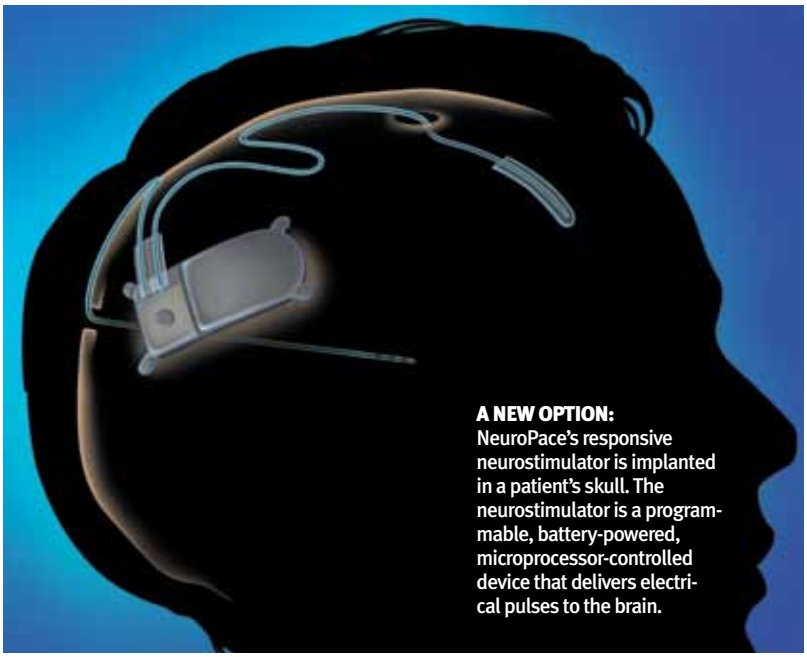
THIS WAY IN

A Healing Jolt: Reducing Seizures With Brain Stimulation

BY GINA SHAW



A NEW OPTION: NeuroPace's responsive neurostimulator is implanted in a patient's skull. The neurostimulator is a programmable, battery-powered, microprocessor-controlled device that delivers electrical pulses to the brain.

COURTESY NEUROPACE

People with epilepsy whose seizures are not controlled by any of the currently available medications may soon have another treatment option. Called "responsive cortical stimulation," it's one of a growing number of different techniques now being studied that directly stimulate the brain in an effort to short-circuit seizure activity.

Responsive cortical stimulation requires that doctors first use advanced imaging, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), to identify one or two areas in the brain where the seizures originate, known as a "seizure focus."

Surgeons then implant a device, called the responsive neurostimulator, into the person's skull (it replaces a small piece of the skull) and connect it to the areas of seizure focus using electrodes. The device continuously monitors the person's brain-wave activity. It can be programmed to identify the earliest sign of each individual patient's seizure pattern and stimulate the brain to interrupt the seizure in response. The person doesn't feel the stimulation.

RESPONSIVE STIMULATION

In a study that appeared in the American Academy of Neurology's medical journal *Neurology* in September 2011, 191 people with medically intractable partial epilepsy who experienced an average of at least three seizures a month were all given the implant. ("Medically intractable partial epilepsy" involves seizures that can be localized to specific areas within a person's brain, but those seizures have not responded to multiple medications.)

Half of the people—the "treatment group"—received responsive stimulation, which means stimulation in response to detected seizure activity. The other half—the "placebo group"—initially received no stimulation ("sham treatment"). None of the participants knew whether they were receiving stimulation or not. After three months, seizures decreased in the treatment group by nearly 38 percent, while they declined in the placebo group by only 17.3 percent. (Even though placebos are not active treatment, many studies have shown that even the perception of treatment can have some effect on patients.)

After the three-month initial period, everyone in the study was given responsive stimulation. Nearly half of the participants who completed two years of the study with the implant achieved a 50 percent or greater reduction in seizures—something that was particularly impressive given how many other treatments had not been able to help this same group of people.

> "Brain stimulation doesn't completely obliterate a seizure focus, but it may **stop the spread of seizures** through the brain."
>
> —ROBERT FISHER, M.D., PH.D.

DEEP BRAIN STIMULATION

In 2010, another trial—the SANTE trial—had similarly encouraging results using a related technique, deep brain stimulation, to reduce seizure frequency. Deep brain stimulation has been used for years to treat Parkinson's disease. Unlike responsive cortical stimulation, which only sends its signals when it detects possible seizure activity, the deep brain stimulation device sends electrical pulses on an automatic schedule (usu-

ally "on" for one minute and "off" for five minutes) to disrupt and prevent the seizure process. Most people do not feel the stimulation as it reduces their symptoms, but some do experience a tingling sensation when the stimulation is first activated.

In SANTE, patients who were treated with deep brain stimulation also experienced a 40 percent reduction in seizures, compared with about 14 percent in the placebo group. The entire patient group continued to improve when the device was turned on for all of them following the initial study period. By the end of two years, they reported a 56 percent median reduction in seizures, and 14 percent of them became seizure-free for six months or more. (The entire patient group had the device turned on after the blinded phase, so there was no long-term effect in the placebo group.)

"Brain stimulation doesn't completely obliterate a seizure focus, but it may stop the spread of seizures through the brain, which may result in seizures that are less intense and cause less injuries," says Robert Fisher, M.D., Ph.D., the Maslah Saul M.D. professor of neurology at Stanford University School of Medicine, director of the Stanford Epilepsy Center, Fellow of the American Academy of Neurology (AAN), and a lead investigator in the SANTE trial. "Our trial also showed a statistically significant reduction in injuries caused by seizures," he says.

The outcomes may even get better in the future, says Jacqueline French, M.D., professor of neurology at the New York University Langone Medical Center, co-director of epilepsy research and epilepsy clinical trials at the NYU Comprehensive Epilepsy Center, and Fellow of the AAN. "I think that as we learn how to manipulate frequencies and which patients are the best candidates for these treatments, results will improve," she says.

STILL WAITING APPROVAL

Both the deep brain and cortical stimulation devices have been approved by European authorities and are available in European countries. So far, however, neither device is available in the United States. The U.S. Food and Drug Administration (FDA) is still deliberating on whether to approve them.

Of course, the devices have drawbacks. Both techniques involve brain surgery, which is invasive and involves risks of bleeding and infection, although the complication rates in both trials were low. In the NeuroPace trial, 2 percent of the patients had significant bleeding, although none had long-term neurologic consequences. About 5 percent had infections at their surgical sites. During the SANTE trial, no patients had noticeable symptoms of bleeding; five instances of bleeding did occur but were only seen on brain imaging studies. About 13 percent of the SANTE patients developed infections at the site of their brain surgery.

Dr. Fisher thinks that these studies represent only the beginning for brain stimulation in epilepsy. "In time, new devices besides these will be developed, including ones that have various sensors and different ways of stimulating," he says. "This is engineering and electronics linked with neuroscience. It's a fast-moving field." But since it is the job of the FDA and other regulatory agencies to assure the safety of new devices, they must move with caution.

"We're hopeful that this will become available to patients in the near future, but don't know when that might be," Dr. Fisher says.

MEMORY LANGUAGE AUDIO SPATIAL LOGIC NUMBER

NEUROBICS

Sock Logic

Use your logic skills to find matching pairs of socks.

1 In a pitch-black room, you reach your arm into a box containing 10 black socks and 10 white socks. What is the smallest number of socks you need to take with you in order to make sure you have at least one pair of matching socks when you step out of the room into the light?

2 In a pitch-black room, you reach your arm into a box containing 10 black socks, 10 red socks, and 10 white socks. What is the smallest number of socks you need to take with you to make sure you have at least two pairs of matching socks when you step out of the room into the light?

3 In a lighted room, you see three boxes labeled "Black," "White," and "Black & White." One box contains just black socks, one contains just white socks, and one contains both, but the labels have been scrambled so that all three boxes are mislabeled. Figure out how to place all the labels correctly by pulling just one sock out of just one box. No peeking into the boxes. Which box should you reach into, and how can you figure out what the labels should really be?

These puzzles was adapted from the book *The Playful Brain: The Surprising Science of How Puzzles Improve Your Mind*, by Richard Restak and Scott Kim (Riverhead Books 2010). For more information, visit **theplayfulbrain.com.** —*Scott Kim,* **scott@scottkim.com**

ANSWERS ON P. 13

NEUROLOGY NEWS

Neurologists Asked to Probe for Violence

In January, the American Academy of Neurology (AAN) published a "position statement" on violence and abuse that encourages neurologists to routinely screen for current and past abuse and neglect with their patients. (To read the statement, go to **aan.com/go/about/position**.)

"We don't have any statistics on how often neurologists inquire about exposure to violence or abuse with their patients, but I believe it's very uncommon," says Elliott Schulman, M.D., Fellow of the AAN, adjunct clinical professor of neurology at Thomas Jefferson School of Medicine in Philadelphia, PA, and professor with the Lankenau Institute for Medical Research, also in Philadelphia.

People with neurologic conditions are more vulnerable to abuse than the general population, Dr. Schulman says. "For example, people who have cognitive impairment, such as from Alzheimer's disease, are at higher risk not only for physical abuse but also for emotional and financial abuse. People who are physically impaired, such as those with Parkinson's disease or who have had a stroke, are at greater risk as well." When cognitively impaired patients can't communicate for themselves, the neurologist may look for signs such as unexplained bruises or cuts or poor hygiene, nutrition, or medical care.

Abuse can also *cause* many neurologic conditions, such as headaches and traumatic brain injury (TBI). "There's a connection between headaches and abuse, and it's been suggested that pain conditions may also be linked to abuse," says Dr. Schulman. (For example, people who report having been abused as children appear to have higher rates of migraine and other pain disorders; this may hold true for abuse in adulthood as well, some experts say.) "Neurologists are seeing a special kind of patient population that really calls for us to screen [for abuse] on a routine basis," he adds.

Dr. Schulman and Anna DePold Hohler, M.D., Fellow of the AAN and assistant professor of neurology at Boston University Medical Center, co-wrote the new position statement. They will be leading a special educational program at the next AAN meeting (April 21-28, 2012, in New Orleans, LA) to prepare neurologists to become designated "abuse experts" with a clear understanding of what abuse is and how to look for it.

Caregivers should recognize that caring for a person with a neurologic disorder can leave someone feeling frustrated or exhausted enough to lash out. "It's important to be able to reach out for help when you're becoming frustrated so that you don't become an abuser yourself," Dr. Schulman says. "Sometimes, when patients come in with dementia, I'm just as concerned about the caregiver as the patient. I don't want them to burn out, become frustrated, and neglect the patient. If you're experiencing that, it's not uncommon. Work with the neurologist to help you find a way to have some down time."

Joining a support group is another way for caregivers to feel less isolated and avoid burnout. See Resource Central, page 35, for a list of patient advocacy organizations. Many of them run support groups for both patients and caregivers. —*Gina Shaw*

ABUSE: MARK COFFEY/ISTOCKPHOTO

GROUNDBREAKER: A new guideline is based on research done in Zambia by neurologist and AAN Fellow Gretchen Birbeck, M.D., M.P.H.

MICHIGAN STATE UNIVERSITY

NEUROLOGY NEWS

Drugs for Epilepsy and for HIV Can Interact Negatively

At least one of every 10 people infected with human immunodeficiency virus (HIV) also experiences seizures. This is due in large part to the fact that many HIV-associated complications—such as central nervous system infections—can increase the risk of seizures. Unfortunately, the antiretroviral drugs used to treat HIV can sometimes interact negatively with antiepileptic drugs (AEDs) used for treating seizures: either the AED decreases the effectiveness of the HIV drug or the other way around. For this reason, the American Academy of Neurology (AAN) recently issued the first-ever guideline for prescribing AEDs to people with HIV. (Go to **www.aan.com/guidelines** to read the guideline.)

> One in 10 people with **HIV** also experiences **seizures**.

The guideline is based on groundbreaking research done in sub-Saharan Africa by neurologist and AAN Fellow Gretchen Birbeck, M.D., M.P.H., a professor in the department of neurology and ophthalmology and the department of epidemiology and biostatistics at Michigan State University. Dr. Birbeck directs an epilepsy care team in Zambia, where she noticed a skyrocketing number of patients in her epilepsy clinic who were also on antiretroviral drugs. Although many AEDs do not interact negatively with drugs for HIV, her patients often have limited access to these other AEDs. It was this experience that prompted Dr. Birbeck to propose the guideline.

One class of epilepsy medications that can be a particular problem for people with HIV is known as enzyme-inducing AEDs. This includes carbamazepine (brand name Tegretol), phenytoin (brand name Dilantin), and phenobarbital (brand name Solfoton). These medications can significantly lessen the concentration of some antiretroviral medications in the blood, reducing the drugs' effectiveness in controlling HIV. (AEDs are also used to treat non-epilepsy neurologic disorders, such as neuropathic pain, and some psychiatric conditions, such as bipolar depression.)

HIV medications can also decrease the blood levels of some AEDs, but that's easier to manage, says AAN Fellow Christina Marra, M.D., professor of neurology and adjunct professor of medicine (infectious diseases) at the University of Washington School of Medicine in Seattle. "We routinely check AED levels as a part of normal clinical care for any patient with epilepsy, and we can adjust the dose as needed. But levels of HIV drugs aren't monitored as routinely and are harder to interpret."

This doesn't mean that people with HIV can never be prescribed those AEDs known to reduce the effectiveness of HIV drugs. "I have a patient with very intractable [difficult-to-control] epilepsy, and [phenytoin] is the only thing that stops his seizures," Dr. Marra says. "Because of that, I have to monitor his levels of raltegravir, atazanavir, and ritonavir [antiretroviral medications] with the help of a pharmacist with expertise in dispensing medications for HIV. We've been able to keep his epilepsy and his HIV under control, but it's more complicated than usual."

The guideline covers only some of the potential interactions between AEDs and antiretroviral drugs. "There are lots of known interactions—and theoretical ones as well," says Dr. Marra. "This guideline should give the patient and his or her physician a starting point. People need to understand that while potential interactions exist between HIV drugs and AEDs, plenty of treatment options for people with HIV and epilepsy are available."

And because both HIV drugs and AEDs can interact with many other kinds of medications, patients should tell their neurologist and/or primary care doctor all of the medications they are taking —*Gina Shaw*

NEUROBICS ANSWERS CONTINUED FROM P. 9

1. Three socks (not 12) is enough to ensure you have at least one white or black pair.

2. Six socks. It is not enough to grab five socks, because you could have, for instance, three black socks, one white sock, and one red sock, which includes only one matching pair.

3. Pull one sock out of the box labeled "Black & White." You know this box is mislabeled, so if the sock is white, for instance, then it actually contains all white socks. In that case, one of the other two boxes—which are labeled "Black" and "White"—must contain black and white socks, and the other box must contain just black socks. Since all boxes are mislabeled, the box labeled "Black" cannot contain all black socks, which leaves just one possibility: The box labeled "Black" contains black and white socks, and the box labeled "White" contains just black socks.

Similarly, if the sock you take out is black, then the "Black & White" box contains all black socks, and the other two boxes—labeled "Black" and "White"—must contain white socks and black and white socks, respectively.