INTRODUCTION

Vast clinical needs exist in Parkinson’s disease (PD), a neurodegenerative disorder that affects approximately 1 million persons in the United States.1 These include strategies for early, accurate disease identification as well as optimal treatment using interventions that go beyond short-term control of motor symptoms to actually slow or halt the disease process. Moreover, there is also a critical need for improved management strategies of PD-associated nonmotor symptoms that can affect health-related quality of life, worsen prognosis, and confound treatment.

GOAL: To update neurologists on current and emerging strategies for the diagnosis and treatment of Parkinson’s Disease.

LEARNING OBJECTIVES:

After completing this activity, participants should be better able to:

† Identify emerging screening and risk assessment tools that facilitate the early diagnosis of Parkinson’s disease (PD)
† Discuss present and emerging states of disease-modifying therapy in early PD
† Discuss options for managing nonmotor disturbances in patients with PD

TARGET AUDIENCE: Neurologists

ACCREDITATION INFORMATION

Jointly sponsored by:

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Release Date: December 28, 2011
Expiration Date: December 27, 2012

ACKNOWLEDGMENT

This educational activity was supported by an educational grant from Teva Pharmaceuticals.
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Dr Saint-Hilaire: research grants: Bayer, Merck Serono, Teva Pharmaceuticals; speakers bureau: Teva Pharmaceuticals.

Dr Friedman: consultant: ACADIA Pharmaceuticals Inc., Addex Pharmaceuticals, Genzyme Corporation, Roche, Teva Pharmaceuticals; research grants: ACADIA Pharmaceuticals, EMD Serono, Inc., GE Healthcare, Merck & Co., Inc., Teva Pharmaceuticals; royalties: Demos; speakers bureau: Boehringer Ingelheim, GE Healthcare, Teva Pharmaceuticals.

Dr Jennings: speakers bureau: Lundbeck.

Dr Ravin: research grants: ACADIA Pharmaceuticals Inc., Bayer, Chelsea Therapeutics, Teva Pharmaceuticals.

Dr Sudarsky has nothing to disclose with regard to commercial interests.

The Planning Committee for this activity included Elizabeth Drury, Ilana Hardesty, and Okeanis Vaou, MD, of Boston University School of Medicine; and Ruth Cohen and Susan J. Moench, PhD, PA-C, of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose.

Genetic testing, imaging methods, and/or screens for premotor symptoms for facilitating early diagnosis of PD are being actively investigated and some are available for use in the clinical setting.\textsuperscript{2,3} Disease-modifying interventions with the potential to slow the progression of PD, thereby preventing or delaying disability, are actively being sought.

In October 2011, a roundtable meeting of experts was convened to discuss the state-of-the-art in the diagnosis and management of early PD and the potential of emerging diagnostic and treatment modalities to impact the clinical outcomes of patients with early PD. Participants included Drs Joseph Friedman, Danna Jennings, Paula Ravin, and Lewis Sudarsky. The discussions were moderated by Marie-Hélène Saint-Hilaire, MD, associate professor of neurology at Boston University School of Medicine, and medical director of the Movement Disorder Program, Boston Medical Center, Massachusetts. The discussions that took place at this recent roundtable meeting are summarized here.

### Diagnosis of PD

#### Currently Available Strategies

The diagnosis of PD is delayed until symptoms reflecting motor impairment are apparent.\textsuperscript{4} In addition, it is estimated that up to 10% of patients with PD are misdiagnosed with other conditions and approximately 25% of patients diagnosed with PD reveal a different diagnosis at autopsy.\textsuperscript{5,7} These misdiagnoses delay accurate identification of patients with early PD and initiation of appropriate therapy.

Dr Saint-Hilaire asked the roundtable participants questions concerning the criteria they use to diagnose PD, and the risks and benefits of diagnosing PD at an early stage.

- The roundtable members concurred that an accurate diagnosis in patients with early motor symptoms can help provide the patient with insight/understanding into his/her motor symptom complex. Nevertheless, they emphasized that earlier diagnosis is more likely to be associated with misdiagnosis.
- None of the roundtable members favored using premotor symptoms as the basis for a diagnosis of PD outside of a research setting although the presence of rapid eye movement (REM) sleep behavior disorder (RBD) is a significant marker.

Tools available to assist in making a diagnosis of PD include the Unified Parkinson’s Disease Rating Scale (UPDRS) score, DaTSCAN imaging, as well as several commercially available genetic tests.

#### UPDRS Score

The UPDRS clinical rating scale has been widely used in the assessment of patients with suspected or diagnosed PD in the clinical setting and as a clinical outcome measure for clinical trials. In the updated version of the UPDRS, called the Movement Disorder Society (MDS)-Sponsored UPDRS, each section has undergone changes, but the 4 parts of the original version with the total summed score have been retained (available at
A criticism of the original UPDRS was the irregular placement of nonmotor symptoms of PD throughout the sections. In the new UPDRS, nonmotor symptoms are in part I (Non-motor Experiences of Daily Living). Furthermore, sections of part I and all of part II (Motor Experiences of Daily Living) are now designed to be completed by the patient/caregiver. Part III in the original and revised versions of the UPDRS is the Motor Examination, and part IV (Motor Complications) focuses exclusively on motor fluctuations and dyskinesias. The MDS-UPDRS has a 0 to 4 rating scale, eliminating the yes/no responses from the original UPDRS. An important difference between the 2 versions of the UPDRS is the focus on the impact of symptoms rather than the presence of symptoms in the updated tool.

Dr Saint-Hilaire asked the roundtable participants for their opinions on the utility of the UPDRS score in clinical practice.

- The roundtable members cited several advantages of the MDS-sponsored revision of the UPDRS, including its ability to capture dyskinesias and nonmotor symptoms and its increased usefulness in patients with milder disease.
- Some participants use only part III of the UPDRS outside the context of a clinical trial. They cited the ability to monitor changes in motor symptoms by administering part III of UPDRS over time as a useful follow-up measure.
- It also was noted that changes in motor activities of daily living as assessed by part II of the UPDRS are likely to be of greatest importance to the patient.
- Nonmotor symptoms usually are addressed in the history at each visit.

DaTSCAN Imaging

The dopamine transporter (DaT) ligand (Ioflupane I 123) is a radiopharmaceutical agent recently approved by the Food and Drug Administration (FDA) for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in evaluating patients with suspected Parkinsonian syndromes. DaTSCAN imaging technology measures the binding of the injected DaT ligand in the basal ganglia and a qualitative “picture” of the density of healthy dopamine neurons associated with uptake of the imaging ligand is provided (Figure 1). Dopamine-based neuroimaging techniques can be combined with clinical assessments to increase the certainty of a PD diagnosis. However, a major limitation of this imaging technique is that dopaminergic dysfunction occurs in other diseases and, therefore, a DaTSCAN is not a definitive diagnostic tool of PD. DaTSCAN imaging is effective in differentiating Parkinsonian syndrome characterized by reduced binding of the imaging ligand in the striatum from essential tremor. Although characterizing tremor is likely the most common use of DaTSCAN in the community neurology setting, this imaging modality also may be used to identify patients who have drug-induced Parkinsonism, an often reversible condition, as such patients are thought to have a normal DaTSCAN, although definitive evidence to support this is lacking.

Dr Saint-Hilaire asked the roundtable participants if they incorporate DaTSCAN imaging into their practices, and, if so, how they use and interpret the results.

- The participants do not recommend this technique for use in clinical practice in individuals who lack signs of PD, even those with a family history of PD, as the interpretation may be unclear in these cases and results would not impact clinical treatment. The likelihood that individuals with mild dopamine transporter deficiency will develop PD is under investigation. The utility of an abnormal finding on DaTSCAN in healthy patients with RBD also is being evaluated in ongoing research studies.
• Parkinson’s disease is primarily a clinical diagnosis and a DaTSCAN result will not impact management of an individual without a clinical diagnosis of PD
• Because treatment of PD is based on clinical presentation, not DaTSCAN progression, DaTSCAN is not recommended for monitoring disease progression, as it will not influence treatment. In addition, DaTSCAN results are too insensitive to be used to assess disease severity

Genetic Testing
Although the majority of PD cases are considered to arise sporadically, several genetic susceptibility factors may be pertinent. A number of monogenic causes of PD have been identified, and up to 15% of patients with PD have a family history of this disorder. Mutations in 5 causative genes may account for about 2% to 3% of all cases of PD with clinical features similar to classical disease. The best studied of these are leucine-rich repeat kinase 2 (LRRK2, autosomal dominant pattern), and Parkin (autosomal recessive pattern). Gene mutations identified in familial PD include Parkin, PINK1, DJ1, LRRK2 and SNCA. LRRK2, Parkin, PINK1 and DJ1 mutations have been identified in sporadic PD. Commercially available genetic tests include Parkin, PINK1, DJ1, LRRK2, and SNCA.

Emerging Strategies for Early Diagnosis
There are no established biomarkers in PD, nor are specific premotor symptoms considered reliable indicators of early PD. Thus, identification of early predictors of the development and progression of PD is an active area of research. Studies to define and extend the clinical uses of available tests, such as DaTSCAN imaging and genetic analyses, also are ongoing.

Parkeon’s-Associated Risk Study (PARS) Study
PARS is a multicenter observational study designed to evaluate individuals for early signs of PD. The goal of this study is to assess early changes in the density of dopamine-producing neurons in the brain prior to onset of motor symptoms in individuals with olfactory deficits. More than 15,000 individuals with or without a relative with PD have been screened using a questionnaire and the University of Pennsylvania Smell Identification Test (UPSIT), and a group of 300 participants are being followed for 5 years. At the time of enrollment, none of the participants have received a diagnosis of PD. These individuals are undergoing clinical evaluations including neurologic examination, cognitive testing, use of questionnaires to assess RBD and autonomic function, mood evaluation, and DaT imaging using SPECT. Approximately 300 participants are being followed longitudinally in the study with 200 of these individuals exhibiting an olfactory deficit and 100 having normal olfactory sense. Preliminary data from this study show that of the 303 subjects (203 hyposmic, 100 normosmic) who underwent baseline DaT imaging, 11% (23/203) of the hyposmic subjects demonstrated DaT deficiency in the range expected to develop a parkinsonian syndrome compared with 1% (1/100) of the normosmic subjects, suggesting that hyposmic participants are more likely to have a DaT deficit on imaging compared with normosmic participants (D. Jennings, MD, written communication, November 15, 2011).

Although the percentage of currently enrolled subjects with a family history of PD is 50%, positive findings did not appear more likely in this subgroup compared with subjects without a family history of PD.

Parkinson’s Progression Markers Initiative (PPMI) Study
The Michael J. Fox Foundation recently launched the PPMI study, a large prospective observational cohort study. The study objectives are to identify biomarkers of PD progression and validate existing candidate markers to provide researchers with the tools needed to develop more informative clinical trials for disease-modifying therapy. Specific aims of the study include the development of a comprehensive and uniformly acquired clinical/imaging dataset with correlated biologic samples that can be used in biomarker verification studies; establishment of standardized protocols for acquisition, transfer, and analysis of clinical and imaging data and biologic samples that can be used by the research...
community; investigation of existing biomarkers and identification of new clinical, imaging, and biologic markers to determine interval changes in these markers in PD patients compared with control participants. This biomarker study is following 400 de novo unmedicated PD patients with a positive DaTSCAN, and 200 age- and gender-matched controls for 3 to 5 years. A biorepository/databank of specimens will be created and shared with the research community. Motor assessment, cognitive testing, olfaction, and DaTSCAN imaging data are being collected along with biologic specimens of DNA collected during the initial visit; serum and plasma collection at each visit; urine collected annually; and cerebrospinal fluid (CSF) collected at baseline, 6 months and then annually. The lead biomarker candidates to be tested include α-synuclein, DJ1, total tau, phospho-tau (P-181), β-amyloid 1-42, and urate. The stored biologic samples will be available for future biomarker studies (Table 1). In discussing the PPMI study, the panel emphasized the need for biomarkers of both motor and nonmotor progression of disease.

Management of PD
Addressing Motor Symptoms in Early PD

Treatment to address motor symptoms of PD focuses on increasing dopamine levels in the brain and providing symptomatic control in early/intermediate stages of the disease. L-DOPA or levodopa, a dopamine precursor, remains the most effective form of oral symptomatic treatment for motor symptoms, and ultimately is required by most patients. Other drugs providing symptomatic benefits include synthetic dopamine receptor agonists (eg, pramipexole; ropinirole; apomorphine) and monoamine oxidase-B (MAO-B) inhibitors (eg, selegiline; rasagiline), the latter agents providing mild symptomatic benefit by inhibiting the breakdown of dopamine in the brain. Amantidine and anticholinergic drugs, although used less frequently, can be used for improving tremor in some patients.

Decision making regarding when to initiate dopaminergic therapy for PD is individualized and can depend on age, employment status, family concerns, and patient preference.

Dr Saint-Hilaire asked the roundtable participants to identify the factors they consider when selecting initial dopaminergic therapy for a patient with early PD.

- Roundtable members noted the development of dyskinesias and motor fluctuations associated with prolonged use of levodopa and impulsivity behaviors experienced by some patients receiving dopamine receptor agonist therapy.
- The majority of the participants support initiation of therapy with a dopamine receptor agonist in younger patients as a means of delaying dyskinesias associated with levodopa. It was

<table>
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<th>TABLE 1. Parkinson’s Progression Markers Initiative (PPMI) Study</th>
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<td><strong>Clinical data assessment</strong></td>
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<td><strong>Data access</strong></td>
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CSF = cerebrospinal fluid; DTI = diffusion tensor imaging; MRI = magnetic resonance imaging.
suggested that a combination of a dopamine agonist and levodopa (starting with a dopamine agonist then adding levodopa) may provide long-term benefit in patients able to tolerate the side effects of dopaminergic therapy

- Impulsivity screening and an assessment of the potential for other adverse drug effects is recommended before starting a patient on dopamine agonist therapy
- Finally, several panel members support use of an MAO-B inhibitor as a good first-choice option for patients with mild symptoms who do not require levodopa, citing the excellent safety profile and good dosing schedule of these agents.

**Addressing Nonmotor Symptoms in Early PD**

Symptoms that do not directly affect motor function are common in early PD. These nonmotor symptoms include depression, anxiety, RBD, constipation, cognitive decline, fatigue, apathy, and urinary incontinence. Some of these symptoms may be evident prior to the onset of motor symptoms.

Mood disorders are common in early PD, eg, anxiety disorders including panic attacks and social phobias are seen in about 40% of PD patients. A number of rating scales including the Beck Anxiety Inventory, and the Hamilton Anxiety Rating Scale are used to assess anxiety although their validity has not been well assessed. Data supporting treatment of anxiety in PD are lacking.

Cognitive decline is another common nonmotor problem. Acetylcholinesterase inhibitors used in treating cognitive decline in Alzheimer’s disease also have been used in PD. A randomized, placebo-controlled cross-over study of acetylcholinesterase inhibitors was conducted in PD patients reporting falls >2 times a week. Patients were randomly assigned to 6 weeks of donepezil or placebo with a 3-week washout between phases, and the primary outcome measures included daily falls and near falls as reported on postcards. The results of the study showed approximately half the number of falls in patients on donepezil compared with

**IMPORTANCE OF EXERCISE**

The National Parkinson Foundation recommends regular exercise to improve strength and balance and help reduce risk of falling. A number of studies have evaluated the association between exercise and motor function in the setting of PD. For example, 413 patients of the 143,325 participants followed for 9 years in the Cancer Prevention Study II Nutrition Cohort developed confirmed PD. When the association of exercise with development of PD was investigated, the relative risk was 0.6 when individuals in the highest category of moderate to vigorous physical exercise were compared with those in the lowest category ($P = .02$). Nevertheless, it was unclear whether these results were attributable to PD risk reduction due to vigorous physical exercise or decreased baseline activity in individuals with preclinical PD.

Several studies in animal models of PD showed improvement in balance with weeks of forced exercise training (ie, regular maintenance of an exercise rate beyond that preferred during voluntary exercise through use of a mechanical augmentation device). In addition, there is recent evidence that forced exercise involving use of a tandem bicycle also may be associated with improvement in motor function in patients with PD. This hypothesis is being evaluated in a randomized controlled trial.

When asked whether they consider exercise to be an important part of the management of patients with early PD:

- All participants stressed the importance of encouraging PD patients to exercise
- It was recommended that patients be given a customized, personalized written prescription to exercise on a regular basis with instructions to display it in a prominent place in the home (eg, on refrigerator door). Cited in support of such a strategy was a study showing increased compliance with such recommendations when patients were given written prescriptions
- A well-defined exercise program involving dynamic movement (eg, dance therapy) was cited as particularly beneficial
- An attendee said patients should be encouraged to keep in mind that medicine is useful for how they feel now, but exercising is an investment in their future

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*Agent is not indicated for usage by US Food and Drug Administration*
Another randomized, placebo-controlled study investigated the effects of the dual cholinesterase inhibitor, rivastigmine in PD patients with mild-to-moderate dementia. Patients were randomly assigned to placebo or rivastigmine (3 or 12 mg/d) for 24 weeks and the primary outcomes were the scores for the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and the Alzheimer’s Disease Cooperative Study-Clinician’s Global Impression of Change (ADCS-CGIC). Rivastigmine produced moderate but significant improvement in dementia but nausea, vomiting, and tremor increased. Another study addressed the effects of rasagiline on cognitive deficits in PD patients without dementia who received stable dopaminergic therapy. In a randomized, double-blind, placebo-controlled trial, 55 patients with impairment in 2 of 4 cognitive domains (attention, executive functions, memory, visuospatial functions) were randomized to rasagiline or placebo. Results of the study showed significant improvement in digit-span backwards, verbal fluency, composite domain Z scores when the rasagiline arm was compared with the control arm.

Effective management of nonmotor symptoms can have a profound effect on quality of life of patients with early PD. Nevertheless, dopaminergic therapy has less impact on these symptoms and clinical studies evaluating strategies to address these symptoms are limited. When asked how they address nonmotor symptoms in patients with early PD, participants stated:

- Mirtazapine, citalopram, and tricyclic antidepressants are potentially useful therapies for anxiety that is not fluctuation-dependent and not levodopa responsive
- Given the likelihood of the need for multiple medications to manage patients with PD, participants emphasized the importance of being cognizant of potential drug interactions

<table>
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<th>End Point</th>
<th>Limitations</th>
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<tr>
<td>Time to event (eg, time to additional motor fluctuations or disability or need for additional antiparkinsonian therapy)</td>
<td>Lack of standardized definitions; may necessitate long-term follow-up</td>
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<tr>
<td>Change from baseline in total UPDRS score</td>
<td>Confounded by symptomatic effects</td>
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<tr>
<td>Change from baseline in UPDRS subscore (eg, ADL)</td>
<td>Confounded by symptomatic effects</td>
</tr>
<tr>
<td>Change from baseline in other PD assessment tools (eg, Hoehn and Yahr and Schwab-England scales)</td>
<td>Confounded by symptomatic effects</td>
</tr>
<tr>
<td>Neuroimaging biomarkers of dopaminergic function</td>
<td>Possible effect of pharmacologic agent on ligand uptake</td>
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ADL = activities of daily living.

There is no approved treatment for altering the progression of PD. Complicating investigations to address this need are the dearth of reliable markers of disease progression, as well as possible confounding effects of study agents with symptomatic activity. Rather than using end points involving changes in biomarker levels, clinical outcome measures (many of which are also used to evaluate

TABLE 2. Examples of Clinical Trial End Points Used in Studies of Potential Parkinson’s Disease-Modifying Therapy

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*Agent is not indicated for usage by US Food and Drug Administration*
symptomatic benefit) have been used to evaluate the effects of candidate agents on disease progression in PD (Table 2). Some of the clinical study designs of potential disease-modifying agents have been adjusted to separate possible confounding effects of symptomatic activity of the candidate therapy from disease-modifying effects. Study designs used in clinical trials of investigating potential disease-modifying effects of candidate agents are shown in Figure 2.

Agents that have been and/or are being evaluated as potential disease-modifying therapies include coenzyme Q10 (CoQ10), creatine, minocycline, isradipine, selegiline, rasagiline, and inosine. For example, there is evidence that levels of CoQ10, a potent antioxidant and an essential cofactor in the mitochondrial respiratory chain, are reduced in PD patients compared with nonparkinsonian subjects. However, a recent phase 3 randomized, double-blind study (the QE3 study) that enrolled 600 patients with early PD to evaluate CoQ10 versus placebo was terminated early when results of a preplanned analysis showed study completion to be futile.

A number of studies investigating the potential disease-modifying effects of dopaminergic agents with symptomatic benefits used a clinical trial design incorporating either a washout or a delayed start (Figure 2). The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study was a pivotal trial investigating selegiline as disease-modifying therapy in the setting of early PD (Table 3). However, at the time of trial initiation the symptomatic benefit of MAO-B inhibitors was not known. Although initial results showed reduced disability and delayed need for levodopa in the selegiline arm, the randomized placebo-controlled trial design comparing selegiline and placebo with or without tocopherol was not adequate to address this confounding effect. In the Swedish study, patients were randomized to selegiline (10 mg/d) or placebo until need for levodopa therapy followed by an 8-week washout phase. The patients in the selegiline and placebo arms then continued on selegiline plus levodopa or placebo plus levodopa for up to 7 years or until the patient needed additional

![Figure 2. Clinical trial strategies used in the evaluation of potential disease-modifying therapy in PD. A. Randomized placebo-controlled trial; B. Randomized controlled trial with washout; C. Randomized controlled trial with delayed-start arm; D. Futility study. ITT= intention to treat; R = randomized.](image-url)
antiparkinsonian therapy. Compared with placebo, patients receiving selegiline had delayed initiation of levodopa therapy, and in the combination therapy phase, selegiline plus levodopa slowed the progression of symptoms of PD (Table 3).\(^4\)

The efficacy of rasagiline as disease-modifying therapy has been investigated in 2 delayed-start clinical trials: TVP-1012 in Early Monotherapy for PD Outpatients (TEMPO) and Azilect Given Once-daily (ADAGIO). This trial design has been proposed as a strategy for overcoming some of the potential weaknesses of trials involving a washout phase, such as uncertainty of the length of the washout phase and patient withdrawal during the washout phase.\(^4\)

In the TEMPO trial, patients were randomly assigned to 1 of 3 groups: 1 or 2 mg/d of rasagiline for 1 year or placebo for 6 months followed by 2 mg/d of rasagiline for 6 months (Table 3).\(^4\) Compared with the delayed treatment group, the patients receiving rasagiline at either dose had smaller increases in total UPDRS score, suggesting a possible disease-modifying effect of rasagiline.

The design of the ADAGIO study was similar to the randomized, placebo-controlled double-blind TEMPO study, but considerably more patients were enrolled and it was conducted over a longer time period. Meeting all 3 primary end points, as detailed in Figure 3, was specified as a requirement for the ADAGIO trial to be declared a positive study. Results for patients receiving early-start rasagiline at a dose of 1 mg/d met all

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**TABLE 3. Summary of Representative Clinical Trials Investigating Potential Disease-Modifying Effects of MAO-B Inhibitors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Components</th>
<th>Primary Outcome</th>
<th>Result</th>
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<tr>
<td>DATATOP</td>
<td>Selegiline (10 mg/d) or tocopherol (2000 IU/d) or combination vs placebo</td>
<td>Delay to levodopa</td>
<td>Delay to levodopa greater with selegline</td>
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<tr>
<td>SWEDISH</td>
<td>Selegiline (10 mg/d) or placebo until need for levodopa followed by an 8-week washout phase and restart of selegiline or placebo, both in combination with levodopa</td>
<td>Occurrence in fluctuations in disability defined as wearing off in the efficacy of levodopa therapy in patients taking levodopa 4×/d; time to addition of another antiparkinsonian treatment</td>
<td>Selegiline delayed initiation of levodopa therapy and the combination of selegiline plus levodopa slowed the progression of symptoms of PD</td>
</tr>
<tr>
<td>TEMPO</td>
<td>Rasagiline (1 mg or 2 mg/d) for 1 year vs placebo for 6 months followed by rasagiline 2 mg/d for 6 months</td>
<td>Change in UPDRS</td>
<td>Improvement in UPDRS at 12 months at both rasagiline doses in early-start arms</td>
</tr>
<tr>
<td>ADAGIO</td>
<td>Rasagiline (1 mg or 2 mg/d) for 72 weeks vs placebo for 36 weeks followed by rasagiline 1 or 2 mg/d for 36 weeks</td>
<td>Change in UPDRS between baseline and week 72; UPDRS slope superiority from weeks 12-36; UPDRS slope noninferiority from weeks 48-72</td>
<td>Early-start 1 mg/d dose of rasagiline met all primary end points; early-start 2 mg/d dose did not meet one of the end points as the UPDRS score between baseline and week 72 was not significantly different compared with delayed-start arm</td>
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ADAGIO = Azilect Given Once-Daily; DATATOP = Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; TEMPO = TVP-1012 Early Monotherapy for PD Outpatient.
primary end points. However, for patients in the early-start rasagiline arm receiving 2 mg/d, the total UPDRS score between baseline and week 72 was not significantly different compared with the placebo group. The results of the ADAGIO study suggest a possible benefit of early initiation of rasagiline at a dose of 1 mg/d, although the difference in total UPDRS score was only –1.7 points. It is possible that greater symptomatic benefit associated with the higher dose of rasagiline may have masked a possible disease-modifying effect in PD subjects with milder disease; it is also possible that the lower dose yielded a false-positive response (Table 3). In recently published secondary and post-hoc analyses of the ADAGIO study, rasagiline was shown to significantly delay the need for symptomatic antiparkinsonian drugs at both 1 and 2 mg/d doses.

**Figure 3. ADAGIO study design.** The 3 primary end points had to be met in a hierarchical fashion to declare positive results. Green arrows indicate the first end point: the superiority of early start treatment vs placebo with respect to the estimate of the rate of change from baseline in the total UPDRS score between weeks 12 and 36. Red arrow indicates the second end point: the superiority of early start treatment vs delayed start treatment with respect to estimate of change in the total UPDRS score between baseline and week 72. Blue arrows indicate the third end point: the noninferiority of early start treatment compared with delayed start treatment with respect to estimated rate of change from baseline in the slope for the total UPDRS score between weeks 48 and 72. The dashed blue line indicates placebo, and the solid blue lines indicate rasagiline. With permission from Olanow CW, et al. ©2009 Massachusetts Medical Society. All rights reserved.

When asked to comment on studies investigating potential disease-modifying therapies in early PD, roundtable participants:

- Discussed clinical significance compared with statistical significance in the ADAGIO study, and one participant speculated that a small beneficial effect of treatment on disease progression may become significant if it continues to accrue over a long period of time
- With respect to other candidate therapies for slowing disease progression in PD, the roundtable participants support use of single-arm phase 2 futility studies (Figure 2) to screen large numbers of potential agents

**Summary**

Despite advances in the diagnosis and management of early PD, many patients’ clinical needs are not being met. In their closing remarks, the roundtable participants emphasized the importance of individualizing the approach to the management of the patient with early PD and making the patient aware that their disease experience is likely to differ substantially from that of another patient with PD. Finally, they stressed the importance of uncovering the underlying mechanisms of PD as a critical step in advancing treatment.

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