



# Battling the Black Dog

What to do when neurological disease goes hand in hand with depression.

BY GINA SHAW

**S**usan Randall\* had always been skeptical of medication for depression. During periodic battles with low-grade depression and anxiety, which she's had throughout much of her life, "I've always been one to go the psychotherapy route," says the central New Jersey woman, who is a therapist herself.

That was before she was diagnosed with Parkinson's disease three years ago, at the age of 48. At first she thought it was simply more anxiety, as she felt nervous driving at night because she thought the glare from oncoming headlights was too bright. Then, the brightness of the sun during the day made it seem like everything was coming at her too quickly. After several ophthalmologists told her that her eyes were fine, Randall finally saw a neurologist. "It took him one minute to tell me I had Parkinson's," she recalls. "I asked, 'How do you know?' and he said, 'Look at your face—you look like a judge!'"

Randall began medication for Parkinson's, which improved the lack of facial expression caused by the disease. She also wondered if the disease wasn't somehow tied to her depression. "I was worrying so much, and my husband had noticed how depressed I was," she says.

She entered a clinical trial through the Robert Wood Johnson Medical School of the University

of Medicine and Dentistry of New Jersey comparing two different antidepressants—nortriptyline (Pamelor) and paroxetine (Paxil)—to placebo for people with Parkinson's disease. "After a couple of weeks, I just noticed that one day I felt great," she says. "I thought, 'Why did I wait so long? Why did I suffer? It was a huge learning experience for me.'"

Randall wasn't alone. While about 10 percent of people in the U.S. have a depressive disorder in any given year, the rates are much higher for people with neurological conditions: around 35 percent for Parkinson's, nearly 40 percent for epilepsy, and as high as 50 percent for migraine and multiple sclerosis.

You might assume that this is simply a reaction to having a chronic, serious medical condition. After all, if you're diagnosed with cancer or heart disease, you are more likely to experience depression as well, right?

Not exactly. Although people with other chronic illnesses are at greater risk of depression than the general population, even cancer and heart disease don't seem to boost depression rates the way many major neurological disorders can. And as scientists learn more about the neurobiology of both

*Depression rates are much higher for people with neurological disorders.*



these conditions and of depression, they're discovering that it's not as simple as feeling down because you have a disease.

### SEIZED BY DEPRESSION

Which came first—the epilepsy or the depression? Neither, says Alan Ettinger, M.D., director of the North Shore-Long Island Jewish Medical Center Comprehensive Epilepsy Centers in New York. Epilepsy and depression are what he calls “bi-directional”—sometimes the patient develops epilepsy first and then depression; and vice versa.

*There are many chemical commonalities between epilepsy and depression.*

Another piece of the puzzle: the many chemical commonalities between epilepsy and depression. “A number of anti-depressants and anti-epileptic therapies seem to have similar effects on some aspects of brain chemistry,” says Dr. Ettinger. “One example might be the antidepressants known as SSRIs (selective serotonin reuptake inhibitors) and the anti-epileptics such as lamotrigine (Lamictal). Both enhance the transmission of norepinephrine.”

Rats that are genetically modified to be prone to epilepsy—they're called GEPRs, for “genetically epilepsy-prone rats”—are very deficient in norepinephrine, a chemical messenger in the brain that is also closely associated with depression.

In a study published in the journal *Neurology*

in January, scientists from Columbia University in New York used imaging techniques to demonstrate that abnormalities in the hippocampus of the brain are associated with depression among people with epilepsy. In fact, these abnormalities were even stronger predictors of depression than the number and severity of seizures that patients had. Abnormalities in the hippocampus are also associated with depression, independent of epilepsy, which might explain the frequent co-occurrence of these conditions.

“This suggests that some day, we may have some very refined ways of predicting who's most at risk for depression,

based on structural or functional changes in the brain,” says Dr. Ettinger.

That means that people with epilepsy who think they might also have depression must come to their doctor visits very well prepared, says Dr. Ettinger. “They need to organize the information in their medical history and understand the medical interview process,” he says. His center's Web site, [epilepsylongisland.com](http://epilepsylongisland.com), offers downloadable forms to make this process easier.

### MIGRAINE AND MELANCHOLY

Like epilepsy and depression, migraine and depression are also bidirectional. “Each disorder predisposes you to the other, and it doesn't matter which one you have first,” says Richard Lipton, MD, professor of neurology and epidemiology at the Albert Einstein College of Medicine in the Bronx, NY.

And just as with epilepsy, depression and migraine have overlapping treatments. Tricyclic antidepressants, for example, are often used as preventive medications for migraine. “The two disorders might share a common brain substrate, which could account for why a single medicine might make both disorders better,” says Dr. Lipton.

Again, both migraine and depression involve overlapping sets of brain chemicals—in this case, serotonin and norepinephrine. But the puzzle isn't quite so simple: some medications work for one disorder and not the other. “There may be a point at which bio-

chemical pathways in the brain converge, and if you find a drug that works at that point of convergence, it treats both disorders.”

In fact, Dr. Lipton calls migraine, epilepsy, and depression fellow travelers. “Migraine travels with epilepsy, and epilepsy and depression also travel together,” he says.

At least part of what is thought to contribute to depression in diseases like migraine and epilepsy is what Dr. Lipton calls the “interictal burden of illness,” the interval between attacks of pain or seizures—the period during which most patients don’t know when the disease will strike next. “If you have to live your life not knowing when you’ll next be incapacitated by pain or a seizure, that can contribute to depression,” he says. “If we can develop better methods for predicting migraines and seizures, this can both give us a treatment window and allow the patient to plan their lives better. For example, if you know you’re likely to get a migraine today, maybe you’ll skip that meeting in the city and stay home.”

Patients with migraine are often afraid to report their depression to their doctors. “They’ve often lived for many years with their pain being dismissed,” says Dr. Lipton. “They’re afraid of being told to just buck up, get a shrink, get a life. But they’re doing themselves a real disservice.”

## **PARKINSON’S AND THE BLACK DOG**

Parkinson’s disease also involves key chemical messengers in the brain, primarily the serotonin system and the dopamine system. Here, too, scientists are just beginning to understand the effects of these chemical alterations. It’s currently thought that people with Parkinson’s have a biological predisposition to depression because they have decreased levels of these neurotransmitters.

Depression in Parkinson’s appears to manifest itself a bit differently than depression in the general population. “There’s less guilt and thoughts of suicide among people with Parkinson’s disease and depression, and more apathy, anhedonia—the

*Patients with migraine are often afraid to report depression to their doctors.*

## **OUT OF THE BLUE**

In September 2001, SYLVIA POSEY woke up in New York’s Long Beach Hospital. “I had no idea what had happened. They told me I had a grand mal seizure,” she says. She’d worked as a bookkeeper for New York’s Waldbaum’s supermarket chain for many years, but soon she had to give up her job and go on disability as she began suffering five to seven seizures every week.

“I’ve been in Long Beach Hospital 50 times over the past year,” says Posey, 42.

In January, she had surgery to implant a vagus nerve stimulator (VNS) device, which has been shown to help reduce seizures in some people with epilepsy, and now the only time she has seizures are when her menstrual period is due. “It’s definitely helped, but I still don’t know exactly when they’re going to hit.”

The isolation imposed by her unpredictable seizures has only worsened a depression that was first diagnosed in 1995. “It had probably been coming on since I was a teenager, but I never faced it.” Posey says. “As I got older, all I did was work and come home and stay home alone. And then I started to use drugs. And then I saw that things were going wrong at work, and I wasn’t paying my rent or my phone bill, and my mother said, ‘Sylvia, this is not how I taught you.’ I knew I needed to get help.” She sought treatment at a community counseling center and was diagnosed with severe depression and bipolar disorder.

But she’s hopeful that better management of her epilepsy, with the help of the VNS, will also improve her depression. She’s also taking daily topiramate (Topamax), a seizure medication that has also been used in the treatment of depression. “What I really want to do is go back to work. I hate being so isolated, and I think it makes the depression worse.”

inability to experience pleasure from things you normally enjoy—and disturbances in sleep and fatigue,” explains Bernard Ravina, M.D., associate professor of neurology and director of the Movement Disorders Unit at the University of Rochester School of Medicine and Dentistry.

Of course, sleep disturbances and fatigue are also common in Parkinson’s in general, even when the person does not have depression, so the underlying cause of these symptoms can be difficult to tease out. But if you or a loved one have Parkinson’s, it’s important to be vigilant about depression. “Look for low mood, lack of energy, and lack of interest in the things that you used to do and enjoy,” says Dr. Ravina. “These things should not just be written off as a part of the Parkinson’s. Don’t focus only on motor symptoms and relegate them to the back burner when you talk to your doctor.”

Patients who have depression along with Parkinson’s also tend to report more disability than

## TOO YOUNG TO QUIT

JOAN MACK was 38, the mother of three daughters, and a secretary-receptionist for a busy mortgage company in upstate New York when her Parkinson's disease was first diagnosed three years ago. "I'd go to get a piece of paper or answer the phone, and my hand would move in slow motion," she says. "I'd grab for something and miss it. I wouldn't eat. I went home and just slept."

After a week in Utica Hospital, with MRIs, CT scans, and other tests ruling out multiple sclerosis, lupus, and other similar diseases, Mack was started on a Parkinson's drug called ropinirole hydrochloride (Requip). If it wasn't Parkinson's, they told her, the medication wouldn't touch her symptoms. Within days, her movements went back to normal.

"It was such a shock to me. I was only 38 years old! I'd heard stories and seen Michael J. Fox and Muhammad Ali on TV, and I thought, I'm looking in the mirror at what I may be like five or 10 or 15 years down the road," she says.

Early on in the course of the disease, Mack shut herself away from everyone else. "Without support, I can see where someone with this disease would get into a depression and just fade away," she says. "I was at that point, and it wasn't any fun. I was pushing myself to make everyone else happy and not taking care of myself. When I met my second husband, a year ago, I almost looked anorexic. If I hadn't found someone that was supportive, I think I would have been suicidal."

She also credits her doctors at the University of Rochester for helping her to manage medication for both the Parkinson's and the depression. She's now on Requip, Sinemet (another Parkinson's drug), and Anafranil, a tricyclic antidepressant. "It helps a lot. I've seen a big improvement since I've been on the antidepressant. I sleep better at night and it relaxes me," she says. "They're very good about adding medications a little at a time to see how they affect me."

"Some days are bad days," Mack says. "But most of the time, I'm happy. I rest if I need to rest, and try to have a normal life and live it to the fullest."

those who don't. "They have a more rapid course through both their motor illness and their cognitive decline, as well as their ability to care for themselves," says Matthew Menza, M.D., professor and vice chair of the department of psychiatry at the Robert Wood Johnson Medical School. "We're not absolutely certain at this point that treatment for depression changes that, although we do know that it will improve a person's quality of life. Whether or not it would actually change the course of the disease, we don't yet know."

Several studies now underway may begin to answer those questions. Dr. Menza and his colleagues are about to close enrollment on a three-year trial comparing one tricyclic antidepressant, an SSRI, and a placebo in treating depression in Parkinson's. They want to see if these drugs successfully treat

Parkinson's-associated depression, as well as affect the cognitive and motor problems in the illness. A similar, slightly larger trial is taking place at the University of Rochester.

"This is an illness that's treated with a lot of medications that can affect mood," says Dr. Menza. "It can be strongly influenced by depression and vice versa, so it's very important to have a doctor who understands these connections." The American Parkinson Disease Association (APDA) can help through their local information and referral centers ([apdaparkinson.org/user/InfoReferral.asp](http://apdaparkinson.org/user/InfoReferral.asp) or 1-800-223-2732.)

### DEMYELINATION AND DEPRESSION

The relationship between multiple sclerosis (MS) and depression seems to be different from other neurological disorders. Instead of fluctuating levels of neurotransmitters like serotonin, dopamine, and norepinephrine, MS involves lesions on the brain and spinal cord where they have been stripped of their insulating myelin. Could demyelination play a role in depression?

*"The depression is worse than the Parkinson's," Randall says.*

It's possible, says Scott Patten, M.D., professor in the departments of commu-

nity health sciences and psychiatry at the University of Calgary, Alberta, Canada. "Some brain imaging studies show a correlation between MS lesion burden in locations of the brain thought to be associated with mood and affect, particularly in the white matter regions that are connected to the limbic areas. But it's likely that lesions in a large number of specific places could affect a person's vulnerability to depression, so we're probably not going to narrow it down to one location."

Other factors likely play a role, including the medications used to treat MS. Corticosteroids in particular are known to be associated with depression and mood disturbances.

Says Dr. Patten: "The level of depression is the driving force in the quality of life of people with MS, probably more so than the overall burden of the dis-

ease itself.” There is also evidence that depression impairs the management of MS symptoms, by reducing adherence to treatment.

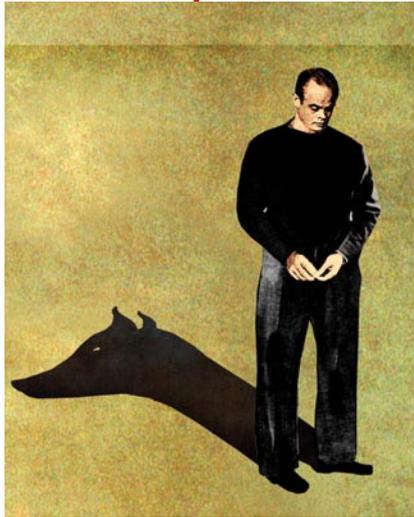
As with other neurological conditions, patients with MS—and their doctors—may find that they focus on the physical symptoms of their primary disease and pay less attention to the depression. But that’s improving, says Dr. Patten. “In 2005, the Multiple Sclerosis Society put out a consensus statement on screening for depression in MS, and I think it’s had an impact.... I think eventually we’re going to learn that if we deal better with depression in our patients, they’ll do better overall.”

But managing this multifactorial susceptibility to depression isn’t easy, as Susan Randall learned. The time-release carbidopa-levodopa (Sinemet CR) she began taking for her Parkinson’s left her with what Dr. Menza described as a “dopamine-derived depression,” a crash that occurred when the drug began to wear off. “It would just take me over. It had nothing to do with being sad about anything, but I would be a totally different person, completely depressed and anxious,” she says.

This isn’t uncommon, says Dr. Menza. “We see people who have mild depression that becomes much worse when they go through the ‘on/off period’—the point at which dopamine drugs stop working over the course of the day,” he explains.

“We believe it’s partially biochemical changes in the brain that are driving the temporary worsening of the depression. When the patient goes back on the medication, they’re fine again.” Depression during this “wearing-off period” can also occur in Parkinson’s patients who don’t otherwise experience depression.

With Dr. Menza, Randall is working to find the right balance of medications to treat both conditions. “Right now, in terms of its impact on my daily life, I think the depression is worse than the Parkinson’s,” she says. “Depression is a very serious thing, and it’s so important not to neglect it because you’re focused on managing your other disease.”



## SYMPTOMS OF DEPRESSION

In 2004, Frank Gilliam, M.D., who directs the Comprehensive Epilepsy Center at Columbia University, surveyed a group of neurologists and found that 80 percent did not routinely screen their epilepsy patients for depression. Many people with Parkinson’s

who have depression probably aren’t getting the treatment they need either, says Bernard Ravina, M.D., associate professor of neurology and director of the Movement Disorders Unit at the University of Rochester School of Medicine and Dentistry. “In our study, to be published soon in *Neurology*, about 40 percent of the [Parkinson’s] patients who screened positive for depression were neither referred for further mental health evaluation nor started on any kind of pharmacological therapy.”

Depression is generally diagnosed when most of the following symptoms have been present every day for at least two weeks, according to the National Institute of Mental Health:

- ▶ **Persistent sad, anxious, or “empty” mood**
- ▶ **Diminished ability to enjoy activities that were once enjoyable**
- ▶ **Restlessness or irritability**
- ▶ **Changes in appetite**
- ▶ **Insomnia, early morning wakening, or excessive sleepiness**
- ▶ **Decreased energy level**
- ▶ **Slowed movements**
- ▶ **Difficulty concentrating, remembering, or making decisions**
- ▶ **Recurrent thoughts of death or that life is not worth living**

If you are experiencing any of these symptoms, talk to your neurologist about getting screened for depression.

Gina Shaw is a health and science writer whose articles have appeared in Redbook, Fitness, Glamour, and WebMD: The Magazine.



For more information on depression, see **RESOURCE CENTRAL** on page 46.