sup>123</sup>I] β-CIT uptake sub-study demonstrated a mean percent decline of [<sup>123</sup>I]β-CIT uptake (assessment of striatal dopamine-transporter density) that was significantly greater with carbidopa-levodopa (-4% to -7.2%) than with placebo (-1.4%; *P* = .036). Patients receiving the highest levodopa

■ **Table.** Landmark Trials of Early Treatment of Parkinson's Disease<sup>11-19</sup>

Trial	Intervention	Comparator	N	Follow-up	Primary End Point and Imaging Outcome
ELLDOPA <sup>11</sup>	Carbidopa-levodopa at various doses	Matched placebo	361	42 weeks	Intervention improved UPDRS score; dose-related Intervention worsened SPECT score
STRIDE-PD <sup>12</sup>	Carbidopa-levodopa plus entacapone	Carbidopa-levodopa	747	134 weeks	Intervention group had shorter time to dyskinesia onset ( $P = .04$ )
Rascol et al <sup>13</sup>	Ropinirole	Benserazide-levodopa	268	5 years	Intervention had longer time to dyskinesia ( $P < .001$ )
REAL-PET <sup>14</sup>	Ropinirole	Carbidopa-levodopa	186	2 years	Intervention worsened UPDRS score relative to comparator Intervention was associated with slower progression as assessed by PET scan
CALM-PD-CIT <sup>15</sup>	Pramipexole	Carbidopa-levodopa	82	46 months	UPDRS similar in both groups, but worsened from baseline in both Intervention associated with decline in striatal dopamine uptake of 5.2% per year
CALM-PD <sup>16</sup>	Pramipexole	Placebo-levodopa or carbidopa-levodopa	301	48 months	Intervention resulted in significant reduction in dyskinesia ( $P < .001$ )
DATATOP <sup>17</sup>	Selegiline 10 mg daily and/or tocopherol	Placebo	800	24 months	Selegiline delayed the time to initiation of levodopa for disability by about 9 months ( $P < .001$ )
TEMPO <sup>18</sup>	Rasagiline 1 mg or 2 mg	Placebo	404	26 weeks	Rasagiline improve UPDRS scores, but there was no difference in time to additional therapy
ADAGIO <sup>19</sup>	Rasagiline 1 mg or 2 mg daily for 72 weeks	Placebo for 36 weeks, then rasagiline 1 mg or 2 mg daily for 36 weeks	1176	72 weeks	Initial rasagiline 1 mg improved UPDRS scores to a greater extent for 72 weeks ( $P = .02$ ). By 72 weeks, there was no difference between rasagiline 2 mg and placebo

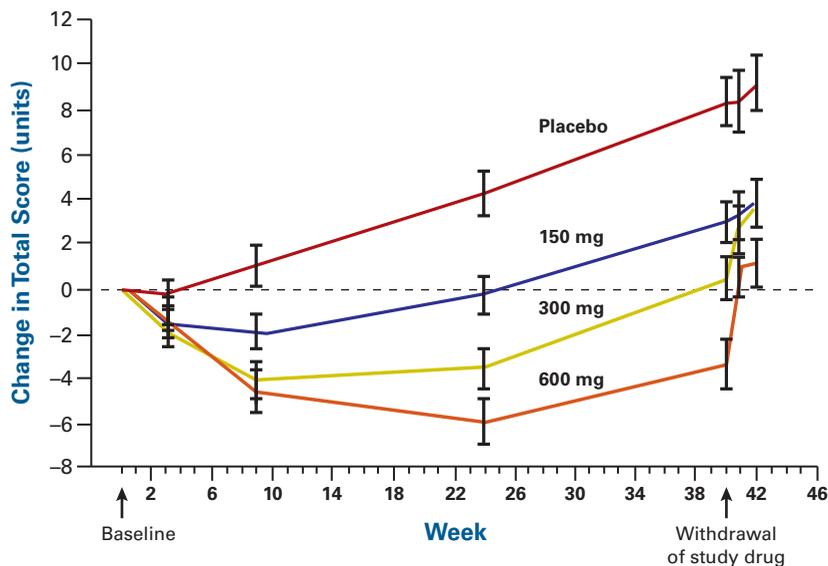
ADAGIO indicates Attenuation of Disease Progression with Azilect Given Once-Daily; CALM-PD, Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease; CIT, 2 $\beta$ -carboxymethoxy-3 $\beta$ (4-iodophenyl)tropane; DATATOP, Deprenyl and Tocopherol Antioxidative Therapy in Parkinsonism; ELLDOPA, Earlier versus Later Levodopa Therapy in Parkinson's Disease; PET, positron emission tomography; REAL, Requip as Early Therapy versus L-dopa; SPECT, single photon emission computed tomography; STRIDE-PD, Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease; TEMPO, TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients; UPDRS, Unified Parkinson's Disease Rating Scale.

dose (carbidopa 150 mg and levodopa 600 mg per day) experienced more dyskinesia, hypertonia, infection, headache, and nausea than placebo. The results of these studies suggest that clinical/function-related benefits of levodopa compared with placebo did not translate into pathological improvement; however, accelerated loss of nigrostriatal dopamine nerve terminals was demonstrated.<sup>11</sup>

A more recent study, the Stalevo Reduction in Dyskinesia Evaluation in PD (STRIDE-PD), compared carbidopa-levodopa with or without entacapone, a catechol-O-meth-

yltransferase (COMT) inhibitor used to extend the plasma half-life of levodopa, administered 4 times daily.<sup>12</sup> The prospective, randomized, double-blind study enrolled patients with PD who required initiation of levodopa therapy. At 134 weeks, the carbidopa-levodopa-entacapone group had shorter time to dyskinesia ( $P = .04$ ) and increased frequency of dyskinesia (42% vs 32%;  $P = .02$ ), which was more pronounced in patients receiving dopamine agonists at baseline. There was no difference in total UPDRS scores between the groups, but the incidence of myocardial infarction was 1.9% in the

■ **Figure 1.** Primary End Point of the ELLDOPA Study (UPDRS score)<sup>11</sup>



ELLDOPA indicates Earlier versus Later Levodopa Therapy in Parkinson's Disease; UPDRS, Unified Parkinson's Disease Rating Scale. Reprinted with permission from Fahn S, Oakes D, Shoulson I, et al; Parkinson Study Group. *N Engl J Med.* 2004;351:2498-2508.

carbidopa-levodopa-entacapone group versus 0% in the carbidopa-levodopa group (*P* value not reported). These results indicate that addition of entacapone to carbidopa-levodopa is not warranted in early PD, and may actually be deleterious with the increased risk of myocardial infarction (which led to a labeling change for entacapone).<sup>12</sup>

#### Levodopa Compared With Dopamine Agonists

In the context of levodopa's uncertain benefit in early PD and entacapone's failure to improve outcomes through continuous dopamine delivery, it is useful to evaluate effects of dopamine agonists relative to levodopa. In a 5-year, prospective, randomized, double-blind study, ropinirole was compared with levodopa-benserazide (a decarboxylase inhibitor similar to carbidopa).<sup>13</sup> Treatment prior to enrollment was limited to 6 weeks of levodopa or dopamine agonists. Only 47% of the ropinirole group and 51% of the levodopa group completed 5 years of follow-up; treatment-related adverse effects led to study withdrawal in 27% and 33% of patients in the ropinirole and levodopa groups, respectively. Time to dyskinesia was prolonged in the ropinirole group (hazard ratio [HR] 2.82; 95% confidence interval, 1.78-4.44; *P* <.001). Among study completers, the difference in the mean change in UPDRS activities of daily living subscale scores was not significantly different between the groups; however, the mean

UPDRS motor subscale score favored levodopa (*P* = .008).

Another randomized study (Requip as Early Therapy versus L-dopa—PET; REAL-PET) evaluated ropinirole and its effect on <sup>18</sup>F-dopa PET scan at 4 weeks and 2 years in treatment-naive patients in order to assess loss of dopamine-terminal function compared with carbidopa-levodopa.<sup>14</sup> The clinical outcome (UPDRS motor score) was worsened by ropinirole as compared with levodopa; however, in the ropinirole group, fewer patients developed dyskinesia (*P* <.001) and patients exhibited a longer time to dyskinesia (*P* <.001). In addition, the PET scan demonstrated less reduction in the putamen uptake of <sup>18</sup>F-dopa at 2 years in the ropinirole versus the levodopa group, suggesting slower progression of PD in the ropinirole group.<sup>14</sup> As with prior levodopa studies, the imaging results in this trial

were in contrast to the clinical outcomes.

In another double-blind, randomized, controlled trial, an imaging substudy (Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease—CIT; CALM-PD-CIT) compared pramipexole with carbidopa-levodopa (both given 3 times daily) with respect to their effects on the total UPDRS score and SPECT striatal uptake (assessed by 2β-carboxymethoxy-3β [4-iodophenyl] tropane [β-CIT] labeled with iodine).<sup>15</sup> At 2-year follow-up, the total UPDRS scores were not significantly different between the carbidopa-levodopa and pramipexole groups, but they worsened from baseline in both groups. In contrast, SPECT imaging demonstrated a mean 5.2% yearly loss of striatal dopamine uptake, which was less in the pramipexole group (7.1% at 22 months; 16% at 46 months) than in the carbidopa-levodopa group (13.5% at 22 months [*P* = .004]; 25.5% at 46 months [*P* = .01]). Loss of striatal dopamine uptake from baseline correlated with the change in baseline to the 46-month UPDRS score (*r* = -0.4; *P* = .001).<sup>15</sup> The main trial (CALM-PD) evaluated pramipexole versus carbidopa-levodopa or placebo-levodopa in patients with PD diagnosed within 7 years, who had not taken medication within 2 months prior to study entry.<sup>16</sup> Doses were titrated over 10 weeks and then investigators were permitted to add open-label levodopa, or other agents,

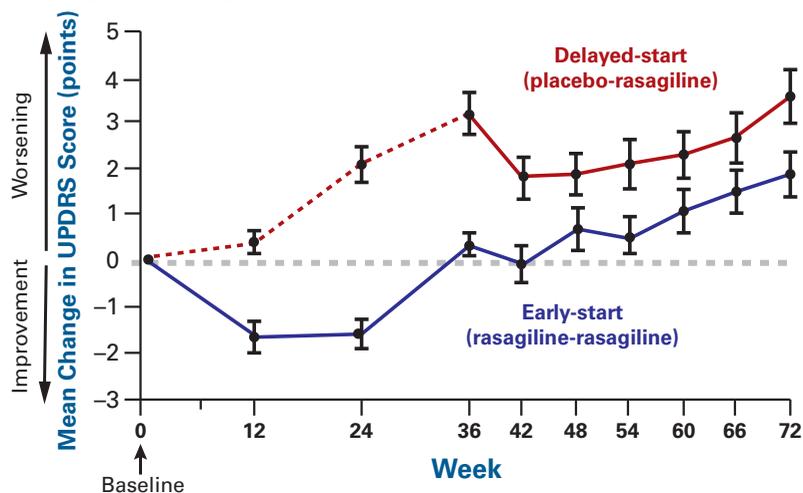
as needed. Pramipexole resulted in a significant reduction in dyskinesia (24.5% vs 54%;  $P < .001$ ) and wearing-off (47% vs 62.7%;  $P = .02$ ). Levodopa was associated with a lower risk of freezing (37.1% vs 25.3%;  $P = .01$ ), somnolence ( $P = .005$ ), and edema ( $P < .001$ ). Total UPDRS ( $P = .003$ ), UPDRS motor subscale ( $P = .001$ ), and UPDRS activities of daily living subscale scores ( $P = .02$ ) were greater in the levodopa group at 48 months. Total score and motor score improved from baseline in the levodopa group, but activities of daily living declined from baseline in both groups. Quality of life scores did not differ between the groups.<sup>16</sup>

In a Cochrane review that evaluated dopamine agonists in 5247 patients with early PD, patients randomized to dopamine agonists were less likely to develop dyskinesia ( $P < .00001$ ), dystonia ( $P = .0002$ ), and motor fluctuations ( $P = .002$ ), but were more likely to discontinue therapy due to adverse events ( $P < .00001$ ).<sup>20</sup> Adverse effects were more common with dopamine agonists, including edema ( $P < .00001$ ), somnolence ( $P = .007$ ), constipation ( $P = .01$ ), dizziness ( $P = .01$ ), hallucinations ( $P = .01$ ), and nausea ( $P = .02$ ). Symptomatic control of PD appeared to be better with levodopa.<sup>20</sup> According to another Cochrane review, there is insufficient evidence

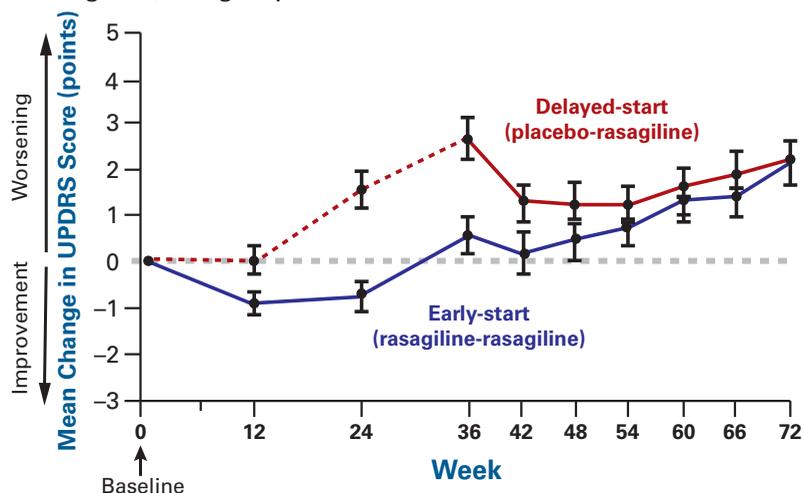
to determine the superiority of one dopamine agonist versus another at this time.<sup>21</sup> For the sake of convenience and compliance, clinicians may consider that pramipexole is available as a once-daily extended-release formulation; however, clinical experience with the immediate-release formulation is more extensive, and transition to the extended-release formulation should be approached with caution since there is a lack of comparative data with levodopa.<sup>22</sup> Taken together, these results suggest that compared with levodopa, dopamine agonists may delay dyskinesia and improve decline of striatal dopamine handling, although the value of this clinical effect

■ **Figure 2.** Time to Changes in UPDRS Score in 4 Rasagiline Study Groups in the ADAGIO Trial<sup>19</sup>

#### A Rasagiline, 1 mg/day



#### B Rasagiline, 2 mg/day



ADAGIO indicates Attenuation of Disease Progression with Azilect Given Once-Daily; UPDRS, Unified Parkinson's Disease Rating Scale. Reprinted with permission from Olanow CE, Rascol O, Hauser R, et al; ADAGIO Study Investigators. *N Engl J Med.* 2009;361:1268-1278.

remains uncertain and these agents do not improve total UPDRS scores.

#### Monoamine Oxidase Type-B (MAO-B) Inhibitors

In 2004, a meta-analysis evaluating MAO-B inhibitors in 3525 patients with early PD found no difference in mortality among treatment versus control subjects.<sup>23</sup> Patients randomized to MAO-B inhibitor therapy had significantly improved total UPDRS scores, as well as subdomain UPDRS motor scores and activities of daily living scores at 3 months. The MAO-B inhibitors were also well tolerated, with adverse

## Reports

effects and patient withdrawals from the study similar in both groups.<sup>23</sup> These results illustrated a potential benefit of MAO-B inhibitors, which reduce catabolism of dopamine and potentially reduce formation of free radicals, which are implicated in degeneration of neurons in the substantia nigra.<sup>17</sup>

One landmark trial, the Deprenyl and Tocopherol Antioxidative Therapy in Parkinsonism (DATATOP) study, evaluated the MAO-B inhibitor selegiline 10 mg per day (5 mg twice daily) and tocopherol (in combination and independently) versus placebo in patients with early PD (diagnosed for less than 5 years).<sup>17</sup> Tocopherol did not benefit when given alone and lacked interaction with selegiline. Compared with placebo or tocopherol, selegiline delayed the time to initiation of levodopa for development of significant disability (719 days vs 454 days,  $P < .001$ ) and delayed the decline in UPDRS total score by about 50% ( $P < .001$ ). In all subjects, selegiline resulted in approximately a 75% ( $P < .001$ ), 50% ( $P < .001$ ), and 50% ( $P < .001$ ) reduction in the UPDRS mental subscale, motor subscale, and activities of daily living subscale, respectively. The effects of selegiline were most prominent during the first 12 months of treatment, and motor performance declined after treatment was withdrawn.<sup>17</sup>

Another study (TVP-1012 in Early Monotherapy for PD Outpatients; TEMPO) evaluated the MAO-B inhibitor rasagiline (1 mg or 2 mg daily) versus placebo in patients who were able to take anticholinergic but not other antiparkinsonian medication.<sup>18</sup> In the TEMPO trial, rasagiline (at both doses) improved total UPDRS scores relative to placebo at the 26-week evaluation; however, there was no significant difference in the time to require additional antiparkinsonian therapy in any of the groups. Treatment was well tolerated and adverse events were similar in all groups.<sup>18</sup>

To evaluate the value of early versus delayed treatment of PD with a MAO-B inhibitor, the Attenuation of Disease Progression with Azilect Given Once-Daily (ADAGIO) study was conducted.<sup>19</sup> This trial randomized patients to rasagiline at doses of 1 mg or 2 mg daily for 72 weeks, or placebo for 36 weeks followed by 36 weeks of rasagiline at doses of 1 mg or 2 mg daily. Enrolled patients had to have been treated with antiparkinsonian medications for less than 3 weeks, and the primary end point (UPDRS score) was evaluated at 12, 36, 48, and 72 weeks. The results of the main publication<sup>19</sup> revealed that rasagiline (at 1 mg) had a smaller mean increase in the total UPDRS score from weeks 12 to 36, less worsening of score from baseline to week 72 in the early-start group, and noninferiority between the delayed-start group and the early-start group from weeks 48 to 72 (**Figure 2**). These 3

end points were not met in the rasagiline 2 mg group. The results indicated that early treatment with rasagiline 1 mg had a more beneficial effect than delayed-start therapy with rasagiline 1 mg.<sup>19</sup> In a prespecified analysis of the ADAGIO trial that evaluated other outcomes (ie, nonmotor symptoms, rates of disease progression), both doses of rasagiline reduced the need for additional antiparkinsonian therapy.<sup>24</sup> At 36 weeks, when comparing the early-start versus the delayed-start groups, the UPDRS motor subscores and activities of daily living subscale were improved with both doses of rasagiline relative to placebo, but the mentation subscore was only improved with rasagiline 1 mg. At 72 weeks, the only improvement in UPDRS subscore between the early- and delayed-start groups was for the activities of daily living subscore in the rasagiline 1 mg group. Furthermore, the rates of worsening UPDRS score were related to the baseline score, where patients with worse scores had more rapid worsening of score.<sup>24</sup> These results may indicate that disease modification has more of an impact on nonmotor symptoms than motor symptoms, although these post hoc analyses should be confirmed prospectively. The findings are consistent with the literature that demonstrates that quality of life in PD is more significantly impacted by the nonmotor aspects of the disease than the motor symptoms.<sup>25</sup> These results are also consistent with a 6.5-year extension of the TEMPO study.<sup>18,26</sup> After the initial 6-month TEMPO publication, 306 patients elected to participate in an open-label extension, in which all patients received rasagiline 2 mg and any other Parkinson's medication deemed necessary. The initial rasagiline group was the early-start group, and the placebo group was the delayed-start group in the follow-up study. After analysis of the TEMPO study demonstrated a lack of improvement with rasagiline 2 mg compared with 1 mg, the dose was decreased to 1 mg. Over 6.5 years, early-start rasagiline produced a 16% improvement in total UPDRS score ( $P = .006$ ) throughout the duration of follow-up. Improvements in motor (11.9%,  $P = .046$ ) and activities of daily living (39.1%,  $P = .028$ ) UPDRS subscores also favored early-start, although the activities of daily living subscore benefit was more pronounced.<sup>26</sup> Further study is necessary to determine if disease progression is more closely linked to nonmotor symptoms of PD.

## Summary

Diagnosis of PD is complicated and generally based on motor symptoms of the disease. The realization that nonmotor symptoms are often present before motor symptoms increases the opportunity to recognize, diagnose, and treat PD earlier. Recent evidence indicates an uncertain effect of levodopa in early treatment, and that dopamine agonists and

MAO-B inhibitors, particularly rasagline 1 mg, appear to be better tolerated and may delay onset of dyskinesia relative to levodopa. More work is needed to determine the most appropriate long-term outcome measures for assessing benefits of early therapy.

**Author Affiliations:** Department of Pharmacy Practice, College of Pharmacy and Health Sciences, Mercer University, Atlanta, GA.

**Funding Source:** This activity is supported by an educational grant from Teva Neuroscience, Inc.

**Author Disclosure:** Dr Jann reports serving as a speaker/advisory board member for Janssen.

**Authorship Information:** Concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and supervision.

**Address correspondence to:** E-mail: jann\_mw@mercer.edu.

## REFERENCES

- Pahwa R, Lyons KE.** Early diagnosis of Parkinson's disease: recommendations from diagnostic clinical guidelines. *Am J Manag Care.* 2010;16:S94-S99.
- Maranis S, Tsouli S, Konitsiotis S.** Treatment of motor symptoms in advanced Parkinson's disease: a practical approach [published online ahead of print May 30, 2011]. *Prog Neuropsychopharmacol Biol Psychiatry.* doi:10.1016/j.pnpb.2011.05.014.
- Hickey P, Stacy M.** Available and emerging treatments for Parkinson's disease: a review. *Drug Des Devel Ther.* 2011;5:241-254.
- Haycox A, Armand C, Murteira S, Cochran J, Francois C.** Cost effectiveness of rasagiline and pramipexole as treatment strategies in early Parkinson's disease in the UK setting: an economic Markov model evaluation. *Drugs Aging.* 2009;26:791-801.
- Von Campenhausen S, Winter Y, Rodrigues e Silva A, et al.** Costs of illness and care in Parkinson's disease: an evaluation in six countries. *Eur Neuropsychopharmacol.* 2011;21:180-191.
- Aminoff MJ, Christine CW, Friedman JH, et al; for the National Parkinson Foundation Working Group on Hospitalization in Parkinson's Disease.** Management of the hospitalized patient with Parkinson's disease: current state of the field and need for guidelines. *Parkinsonism Relat Disord.* 2011;17:139-145.
- Breen DP, Michell AW, Barker RA.** Parkinson's disease – the continuing search for biomarkers. *Clin Chem Lab Med.* 2011;49:393-401.
- Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ.** Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:968-975.
- Chen JJ.** Parkinson's disease: health-related quality of life, economic cost, and implications of early treatment. *Am J Manag Care.* 2010;16:S87-S93.
- Clarke CE, Patel S, Ives N, Rick C, Wheatley K, Gray R.** Should treatment for Parkinson's disease start immediately on diagnosis or delayed until functional disability develops? *Mov Disord.* 2011;26:1187-1193.
- Fahn S, Oakes D, Shoulson I, et al; Parkinson Study Group.** Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004;351:2498-2508.
- Stocchi F, Rascol O, Kieburtz K, et al.** Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson's disease: the STRIDE-PD study. *Ann Neurol.* 2010;68:18-27.
- Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE.** A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med.* 2000;342:1484-1491.
- Whone AL, Watts RL, Stoessl AJ, et al.** Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol.* 2003;54:93-101.
- Parkinson Study Group.** Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA.* 2002;287:1653-1661.
- Parkinson Study Group.** Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized trial. *Arch Neurol.* 2004;61:1044-1053.
- Parkinson Study Group.** Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1993;328:176-183.
- Parkinson Study Group.** A controlled trial of rasagiline in early Parkinson's disease: the TEMPO study. *Arch Neurol.* 2002;59:1937-1943.
- Olanow CE, Rascol O, Hauser R, et al; ADAGIO Study Investigators.** A double-blind, delayed start trial of rasagiline in Parkinson's disease. *N Engl J Med.* 2009;361:1268-1278.
- Stowe R, Ives N, Clarke CE, et al.** Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database Syst Rev.* 2008;2:CD006564.
- Clarke CE, Speller J, Clarke JA.** Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease. *Cochrane Database Syst Rev.* 2000;3:CD002259.
- Antonini A, Calandrella D.** Once-daily pramipexole for the treatment of early and advanced idiopathic Parkinson's disease: implications for patients. *Neuropsychiatr Dis Treat.* 2011;7:297-302.
- Ives NJ, Stowe RL, Marro J, et al.** Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ.* 2004;329(7466):593.
- Rascol O, Fitzer-Attas CJ, Hauser R, et al.** A double-blind, delayed start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and nonmotor outcomes. *Lancet Neurol.* 2011;10:415-423.
- Soh SE, Morris ME, McGinley JL.** Determinants of health-related quality of life in Parkinson's disease: a systematic review. *Parkinsonism Relat Disord.* 2011;17:1-9.
- Hauser RA, Lew MF, Hurtig HI, Ondo WG, Wojcieszek J, Fitzer-Attas CJ.** Long-term outcome of early versus delayed rasagiline treatment in early Parkinson's disease. *Mov Disord.* 2009;24:564-573.