

# Not Just Tremor

Recognizing depression and other non-motor symptoms of Parkinson's disease.

BY TOM VALEO



“People who develop PD have a higher rate of **anxiety disorders** and **depression** than people without the disease—even up to 20 years before motor symptoms appear.”

—LAURA MARSH, M.D.

People like boxing legend Muhammad Ali and actor Michael J. Fox have helped to deepen the understanding of Parkinson's disease (PD) as a movement disorder. Ali

shows the most conspicuous symptoms of PD—a slow, shuffling gait; rigid movements; hand tremors; and an expressionless face. Fox, on the other hand, shows many common side effects of treatment for the disease—dyskinesias, which are involuntary movements that produce rocking; unintended facial expressions; and random arm motion.

The motor symptoms of PD—those related to movement—develop when a portion of the brain known as the substantia nigra stops producing enough of the neurotransmitter dopamine, which makes normal movement possible. (See box, “Parkinson's Disease: The Basics.”)

But PD also causes an array of non-motor problems. These symptoms may elude detection by doctors and even by patients themselves. Many of these symptoms seem to affect the mind more than the body; in reality, they illustrate the intimate connection between the mind and the body.

For example, depression, anxiety, irritability, and social withdrawal are all recognized now as non-motor symptoms of PD. Experts believe they are caused not by the person's reactions to having PD but by the disease itself and how it changes the physical brain.

Because so many non-motor symptoms of PD can be attributed to other causes, such as aging, stroke, or other neurologic disorders, it's important for patients and caregivers to inform their neurologist about any changes in mood, attitude, and behavior, says Christopher G. Goetz, M.D., professor of neurological sciences and pharmacology and director of the Parkinson and Movement Disorders program at Rush University Medical Center in Chicago, IL, and Fellow of the American Academy of Neurology (AAN).

“Patients and caregivers feel the burden of these non-motor symptoms,” Dr. Goetz says. “In my experience, they are relieved to find that the lack of energy, loss of endurance, and cognitive problems are part of PD itself. It means that these symptoms are not the patient's fault, nor are they part of another, separate disease the person has to contend with.”

## FATIGUE IN PARKINSON'S DISEASE

Many people with PD experience profound fatigue. However, because fatigue in PD does not improve with the use of medications that increase dopamine, such as levodopa, patients and doctors may blame exhaustion on the person's reaction to the disease.

“Everybody experiences fatigue,” says Benzi M. Kluger, M.D., an assistant professor at the University of Colorado Hospital in

Aurora, who studies the overlap between the motor and non-motor symptoms of PD. “But patients with PD say their fatigue is different. Their fatigue can be unpredictable and come on with little or no exertion. It also takes them a long time to recover. About one-third of people who experience fatigue say it's their most disabling symptom, and the main reason they can't work.”

So far, research into fatigue in PD has not clearly distinguished it from sleep problems or depression in the disease, and no medication is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of fatigue in PD. However, neurologists generally try to improve fatigue in several ways: by adjusting medications to improve motor function, since moving slow, rigid limbs expends more energy; by prescribing medication to improve sleep; by prescribing antidepressants, since depression may be associated with fatigue; or by recommending exercise, since physical activity can relieve fatigue.

## ANXIETY AND DEPRESSION

Fatigue often overlaps with depression, another problem so common that some patients assume it's a normal reaction to their disease. Actually, the depression may begin long before the motor symptoms.

“People who develop PD have a higher rate of anxiety disorders and depression than people without the disease—even up to 20 years before motor symptoms appear,” says Laura Marsh, M.D., Mental Health Care Line executive at the Michael E. DeBakey Veterans Affairs Medical Center, professor in the departments of psychiatry and neurology at Baylor College of Medicine in Houston, and co-author, with Matthew Menza, M.D., of *Psychiatric Issues in Parkinson's Disease: A Practical Guide*. “Up to one-half of patients will have had a first episode of depression during the five years prior to being diagnosed with PD. This suggests that the disease affects multiple brain systems.”

## Losing Religion?

People with PD even have a tendency to lose their interest in religion—a change more readily considered philosophical than pathological. According to research by Patrick McNamara, Ph.D., of Boston University School of Medicine, people with PD report significantly lower levels of interest in religion. Brain scans show that this lack of interest coincides with changes in the prefrontal cortex but does not correlate with depression, age, education, intelligence, or medication.

About 20 percent of PD patients experience some degree of **alexithymia**, which is the loss of the ability to recognize one's own emotions as well as emotions expressed by others.

Two subtle symptoms of depression that may develop in patients with PD are anhedonia—the loss of the ability to experience pleasure—and apathy. Since both symptoms involve the absence of an emotion or behavior rather than the appearance of something troubling (such as crying spells or panic attacks), anhedonia and apathy may go unnoticed.

No medications are currently approved by the FDA specifically for treatment of anxiety or depression in PD. However, many neurologists prescribe antidepressants and anti-anxiety medications to treat these symptoms.

### ALEXITHYMIA

About 20 percent of people with PD experience some degree of alexithymia, which is the loss of the ability to recognize one's own emotions as well as emotions expressed by others. People with alexithymia also show a limited ability to fantasize. Even their dreams tend to depict ordinary events.

"People with alexithymia may have difficulties in experiencing empathy," said Gianfranco Spalletta, M.D., Ph.D., a psychiatrist at the Santa Lucia Foundation in Rome, Italy, who has expertise in the relationship between the physical brain and behavior. "They are frequently unable to comprehend, give meaning to, and recognize their emotions. As a result, they often have difficulty understanding and responding to other people's emotions."

People with alexithymia tend to experience emotions primar-

ily as physical sensations: an upset stomach instead of fear, for example, or muscle tension instead of anger. In addition to having difficulty recognizing emotions such as irritation or sadness in themselves, they may be unable to read the signs of emotion in the facial expressions of others. This makes

communicating and empathizing very difficult. "Emotions often create in people with alexithymia an intense but vague sensation of unease," says Dr. Spalletta, who has researched the symptom extensively. "For example, many people with alexithymia cannot tell if signals from the body correspond to anger or distress. As a result, they may not be able to modulate their own emotional behavior during social interactions. They may react excessively to their environment—such as with intense panic or violent outbursts of anger—or not react at all even when it's appropriate."

In a recent paper, Dr. Spalletta and his colleagues argue that alexithymia may result from dysfunction in the frontal lobes and connected brain areas where emotions are processed and organized. They believe alexithymia represents an important and under-recognized symptom of PD. However, no medications exist right now for the treatment of alexithymia.

### TALK THERAPY FOR DEPRESSION IN PD

Although the depression and anxiety associated with PD may be rooted in dysfunction of the physical brain, patients can still benefit from forms of talk therapy.

For example, Roseanne D. Dobkin, Ph.D., a clinical psychologist at the Robert Wood Johnson Medical School in Piscataway, NJ, has adapted cognitive behavioral therapy (CBT), which relies on questioning and changing maladaptive thinking and behaviors, for people with PD.

"Even though we know there's a strong biological component to depression in PD, other factors affect the high rate of mood disorders in the disease," Dr. Dobkin says. "How people think about their illness—the coping skills they use, how they respond to symptoms, and how they perceive themselves—can have a big impact. Addressing negative thoughts and maladaptive behavior patterns can relieve some of the depression and related non-motor symptoms of PD, including sleep problems and anxiety."

About half of the patients with PD she has studied have been on antidepressants. However, she says, CBT seems to produce its own benefits separate from the action of antidepressants.

"CBT focuses on the here and now and gives people concrete coping skills," Dr. Dobkin says.

For example, she recalls one man in his 60s with relatively mild motor symptoms who almost never left the house. The rea-

## Alpha-Synuclein

Because drugs that alleviate the motor symptoms of PD usually do nothing for the non-motor symptoms, Dr. Goetz suspects that PD involves more than the loss of dopamine-producing cells in the substantia nigra. The link binding the motor and non-motor symptoms, he suspects, involves the deposition in the brain of synuclein, a common protein whose function is largely unknown. One form of this protein, known as alpha-synuclein, collects into stringy fibrils in the brains of people with PD. Alpha-synuclein also accumulates in people with other brain diseases that cause physical, psychological, and behavioral symptoms, suggesting it could be an important domino that, once it has tipped over, causes a cascade of problems in the brain.

The key question then, according to Dr. Goetz, is how to stop alpha-synuclein from accumulating in brain cells. Researchers are trying to answer this question.



son? He was ashamed of his disability. “He had his ‘man cave’ in the basement and spent the day on the computer,” Dr. Dobkin says. “He wouldn’t do yard work or exercise. He wouldn’t go out with his wife. He wouldn’t even go to the grocery store.”

To get him re-engaged with people, Dr. Dobkin suggested he call a friend and make a lunch date and then monitor his mood throughout the experience. She encouraged him to exercise, do yard work, and go to the supermarket. She challenged his belief that he was helpless and a burden and incapable of doing meaningful work. These suggestions helped somewhat, but what really changed his thinking was a “cognitive intervention” in which Dr. Dobkin accompanied him on a walk around the medical campus and persuaded him to stop 25 people at random and ask them what they thought when they saw someone with a physical disability.

“Twenty-three of the 25 said positive things,” Dr. Dobkin says, “and that helped him believe that he wouldn’t be judged negatively if he went out in public. That was a turning point. Once his mindset changed, he stopped isolating himself and really became much more active. As a result, his depression and anxiety decreased significantly.”

Dr. Dobkin also gives caregivers an opportunity to have sessions of their own, apart from the patient. “The primary purpose of these sessions is to educate caregivers about the non-motor symptoms of PD and give them information about how they can help the patient practice CBT techniques at home, such as challenging negative thoughts,” she says. “For example, when people are depressed they often speak in a depressed way—using certain words and tones of voice—so when caregivers hear the patient speak in a negative or pessimistic way, they have tools they can use to respond.”

### TALK THERAPY FOR ALEXITHYMIA

Dr. Spalletta has even adapted psychotherapy for PD patients with alexithymia.

“Traditional psychotherapy does not appear to be effective for people with alexithymia because they often show a limited ability to be introspective,” says Dr. Spalletta. “They have difficulty getting in touch with their own emotions and experiences. So we are trying to use an innovative approach aimed at improving their ability to interpret internal and external signals. This seems to help them connect their emotionally linked physical experiences to the related emotions.”

This approach borrows from a cognitive approach based on mindfulness meditation, which involves focused attention on specific mental processes and bodily sensations. “Patients are trained not only to name and interpret their own emotions but also those of others,” Dr. Spalletta says.

He believes patients with alexithymia may also benefit from medication as well, since all thought and emotion springs from the way the physical brain functions. Drugs may calm parts of the brain that overreact to stress and anxiety, for example, and modulate the release of neurotransmitters, which are the chemicals that allow brain signals to jump from one cell to another.

### OTHER NON-MOTOR SYMPTOMS OF PD

Many of the other non-motor symptoms of PD may be overlooked as well. For example, the loss of the ability to smell is often an early symptom of PD.

In addition, people with PD frequently develop sleep problems, such as rapid eye movement (REM) sleep disorder, in which the normal paralysis that takes place during deep sleep fails. This causes sleepers to thrash about as they act out their dreams.

Memory problems may develop in some people with PD, along with difficulties in concentrating, problem solving, multitasking, and planning. These changes may be dismissed as the inevitabilities of aging or a reaction to the stress of having a chronic illness. Such problems, even when subtle, can have serious consequences. “I’ve had patients who are doctors and lawyers who can’t continue to work because of their cognitive impairment,” Dr. Kluger says.

Problems with the autonomic nervous system, which is responsible for involuntary muscle function, may also accompany PD and produce symptoms such as constipation, urinary incontinence, sweating, erectile dysfunction, and low blood pressure (hypotension)—symptoms often blamed on aging. Many patients also experience trouble swallowing.

Even the treatments for PD can cause non-motor symptoms. Treatments that restore dopamine function in PD patients have been known to produce behaviors easily mistaken as charac-

## Parkinson's Disease: The Basics

**What is Parkinson's disease?** Parkinson's disease (PD) is a neurologic condition that results when dopamine-producing cells in the substantia nigra, located at the top of the brainstem, stop producing sufficient levels of dopamine, which is essential for normal movements. (The brainstem connects the spinal cord to the brain.)

**Why does the loss of these cells cause so many symptoms?**

Dopamine neurons account for less than 1 percent of the neurons in the brain. The largest cluster, located at the top of the brainstem, has been estimated to number no more than 400,000. However, individual dopamine neurons have as many as 500,000 connections with other neurons, endowing them with enormous influence over our movements, our motivations, and even our emotions.

**How common is PD?** PD affects about 1 percent of people older than 60 years of age. It affects more men than women. In early-onset PD, symptoms appear between the age of 50. Some reports suggest that 10 percent of all PD cases are early-onset.

**What are the symptoms?** PD causes trembling in the hands, arms, legs, jaw, and face, along with rigidity of muscles in the arms, legs, and trunk. People with PD also move slowly and sometimes “freeze” entirely for a few seconds. They also have trouble with their balance and coordination.

**What are the first symptoms to appear?** Recent research has found that PD begins years and possibly decades before motor problems appear. Often the loss of the ability to smell is the first symptom, but others may follow, including depression and other mood changes, sleep difficulties, constipation, memory problems, difficulty planning and carrying out tasks,

smaller handwriting, trouble swallowing, and a soft voice. The earliest motor symptom usually involves a subtle tremor in the hands or twitching in the arms or legs.

**How is PD diagnosed?** Currently there are no laboratory tests to detect PD in the earliest stages. Once motor problems begin, the diagnosis is based primarily on an exam by a neurologist, although brain scans and other tests may be ordered to support the diagnosis.

**How is PD treated?** While there is no cure for PD, the motor problems can be controlled through medications that restore dopamine function. A common combination involves levodopa, which the nerve cells in the brain can use to make dopamine, and carbidopa, which delays the conversion of levodopa into dopamine until it is in the brain. Other drugs are often used to facilitate the action of dopamine-enhancing medications.

**Do these treatments have side effects?** Over time, levodopa and related drugs may produce unwanted movements (dyskinesias). The rocking and fidgeting displayed by Michael J. Fox are dyskinesias that appear when he is on his medications. When the medications wear off, patients experience the slowness of movement, rigidity, and other classic symptoms of PD itself.

**What non-drug treatments are available?** Some patients benefit from deep brain stimulation, in which electrodes are implanted deep in their brain and attached by a wire to a device implanted under their skin. The device sends electrical pulse signals to the electrodes, which may help reduce the symptoms of PD as well as the dyskinesias that sometimes develop from drugs used to treat the disease. Stem cells that produce dopamine have also been implanted in the brains of people with PD with inconsistent results.

ter flaws, such as compulsive gambling and eating, excessive shopping and spending, sexual promiscuity, and Othello syndrome—the conviction, despite lack of evidence, that one's partner is having sex with other people.

### A COMPLEX DISEASE

How does a decline in dopamine contribute to so many different problems? In a 2010 article in the medical journal *Movement Disorders* titled “New developments in depression, anxiety, compulsiveness, and hallucinations in Parkinson's disease,” Dr. Goetz attempted an answer. He believes that a decline in dopamine disrupts the action of two other neurotransmitters, serotonin and norepinephrine. Since norepinephrine is part of the sympathetic nervous system, which mediates the “fight or flight” response, a disruption of the neurotransmitter could contribute to anxiety, which occurs in about 30 percent of PD patients. Similarly, the loss of dopamine that occurs in PD disrupts the relative balance of serotonin and dopamine, and depression often relates to alterations in serotonin.

In addition, brain images of people with PD have revealed damage to the fatty white coating around axons, which facilitate signal transmission among neurons. Loss of connections

between the frontal lobes and other brain regions could disrupt a variety of brain functions.

Marios Politis, M.D., a researcher and AAN member, suspects that the decline of dopamine neurons in people with PD disrupts the function of serotonin and other neurotransmitters, which would help explain why restoring dopamine in people with PD does not eliminate the non-motor symptoms.

“We have hypothesized that as dopamine neurons die, PD patients are left with a higher proportion of serotonin neurons, which start to alter levels of the dopamine in the synapses,” Dr. Politis says. Simply adding dopamine to the brain does nothing to restore the lost serotonin-producing cells. Even patients who received brain grafts to replace dopamine neurons were left with fewer serotonin neurons than normal in brain areas related to sleep, arousal, feeding, mood, emotion, and other non-motor symptoms.

“It's difficult to tell which symptoms are more linked to dopamine and which are more linked to serotonin,” Dr. Politis says. “From the studies we've done, these symptoms related to mood and appetite seem to be associated with dysfunctions in the serotonergic system. PD is a more complex disease than we initially thought, that's for sure.”