Why Do We Delay Treating Parkinson’s Disease?

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dr, its worst. The introduction of dopamine agonists to the treatment repertoire provided an alternative to L-dopa, but dopamine agonists may cause dopaminergic side effects, and daytime “sleep attacks” may even restrict a patient’s ability to drive a car safely. It is not surprising that neurologists tend to wait as long as possible before initiating therapy for PD. However, with the availability of agents such as once-daily AZILECT® (rasagiline tablets), which is proven as effective monotherapy and has a side effect profile similar to placebo, physicians have another therapy to consider at diagnosis. The question is whether this will have an impact on the treatment of PD and whether neurologists and other physicians who treat patients with PD will begin to make a shift in their early treatment decisions.


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• AZILECT® is contraindicated with meperidine. Serious reactions have been precipitated with concomitant use of meperidine and MAO inhibitors including selective MAO-B inhibitors.
• AZILECT is contraindicated with tramadol, methadone, propoxyphene, dextromethorphan, St. John’s wort, mitrazapine, and cyproheptadine.
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• As with other MAOIs, patients taking AZILECT should not undergo elective surgery requiring general anesthesia and should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors.
• Patients with pheochromocytoma should not take AZILECT.

WARNINGS
• Patients taking AZILECT should avoid foods and beverages high in tyramine content in order to prevent a potential hypertensive crisis. Patients should be instructed about the tyramine content of foods and beverages and amine-containing medications that should be avoided, and about the signs and symptoms of marked blood pressure elevation that could represent a hypertensive emergency requiring immediate treatment/hospitalization.
• It seems prudent, in general, to avoid the combination of AZILECT with all classes of antidepressants. Serious, sometimes fatal safety events have been reported in patients receiving a combination of antidepressants and nonselective MAOIs or the selective MAO-B inhibitor, selegiline.
• At least 14 days should elapse after discontinuation of AZILECT before taking meperidine, antidepressants, other MAOIs, exogenous amines, or general anesthesia for elective surgery, or resuming an unrestricted diet.
• Caution should be used when giving AZILECT concurrently with CYP1A2 inhibitors such as ciprofloxacin.
• Patients with moderate to severe hepatic impairment should not take AZILECT.

PRECAUTIONS
• An increased incidence of melanoma in the AZILECT development program was comparable to that observed in the PD populations examined in epidemiological studies. PD patients are advised to monitor for melanoma frequently and see a dermatologist on a regular basis.

ADVERSE EVENTS
• Side effects of monotherapy (AZILECT 1 mg vs placebo, respectively) include: headache (14% vs 12%), arthralgia (7% vs 4%), and dysphagia (7% vs 4%), and as adjunct to levodopa therapy (AZILECT 1 mg, 0.5 mg, and placebo, respectively) include: dyskinesia (18%, 18%, 18%), accidental injury (12%, 8%, 5%), nausea (12, 10, 8%), weight loss (9%, 2%, 3%), constipation (9%, 4%, 5%), postural hypotension (9%, 6%, 3%), arthralgia (8%, 6%, 4%), vomiting (7%, 4%, 1%), dry mouth (6%, 2%, 3%), rash (6%, 3%, 4%), and somnolence (6%, 4%, 4%).

This issue includes an expert opinion on the treatment of early Parkinson’s disease (PD) by Rajesh Pahwa, MD.

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Before seeking medical attention, patients with Parkinson’s disease (PD) may notice they have developed nonmotor symptoms such as depression or motor symptoms such as tremor. They may attribute these symptoms to older age, drinking too much coffee, or other reasons until they realize that the symptoms are persistent or getting worse. Many patients with PD may be bothered for several months or years before they see a doctor about their symptoms.

Traditionally, neurologists have wanted to treat PD until functional disability is apparent, however, because of the large variability in the presentation of symptoms at diagnosis, an objective system for determining functional disability has not been established. Many neurologists base the level of functional disability on subjective factors such as the employment status, age, and lifestyle of the patient. For some patients with PD, depending on the type of employment, any tremor or loss of physical dexterity may be unacceptable. The point to keep in mind is that these patients were bothered enough by their symptoms to seek a diagnosis and are looking for treatment.

Why do we delay treating patients with PD? Historically, the barrier to treating early PD is based on delaying treatment with levodopa (L-dopa). When L-dopa was first made available, neurologists were very excited to finally have an effective treatment for PD. However, it became evident that long-term treatment with L-dopa produced motor complications, neurologists began to pull back from treating early PD, hoping to save L-dopa for the later stages of PD when disability is at its worst.

AZILECT® (rasagiline tablets): Evidence for Treating Early PD

A New Perspective: Where and When Does PD Begin

Case Study
Patient with early PD with expert commentary on early treatment by Rajesh Pahwa, MD

Visit www.azilect.com to learn more about AZILECT®, the first once-daily treatment option for people with PD.

AZILECT® is indicated for the treatment of the signs and symptoms of idiopathic Parkinson’s disease (PD) as initial monotherapy and as adjunct therapy to levodopa. The effectiveness of AZILECT was demonstrated in patients with early PD who were receiving AZILECT as monotherapy and who were not receiving any concomitant dopaminergic therapy. The effectiveness of AZILECT as adjunct therapy was demonstrated in patients with PD who were treated with levodopa.

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AZILECT® (rasagiline tablets): Evidence for Treating Early PD
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double-blind, fixed-dose, parallel-group phase III clinical trial of monotherapy with AZILECT in patients with early PD." Participants who enrolled in the trial were treatment naive and in the early stages of the disease. The mean time since diagnosis was approximately 1 year, and the mean total Unified Parkinson’s Disease Rating Scale (UPDRS) score was approximately 25, which is indicative of early, mild PD. This patient population was an appropriate group in which to examine the benefits of treating early PD.

AZILECT provided significant benefit for treating PD symptoms at 6 months compared with placebo. The difference in the change from baseline for total UPDRS scores for AZILECT compared with placebo was -3.8 points in favor of AZILECT (P=0.001). There was an overall 16% worsening of total UPDRS scores in the placebo group (P=0.002). (Figure 1). AZILECT also provided benefits as measured by the UPDRS motor and activities of daily living (ADL) subscores (Figure 2). The TEMPO trial data demonstrated that patients treated with AZILECT showed benefit of treatment compared with untreated patients at the end of 6 months of treatment. Many patients were able to stay on monotherapy with AZILECT well past the 6-month phase of the study. As a follow-up of the patients in this study showed, 45% of the 266 patients still in the TEMPO study were on AZILECT monotherapy after 2 years. When additional PD therapy was required, a dopamine agonist was added for most patients as the next step in their treatment.

The potential for side effects is an important consideration for any treatment, and the benefit versus risk of side effects has been a key consideration when deciding whether to treat patients with early PD. In monotherapy studies of AZILECT, there was a low incidence of dopaminergic side effects (Table 1) and the general side effect profile was similar to that of placebo (Table 2). With the added convenience of once-daily dosing, AZILECT is a very good treatment option for patients with early PD.

In 2003, Braak published his landmark findings suggesting that PD does not start in the substantia nigra. Indeed, based on his pathologic staging, PD is already at stage III by the time the substantia nigra is affected. He looked at a spectrum of age-matched postmortem samples from symptomatic and nonsymptomatic subjects and found that the pathology of PD follows a predictable path in the brain. Pathologic findings are first seen in the dorsal motor nucleus of the glossohypoglossal and vagal nerves and anterior olfactory nucleus and then are seen in the thalamus at stage II. At stage III, the midbrain is affected, including the substantia nigra, followed by basal prosencephalon and mesencephlet at stage IV. The neocortex is not affected until stages V and VI.

Some aspects of this pathologic staging fit very well with the presence of non-dopaminergic symptoms in patients and the reported early loss of smell in many patients with PD. However, the vast majority of PD patients with PD symptoms would suggest that Lewy body pathology is not the whole story or that there is variability in the susceptibility of neurons to Lewy body pathology. Indeed, the current theory suggests that dopaminergic neurons are particularly susceptible to Lewy body pathology, which may explain why there is such a devastating loss of dopaminergic neurons and prominent motor symptoms in the early symptomatic stage of the disease. These findings are very likely to have a large impact on PD research and the future development of drugs to treat PD.


A New Perspective: Where and When Does PD Begin
The discovery of dopamine deprivation in the substantia nigra in autopsies of patients with PD marked the beginning of the dopaminergic era of treating PD. Loss of dopaminergic neurons in the substantia nigra has been the landmark for the pathologic diagnosis of PD ever since this discovery. PD research also has shown that Lewy bodies in the substantia nigra are the molecular hallmark of the disease. However, Lewy bodies are also found in normal aging and in other neurodegenerative diseases, such as Alzheimer’s disease and dementia with Lewy body disease, leading to a “chicken or egg” type of debate about the importance of Lewy bodies in PD. Most recently, advances in our understanding of the genetics of PD have given credence to the “egg” hypothesis that Lewy bodies are a causative factor in the development of PD.

Case Study
58-year-old man, right-handed, insurance salesman

Presenting symptoms
- 4-month history of reduced motor activity and aching in right shoulder and hand
- Some clumsiness while typing
- Change in handwriting (smaller)
- Occasional mild postural bilateral tremor when using inhaler

Medical history
- History of right shoulder injury playing high school football
- Nonskier, no history of severe head injury, no family history of PD
- Asthma for 15 years (currently using fluticasone inhaler)

Coexisting conditions
- Asthma
- Overweight

Neurologic examination
- No rest tremor
- Normal facial expression and eye movements
- Muscle strength normal but slower fine finger movements and rapid alternating movements on right
- Mild increased tone (rigidity) on right
- Reduced arm swing on right; otherwise normal gait

Differential diagnosis
- Shoulder injury
- Vascular parkinsonism
- Primary dystonia

Test results
- Tests for shoulder movement and MRI of shoulder showed normal findings
- MRI of the brain was negative for infarcts

Diagnosis
- Idiopathic PD

This man is active and currently employed, with relatively mild symptoms of early PD. Although the issue that he may not be “functionally impaired” may be debatable, his symptoms are bothersome. I suggest in this case that his neurologist discuss treatment options with him. Given his relatively young age, treatment with L-dopa may be delayed to avoid the development of motor complications. His alternatives would be initial treatment with the MAO-B inhibitor AZILECT® , one of the dopamine agonists, or consider amantadine. Due to the lack of tremor, use of anticholinergics would not be a reasonable option. Given the extensive driving required of this patient for his job and mild symptoms, it may be better to initiate treatment with AZILECT because of the potential somnolence side effects that are sometimes seen with dopamine agonists.

Dr. Pahwa is a consultant to and has received honoraria from Teva Neuroscience, Inc.
AZILECT® (rasagiline tablets): Evidence for Treating Early PD
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The TEMPO (Teva Early Monotherapy in Parkinson’s disease Outpatients) trial was a 6-month, multicenter,