

# Parkinson's Disease 2006: Emerging Theories and Therapies

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## Summary

Parkinson's disease is one of the most treatable illnesses seen in neurology. There are some exciting new potential pathogenic theories of Parkinson's disease. There also are some newer therapies which, in addition to working as monotherapy in early disease, are effective adjuncts in late disease. One of these agents, rasagiline, holds the promise of being neuroprotective.

## Key Points

- Parkinson's disease is very treatable.
- The disease process begins many years before classic symptoms.
- Treatment of early symptomatic disease focuses on the use of dopamine agonists and monoamine oxidase inhibitors.
- Treatment of late disease focuses on the use of levodopa with numerous adjunctive agents added to increase time without symptoms.
- The future holds many new medications, and the ability to identify patients very early in the disease process and possibly alter their disease progress path.

IT HAS BEEN ALMOST TWO HUNDRED years since Dr. Parkinson described the clinical phenomenon of Parkinson's disease. In the past, the focus on the clinical symptoms of Parkinson's was on tremors. Currently, the diagnostic criteria for Parkinson's disease emphasize bradykinesia. Bradykinesia, or slow movement, is one of the diagnostic criteria for Parkinson's disease listed in the U.K. Brain Bank Criteria For a Diagnosis of Parkinson's.<sup>1</sup> In addition to bradykinesia, the patient must have one of the other cardinal symptoms—tremor, rigidity, or postural instability. Bradykinesia is responsible for the masked face; difficulty rising from a chair; slow, shuffling steps; and difficulty in initiating and maintaining movement.

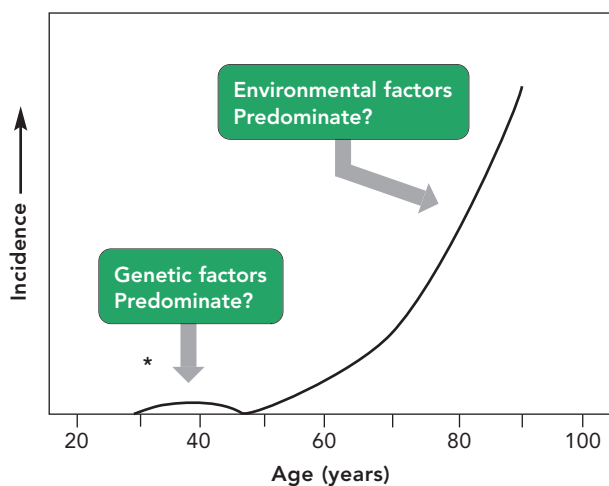
The onset of Parkinson's disease is slow, with a loss in seven-to-10 years of a group of neurons that are primarily responsible for delivering dopamine into the brain. At the time of diagnosis, patients might have 20 to 40 percent of their original dopamine producing neurons.

There has been a lot of research into the pathogenesis of Parkinson's disease. Familial cases of Parkinson's make up less than 2 percent of the total patient pop-

ulation. The genes that are passed on in families have given insight into what causes Parkinson's because they have identified some of the abnormal pathways. The majority of people with Parkinson's have the disease as a result of aging and exposure to different environmental toxins (Exhibit 1). If susceptibility to Parkinson's is combined with aging and exposure to toxin, disease develops, which is similar to the genetic susceptibility to develop diabetes.

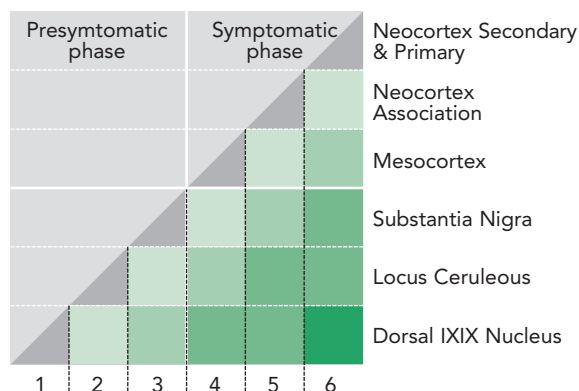
Braak and colleagues examined the brains of more than 130 people who had died with Parkinson's, and identified a most remarkable and startling finding.<sup>2</sup> The Braak team found that two areas of the brain, the base of the brain stem and the olfactory bulb, are where the disease process begins. Involvement does not begin in the mid-brain where most dopamine producing neurons are located. The underlying neuropathological process (the formation of proteinaceous intraneuronal inclusion bodies) begins in the brain stem and olfactory bulb, and advances in a topographically predictable sequence (Exhibit 2).<sup>2</sup> During the presymptomatic stages 1 and 2, the inclusion body pathology remains confined to the medulla oblongata and olfactory bulb. In stages 3 and 4, the

**Exhibit 1: Population Distribution of Causes of Parkinsonism**

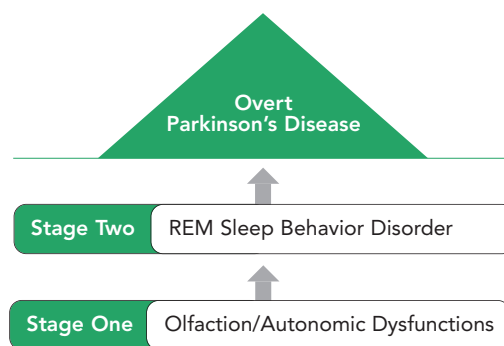


\* Not drawn to scale: Onset under 40 is <1% of all PD

**Exhibit 2: Braak Staging**



**Exhibit 3: The Parkinson's Disease Iceberg**



substantia nigra, midbrain, and basal forebrain are the focus of initially subtle changes that later become severe, when the illness reaches its symptomatic phase. In end-stages 5 and 6, the pathological process encroaches upon the telencephalic cortex, resulting in dementia.

The finding that this disease process begins in the olfactory bulb is both surprising, and, yet, not surprising. Clinicians already knew this from a clinical standpoint. Patients with Parkinson's disease characteristically lose their sense of smell. Parkinson's disease is the one neurodegenerative disease that has the most extreme sense-of-smell loss. In fact, early evidence suggests that if a person over 50 has lost his or her sense of smell; has some autonomic dysfunction, such as irregular heartbeats or changes in their bowel transit time; and has a REM sleep behavior disorder, they likely have very early disease. A REM sleep

behavior disorder is when the patient acts out his or her dreams during sleep (i.e. yelling, fighting, running). Those three early defects can precede the clinical symptoms of Parkinson's by up to two decades.

There is interest in trying to identify early cases and possibly intervening to prevent further loss of neurons. The so-called Parkinson's Disease Iceberg illustrates that many more patients have this disease process that we currently identify (Exhibit 3).

Today there is a whole toolbox of different medications that can be used in a variety of different cases (Exhibit 4). The toolbox is not full yet because not every single person responds adequately to a single agent. In fact, not every patient responds adequately to a combination of agents. Additionally, many patients cannot tolerate some of the agents.

The goal with medications is to try to mimic the normal physiology by bathing the dopamine recep-

**Exhibit 4: Current Therapies for Parkinson's Disease**

- Levodopa
- Dopa decarboxylase inhibitors
  - > Carbidopa
  - > Benserazide
- COMT inhibitors
  - > Tolcapone (Tazmar®)
  - > Entacapone (Comtan®)
- Combinations
  - > Carbidopa/levodopa/entacapone (Stalevo®)
  - > Carbidopa/levodopa
- Dopamine agonists
  - > Pramipexole (Mirapex®)
  - > Ropinirole (Requip®)
  - > Pergolide (Permax®)
  - > Bromocriptine
  - > Apomorphine (Apokyn®)
- Anticholinergics
  - > Trihexyphenidyl
  - > Bzotropine
- Amantadine
- MAO-B Inhibitors
  - > Selegiline (Eldepryl®, Carbox®)
  - > Zydys selegiline®
  - > Rasagiline (Azilect®)

tors with dopaminergic activity continuously because that is the circumstance that allows patients to function best. The brain is able to take up levodopa, a mainstay of therapy, and convert it into dopamine. Early in the disease process, patients started on levodopa will have a “honeymoon period” with dramatic, almost total relief of their symptoms. This period will usually last one to three years. Unfortunately, Parkinson’s is not a static illness. As time goes on, the number of dopamine neurons continues to diminish, and, as a result, the therapeutic window of brain lev-

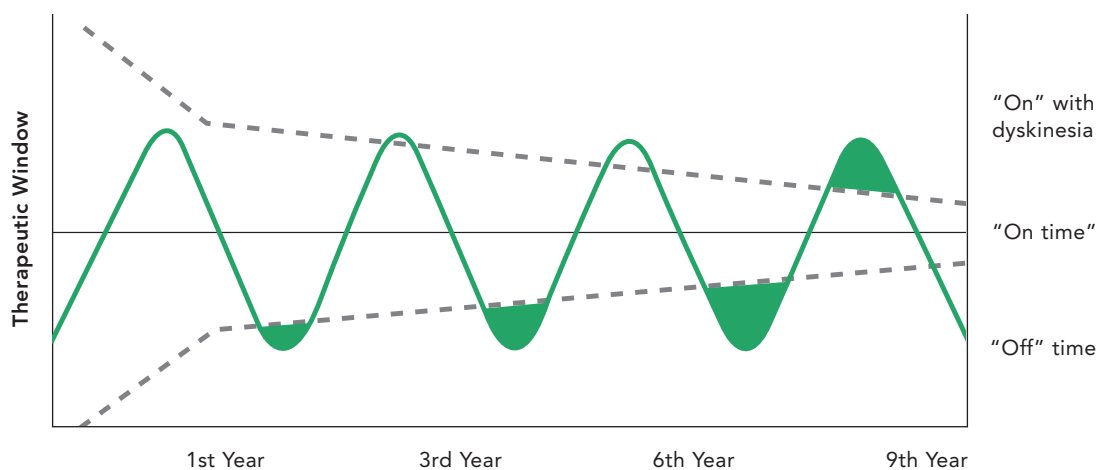
dopa concentration gets narrower and narrower to the point where the same plasma and brain levels of levodopa that were so dramatically therapeutic before, now are actually sub-therapeutic (Exhibit 5). This leads to off periods where the patient is under-medicated and unable to function. In contrast, there are times when the patient is actually over-medicated into a hyper-kinetic state with dyskinesia. Avoiding the two extremes of Off and On with dyskinesia is a goal of Parkinson’s disease therapy.

Levodopa is the cornerstone of therapy because it is the perfect replacement for dopamine. There are compounds that either dissolve rapidly or combination therapies. Levodopa is usually given with agents such as carbidopa, tolcapone, or entacapone, which prevent the breakdown of levodopa before it reaches the brain.

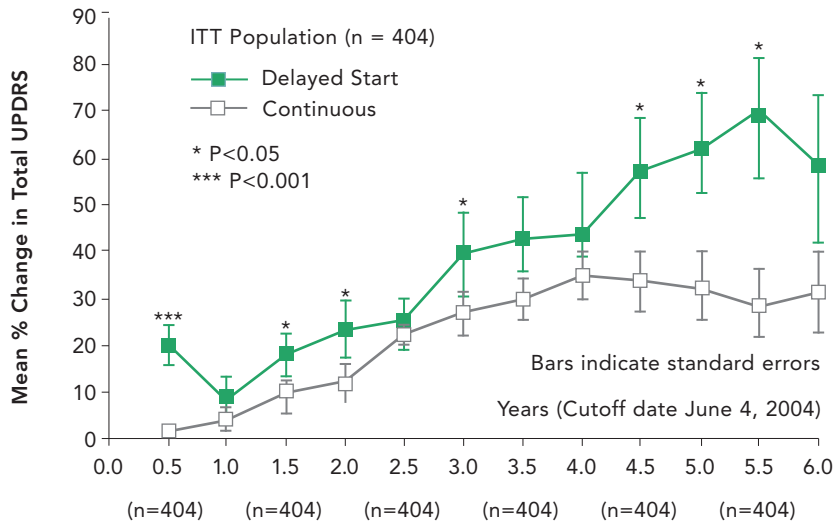
With currently available therapies, about 90 percent to 95 percent of the motor symptoms can be controlled. There is a price for that control because most of the time it requires multiple medications in a complicated regimen. Control can require patients with advanced disease to take multiple medications six or eight times per day. This can lead to noncompliance, drug-drug interactions, and intolerable side effects. Another challenge to management is that end stage control is dependent on the proper timing, delivery and pharmacology of the patient’s exogenous source of dopamine.

Because the disease is not static, patients will not be able to maintain control on the same dose of exogenous dopamine for long periods of time. Over time, the dopaminergic therapy needs to be adjusted to the changing therapeutic window. On average, most advanced Parkinson’s patients need a medication

**Exhibit 5: Therapeutic Window of Brain Levodopa Concentration**



**Exhibit 6: Tempo: Mean Percent Change In Total UPDRS - Continuous versus Delayed Rasagiline Treatment**



**Overall difference between continuous and delayed start groups is 16% (p=0.006)**

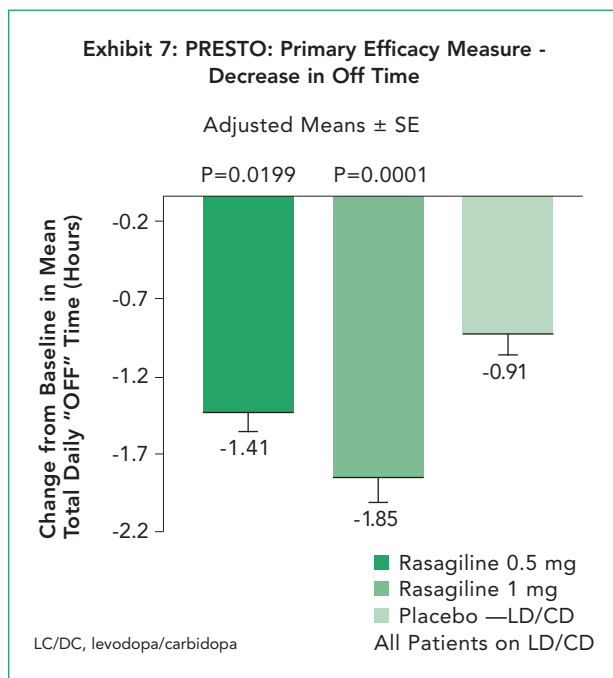
adjustment every six to 18 months. This is probably the biggest deterrent to people living successfully with Parkinson's. Many patients are under-medicated by primary care practitioners.

The early management of young adult-onset (60 and below) Parkinson's disease begins with dopamine agonists such as pramipexole and ropinirole. These agents are less likely to cause motor fluctuations in younger patients than using levodopa. If newly diagnosed patients get started on dopamine agonist monotherapy, their risk of developing dyskinesias is 5 percent to 6 percent over five years. If the patients were started on a levodopa preparation, within five years, roughly 50 percent will have already started to have the motor fluctuations with dyskinesias. The common side effects of dopamine agonists are nausea, sedation, sleep attacks, and peripheral edema. Because the dopamine agonists affect many different receptor systems in the brain in addition to dopamine, they can cause confusion and hallucinations. The atypical side effects include compulsive gambling, other compulsive behaviors and heart valve abnormalities (with bromocriptine and pergolide).

The revolution in the treatment of early PD<sub>1</sub> has been the introduction of rasagiline (Azilect<sup>®</sup>), a monoamine oxidase B (MAO-B) inhibitor which appears to have some disease modifying effects as demonstrated by the TEMPO trial.<sup>3</sup> In this trial, the degree of motor improvement was statistically different at six months when comparing two different

doses of rasagiline and placebo.<sup>3</sup> The Tempo trial used a delayed start design where one group received placebo and then received rasagiline at the end of the placebo-controlled period. If the difference in motor improvement was purely symptomatic, the expectation would be that the patients would see exactly the same degree of clinical improvement once given rasagiline. In fact, the patients whose rasagiline was delayed six months only got about 50 percent of the improvement. At up to six years of open label follow-up, a difference in the degree of progression of each group's diseased state, as measured by their Parkinson's disease ratings score, can be seen (Exhibit 6).<sup>4</sup> The group that got rasagiline earlier continued to do better, in a statistically significant manner, compared to the individuals who were given the drug after six months of delay. This suggests that early treatment actually had a disease modifying effect. The findings of this study prompted the initiation of a much larger study called the Adagio study, which will examine a nine-month delay and a nine-month follow up. In the Tempo study about half of the patients, at two years, were still adequately controlled on monotherapy with regard to their Parkinson's symptoms.<sup>3</sup> The side effects of rasagiline in the premarketing trials were similar to placebo.

Whether this possible disease modifying or neuroprotective effect of rasagiline will be proven in other studies is yet to be determined. Selegiline, another MAO-B inhibitor, was shown not to be neuropro-



tective in the DATATOP study, even though it showed a significant difference in the rate of patients needing levodopa therapy.<sup>5</sup> At the end of two years there was no long-term benefit to starting with Selegiline.

A revolution has occurred in the treatment of advanced PD as well with the introduction of effective adjunctive therapies. In advanced disease, levodopa in combination with carbidopa and/or catechol-O-methyltransferase (COMT) inhibitors is the standard of therapy for all patients. The COMT inhibitors increase the bioavailability of the levodopa and as a result, give a significant motor improvement which lasts longer compared with the same dose of levodopa given alone. Dopamine agonists and MAO-B inhibitors are used as adjunctive therapy. One improvement in MAO-B therapy has been the introduction of Zitas selegiline, which is a buccal dosage form. Buccal administration of selegiline produces blood concentrations that are higher and reduces liver amphetamine byproduct production.<sup>6</sup> Amphetamine is a metabolite of selegiline, which can cause confusion especially in elderly patients. This dosage form of selegiline provides about an hour improvement per day in on time.

PRESTO and LARGO were two large prospective trials that evaluated adjunctive therapy with rasagiline in advanced disease. In the Presto study, there was a half hour reduction in off-time in the half milligram dosage group and an hour for the one milligram group compared with placebo (Exhibit 7).<sup>7</sup> One milligram is the most common starting dose of rasagiline. The Largo study, which was done in

Europe, Israel and Argentina, compared rasagiline once daily plus levodopa and entacapone with each levodopa dose to placebo, levodopa, and entacapone. The mean off-time reduction was 48 minutes.<sup>8</sup> Rasagiline was well tolerated in this advanced patient population.<sup>7,8</sup> Tolerability and efficacy are both important for successful therapy.

With an adjunctive therapy in advanced disease, the patient should get approximately an hour a day more of on time. If they are not getting that amount of efficacy, then the adjunctive therapy should be stopped.

For the future, there are many different agents under development for this disease. Additionally, there are extended-release dosage forms of levodopa, and transdermal- and controlled-release dopamine agonists under development.

## Conclusion

Parkinson's disease is the most treatable problem in all of neurology. Patients can be taken from a disabled state to a functional state. They are then able to remain safe and secure at home, instead of being placed in long-term care. In the very near future, simple screening tests will identify people who are in the pre-clinical state of Parkinson's. They can then be put on neuroprotective therapy so they never experience clinical Parkinsonism. **JMCM**

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