

# An Ounce of Early Intervention

Can early treatment of neurologic disorders such as multiple sclerosis and Parkinson's disease slow disease progression? BY DEBRA GORDON, M.S.

**A**rlie Barber (not her real name) knew something was wrong when, in the spring of 2008, she found herself running to the bathroom all the time. Her gynecologist diagnosed her with overactive bladder. But Barber, then 35, was an avid runner who had never had children. The diagnosis didn't seem to fit.

A few months later, she woke up with half her face numb. Her doctor blamed it on the Botox injection Barber had received a few days earlier, but the numbness spread over the next few weeks to her hands and feet. Along with balance problems and a sense of just not "feeling right," Barber knew something was amiss. But it wasn't until she described her symptoms to a second doctor in October 2008 that she started to get answers that made sense. "When a woman your age describes symptoms like these," the doctor told her, "the medical community thinks multiple sclerosis (MS)."

Sure enough, an MRI of Barber's brain showed multiple lesions, the hallmark of the disease. Because her spinal tap was clear, a neurologist diagnosed her with a clinically isolated syndrome (CIS), defined as a "neurologic episode" that lasts 24 hours or more. The symptoms are caused by inflammation or loss of the protective covering on nerve cells in the brain or spinal cord and often involve vision or balance problems that eventually improve. A second CIS, however, along with evidence of brain lesions, leads to a diagnosis of "clinically definite" MS.

Given Barber's symptoms and lesions, the doctor strongly suspected Barber would eventually be diagnosed with MS, so he offered to start her on treatment. But many of the drugs used to treat the condition require injections and can have significant side

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effects. “He told me that it was really serious stuff and to be really sure that’s what I wanted to do,” she says.

By now, however, Barber’s symptoms had disappeared as mysteriously as they arrived. She decided to forego treatment and just live her life—until an MRI in April 2009 showed more lesions, leading to a confirmed diagnosis of MS. Now her doctor didn’t just offer treatment; he strongly recommended it.

“I was in shock,” Barber recalls. “I felt so good that I didn’t want to believe this was happening.” So Barber did what many patients

disability,” he says. “But when you have a patient come in and you say, you have lesions that are suggestive of MS and we want you to take an injection every day and you’ll get flu-like symptoms and it will cost \$10,000 a year and it may or may not slow a disease we’re not sure you’ll get. . . well, you can see why many patients opt for the wait-and-see approach.” The interferons and glatiramer acetate do not “cure” MS, stresses Dr. Wasserman, but they can slow disease progression when taken early. “I tell patients that they might have an exacerbation in 2017 instead of 2015,” he says.

Doctors don’t wait until someone with diabetes goes blind or develops kidney problems before treating their high blood sugar, notes Dr. Wasserman, or until someone with high blood pressure has a heart attack before treating their hypertension.

Part of the problem is that physicians can’t predict exactly which patients with CIS will go on to develop MS. Data suggest that between 40 to 100 percent will, depending on the type of lesions seen on MRI. In fact, some patients diagnosed with CIS may already have MS even though they don’t meet all the criteria for the disease.

The risk of diagnosing someone with CIS who doesn’t go on to

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do these days—she went for a second opinion and hit the Internet. The second specialist told her that if she were his daughter, he would start her on medication immediately. But it was the response from members of an online support group that decided the issue.

“So many people with disabling problems from MS said they wished they could go back in time and start therapy, but that it wasn’t available,” Barber says. “Others told me they didn’t start because they were scared of the shots, and that they would always regret not starting early. They thought maybe they wouldn’t be as bad off today if they’d started earlier.”

### EARLY TREATMENT IN MULTIPLE SCLEROSIS

Today, several studies—including at least one following patients for 10 years—have found that beginning treatment after a CIS but before a definite diagnosis of MS can significantly reduce the likelihood that someone will be diagnosed with MS in the next two years or longer, even though it can’t prevent MS altogether. (See box, “Slowing the Development of MS.”) Even a two-year delay can be important, however, because MS is a lifelong, progressive disease. The longer you have it, the more likely you are to become disabled.

There is also some evidence that starting treatment as soon as possible after an MS diagnosis can delay disease progression, enabling people with MS to live independently longer.

Yet starting treatment immediately after a CIS is not the standard of care, says Marc Wasserman, M.D., of Phoenix Neurology and Sleep Medicine in Arizona. “Study-wise, there is little doubt that early treatment slows the progression to MS and, from there, to

## Slowing the Development of Multiple Sclerosis (MS)

This table depicts the results of four major studies showing that beginning treatment at the “pre-MS” stage of the disease, after the first clinically isolated syndrome (CIS), extended the time until the MS diagnosis compared to people who were not treated after a CIS.

Study and medication	Time to MS diagnosis		Reduction in risk of developing MS during the study period
	with early treatment	with no treatment	
<b>PreCise</b> Glatiramer acetate	<b>722</b> DAYS	<b>336</b> DAYS	<b>45%</b>
<b>BENEFIT</b> Interferon beta 1-b	<b>618</b> DAYS	<b>255</b> DAYS	<b>45%</b>
<b>ETOMS</b> Interferon beta-1a	<b>569</b> DAYS	<b>252</b> DAYS	<b>49%</b>
<b>CHAMPIONS</b> Interferon beta-1a	NA	NA	<b>40%</b>

CHAMPIONS: Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study; BENEFIT: Betaferon/Betaseron in Newly Emerging MS for Initial Treatment; ETOMS: Early Treatment of Multiple Sclerosis; PreCise: Early Glatiramer Acetate Treatment in Delaying Conversion to CDMS of Subjects Presenting with CIS.

## Multiple Sclerosis: The Basics

Multiple sclerosis (MS) is thought to be an autoimmune disease in which immune system cells and inflammatory chemicals damage the myelin sheath that covers nerve cells in the brain and spinal cord. This, in turn, leaves the neurons open to further damage and impairs their ability to communicate, leading to problems with vision, movement, balance, and thinking. Most people are diagnosed in their twenties and thirties. Although studies suggest that about half of people with MS use a cane for walking and 15 percent require a wheelchair 10 years after diagnosis, the disease-modifying drugs used in treatment today can significantly slow the progression of the disease and the development of disability.

Between 250,000 and 350,000 people in the United States, primarily women, have been diagnosed with MS. The disease is likely related to a combination of genetic and environmental causes. People with a family history of the disease have a much higher risk of developing MS themselves.

The criteria for diagnosing MS have been a moving target over the past few years, as more evidence accumulates about the benefits of early treatment. The latest guidelines from the International Panel on Diagnosis of MS base diagnosis on the type of brain lesions seen on an MRI, allowing for diagnosis on the basis of a single MRI rather than waiting for two or more. While the new criteria do allow for a quicker diagnosis, there is some concern that they could also increase the risk of misdiagnosis.

develop MS is low, says Anthony Reder, M.D., professor of neurology at the University of Chicago Medical Center and MS specialist. “We have large studies of 1,000 or more patients now, and when we go back two to five years later and look at these patients, we almost never see someone who is misdiagnosed,” he says.

Dr. Reder recalls a recent patient who had been seen at another academic institution and came to his clinic after her third attack with a positive spinal tap. She had not been started on any medication yet. The reason? “Too much reliance on the MRI,” which showed very mild changes. “But the clinical history was classic for MS,” he says—a stark reminder that although MRI is a primary means of diagnosis, MS still remains a clinical diagnosis, reliant on the patient’s symptoms and the physician’s assessment.

Another obstacle to having an open discussion about the risks and benefits of early treatment, says Dr. Wasserman, is the mindset of youth. Because so many people diagnosed with CIS or early MS are in their twenties or early thirties, they still have a sense of invulnerability. “Their basic reaction is that they don’t want to be on a drug for something that has never happened,” he says. Even once people receive a diagnosis of clinically definite MS, many still delay treatment.

In a survey conducted between November 2008 and February 2009 by the National Multiple Sclerosis Society, 18 percent of the 250 people living with MS surveyed reported a delay in the start of their MS treatment, saying they were not told why they should start drug treatment early. However, nearly all of the 250 physicians interviewed said they always explain the benefits of starting drug therapy early.



As for Barber, she has now been on therapy for eight months. Unfortunately, she has had at least one other attack. But she’s sticking with her treatment even though she hates the shots. She says they are manageable and she would never suggest someone not start medication because of the shots. If her MRI continues to show disease progression over the next few months, she’ll likely switch to a different drug.

Barber is learning what all patients with a progressive, neurologic disease like MS need to know, notes MS specialist Fred D. Lublin, M.D., who is the Saunders Family Professor of Neurology and the director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai Medical Center in New York, NY: Treatment of such diseases is for the “long haul.” “We want to start you early to try and keep you healthy for a long, long time,” he says.

## EARLY TREATMENT FOR PARKINSON’S DISEASE

Another neurologic disease experts hope can be contained with early treatment is Parkinson’s disease (PD). In recent years, researchers have unearthed tantalizing evidence that there may be a “pre-PD” phase of the disease that begins long before the first tremor or other motor symptom. Symptoms include loss of smell, problems urinating, increased perspiration, sleep difficulties, constipation, restless legs, and fatigue, among others. These symptoms may appear up to 10 years before any movement-related symptoms or diagnosis.

The problem, notes Dr. Wasserman, is that some of these symptoms occur in other neurologic conditions as well, including Alzheimer’s disease. “There is no test for PD,” he says. It’s all up to the neurologist to diagnose it based on the patient’s clinical symptoms and history. (See box, “Parkinson’s Disease: The Basics.”)

Still, there is evidence that changes in the brain, including loss of neurons in the substantia nigra, where most dopamine is produced, begin up to 6.5 years before the first movement-related symptoms.

This got researchers thinking. What if there was a way to not only diagnose PD in the pre-movement phase but to treat it and prevent any further damage? The concept, called “disease modification” or “neuroprotection,” means protecting remaining neurons from further damage. To date, researchers don’t even know how to diagnose people in that pre-PD phase, but they are still hopeful that early treatment after diagnosis could slow the disease.

For instance, there is some evidence that levodopa, the drug most patients with PD eventually take, may slow the progression of PD or even provide some protective effects after patients stop taking it. However, most doctors wait as long as possible before starting levodopa because the benefits eventually fade and side



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effects, such as dyskinesias and motor fluctuations, increase.

That's why PD expert Michael Rezak, M.D., Ph.D., director of the Movement Disorders Center at Central DuPage Hospital Neurosciences Institute, starts his patients on rasagiline. It is also the only drug to show any disease-modifying effects on patients with early PD.

In one study, researchers randomly divided 1,176 people with recently diagnosed, untreated PD into two groups. The first group received 1 or 2 mg of rasagiline for 72 weeks, while the second group received a placebo for the first 36 weeks followed by rasagiline for 36 weeks. The idea was that if the first group had fewer changes after 72 weeks than the second group, the drug was able to slow PD progression. And, indeed, patients receiving 1 mg of rasagiline in the first group did show fewer changes on tests to measure PD symptoms. However, only those with the worst scores prior to taking the drug benefitted from the higher dose. Since researchers expected a greater benefit with the higher dose, most experts consider the results inconclusive, but Dr. Rezak prescribes it to patients even with very minimal symptoms. "It is very controversial," he admits, "but I happen to believe it has some disease-modifying effects."

For now, neurologists must work with their patients to find the right drug cocktail or, in some instances, surgical intervention such as a deep brain stimulation, to keep symptoms at bay. In the meantime, researchers are working hard to identify drugs or other compounds that slow the progression of PD and/or protect remaining dopamine-producing neurons.

The National Institute of Neurological Disorders and Stroke (NINDS) is running a series of clinical trials at more than 50 centers throughout the U.S. and Canada trying to find a way to slow the progression of PD. Currently, researchers are recruiting people who have been diagnosed with PD in the last five years and treated with dopamine agonists, ropinirole, or levodopa for at least 90 days but no longer than two years for a trial evaluating a special formulation of the nutritional supplement creatine being developed by the pharmaceutical company Avicena Group, Inc. In animal studies, the compound has been shown to protect brain cells. Other compounds NINDS researchers are evaluating include coenzyme Q10, a synthetic compound called GPI-1485, and minocycline.

"Where we get stuck with PD is that you have to find a way to replace dopamine," says Dr. Wasserman. "So while we may have drugs that treat PD better, or boost the effect of existing drugs, as far as really stopping the disease . . . I'm not sure that's on the horizon."

One thing you can do on your own is exercise—something Dr. Rezak prescribes to all his PD patients. A study presented at the 2010 AAN meeting in Toronto had people with PD practice "exaggerated movements" such as pushing their arms out before them, lunging forward, swinging their arms while walking, and kickboxing for 45 minutes a day, three days a week for 12 weeks. Symptoms improved significantly in exercisers compared to a similar group who didn't exercise. Dr. Rezak is a big believer in exercise, considering it one of the cornerstones of treatment for PD. "It's probably as important as taking the medications," he says, and he thinks it does slow disease progression as well as help patients better handle the ravages of PD. He maintains a database of his patients and says those who exercise regularly seem to progress more slowly and require less medication.

While researchers continue to search for ways to slow progression in diseases like MS and PD, experts agree that ignoring symptoms until later is a mistake. Discussing them with a neurologist is the critical first step in finding out what—if anything—is wrong, as well as having an informed discussion about the risk and benefits of treatment. NN

## Parkinson's Disease: The Basics

An estimated 1 million people in the US have been diagnosed with Parkinson's disease (PD), a progressive neurologic disease that can result in disabilities in movement, speech, and thinking over decades. The disease results as cells that produce dopamine, a brain chemical important in transmitting messages related to movement, are destroyed. Recent evidence has shown that other areas of the brain may be involved even before the dopamine neurons are lost. People with the disease are typically diagnosed in their fifties or older, although it can occur in those younger than 30. By the time the first movement-related symptoms appear, it is believed that people have usually had the disease for years.

The primary motor symptoms leading to diagnosis include tremor; stiffness of the arms, legs, and trunk; slowed movements, called bradykinesia; and balance problems. Because there are no blood or imaging tests for PD, you need to be as specific as possible in describing your symptoms—when they began, and how they affect your life—so your doctor can make the right diagnosis. Researchers are looking for biomarkers to help diagnose the disease earlier, particularly changes in the brain visible with various brain imaging techniques like single photon emission computed tomography (SPECT) and positron emission tomography (PET). But to date, symptoms are still the only way to diagnose the disease.