

# PARKINSON'S NEWS & VIEWS

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

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

## Why Do We Delay Treating Parkinson's Disease?

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.<sup>1</sup>

Traditionally, neurologists have waited 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.<sup>1</sup> Many neurologists base the level of

functional disability on subjective factors such as the employment status, age, and lifestyle of the patient.<sup>2,3</sup> 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).<sup>2,3</sup> When L-dopa was first made available, neurologists were very excited to finally have an effective treatment for PD. However, when 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

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

Monoamine oxidase type B (MAO-B) breaks down dopamine in the brain and therefore affords a unique target for treating PD.<sup>1</sup> L-dopa and dopamine agonists both act to supply dopaminergic stimulation through an increase in dopamine release or the mimicking of dopamine activity, respectively. Alternatively, the inhibition of MAO-B with an MAO-B inhibitor reduces the breakdown of endogenously made dopamine,

allowing for more dopamine reuptake into the presynaptic neuron. Given that MAO-B activity increases in the brain of aging people,<sup>2</sup> reducing its activity as an early treatment in PD offers the possibility of allowing more endogenously made dopamine to be preserved.

The TEMPO (Teva Early Monotherapy in Parkinson's disease Outpatients) trial was a 6-month, multicenter,

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Visit [www.azilect.com](http://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.



## 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.<sup>1</sup> 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 revealed that Lewy bodies in the substantia nigra are the molecular hallmark of the disease.<sup>2</sup> 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.

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.<sup>3</sup> 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 glossopharyngeal and vagal nerves and anterior olfactory nucleus and then are seen in the brainstem at stage II. At stage III, the midbrain is

affected, including the substantia nigra, followed by basal ganglia and mesocortex 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 nondopaminergic symptoms in patients and the reported early loss of smell in many patients with PD. However, the variability in symptoms of patients with PD suggests that Lewy body pathology is not the whole story or that there is variability in the susceptibility of neurons to Lewy body pathology.<sup>4</sup> 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.

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2. Spillantini MG, Crowther RA, Jakes R, et al.  $\alpha$ -Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc Natl Acad Sci U S A*. 1998;95:6469-6473.
3. Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24:197-211.
4. Lang AE. The progression of Parkinson disease: a hypothesis. *Neurology*. 2007;68:948-952. ■

### Case Study

#### 58-year-old man, right-handed, insurance salesman

##### Presenting symptoms

- 4-month history of reduced mobility 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
- Nonsmoker, 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

### Expert Commentary on the Case Study



#### Rajesh Pahwa, MD

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Director, Parkinson's Disease and Movement Disorder Center  
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*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. ■*

# Why Do We Delay Treating Parkinson's Disease?

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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.<sup>4</sup> 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.<sup>5</sup> 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.

1. Jankovic J. Pathophysiology and clinical assessment. In: Pahwa R, Lyons KE, eds. *Handbook of Parkinson's Disease*. 3rd ed. New York, NY: Informa Healthcare USA, Inc; 2007.
2. Schapira AHV. Treatment options in the modern management of Parkinson disease. *Arch Neurol*. 2007;64:1083-1088.
3. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology*. 2001;56(Suppl 5):S1-S88.
4. Mirapex [package insert]. Ridgefield, CT: Boehringer Ingelheim; November 2007.
5. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol*. 2002;59:1937-1943. ■

## **IMPORTANT SAFETY INFORMATION:**

### **CONTRAINDICATIONS**

- 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, mirtazapine, and cyclobenzaprine.
- AZILECT is contraindicated with other MAOIs, sympathomimetic amines, including amphetamines as well as cold remedies and weight-reducing preparations that contain vasoconstrictors (eg, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine) to avoid a possible hypertensive crisis.
- 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 reactions 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 as monotherapy (AZILECT 1 mg vs placebo, respectively) include: headache (14% vs 12%), arthralgia (7% vs 4%), and dyspepsia (7% vs 4%); and as adjunct to levodopa therapy (AZILECT 1 mg, 0.5 mg, and placebo, respectively) include: dyskinesia (18%, 18%, 10%), 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%, 3%), and somnolence (6%, 4%, 4%).



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