Impulsivity Reported in PD Patients with Deep Brain Stimulators

By Jamie Talan

ARTICLE IN BRIEF:

✔ A new study found that patients who had had deep brain stimulation implants for Parkinson disease showed impulsive behavior when their stimulator was on, compared to when it was off.

The man was wheelchair bound and crippled by Parkinson disease (PD). But he literally jumped at the idea to sit in a more comfortable chair clear across the room. It was the first time that University of Arizona scientist Michael J. Frank, PhD, saw the fruits of his research in action.

Dr. Frank studies the possible negative effects of deep brain stimulation (DBS), and his latest study — published Nov. 23 in the journal *Science* — suggests that PD patients are far more impulsive when the stimulators are turned on. And so they were when his wheelchair-bound patient stood and began walking. His wife shouted in fear, and Dr. Frank and his assistant kept him from falling.

Dr. Frank and his colleagues designed a study to test impulsivity in 17 PD patients who had had DBS. They found that patients made poorer choices when their stimulator was on, compared to when it was off. Still, it is hard to say what this means for their everyday lives.

Investigators who work with DBS patients every day called the study elegant. "They worked hard to figure this out," said Michele Tagliati, MD, associate professor of neurology and division chief of movement disorders at Mount Sinai School of Medicine in Manhattan.

"We clearly need more research," the Mount Sinai doctor said. The problem in designing any study to test the benefits and side effects of DBS is that there are literally thousands of possible electric settings that can be made once the electrodes are in place, he said.

Doctors can alter the amplification, frequency, and pulse rate, Dr. Tagliati said. What's more, each electrode has four different contacts, each placed on a different spot in the subthalamic nucleus. To complicate things even further, the electricity can spread across the region like a wave, making it almost impossible to figure out why and how it works in calming the motor symptoms of Parkinson disease.

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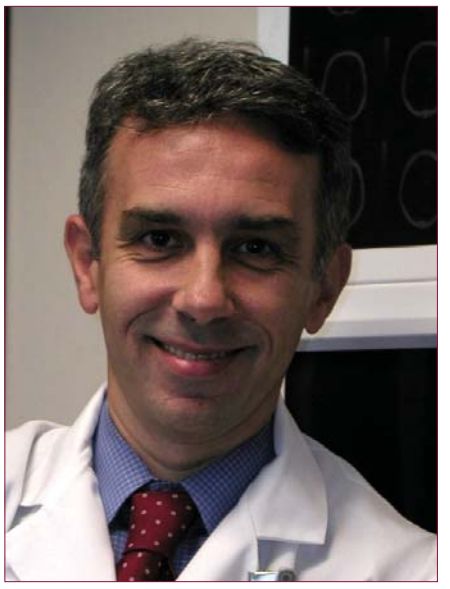
Impulsivity in PD

Several years ago reports started surfacing warning that some PD drugs — dopamine agonists — can trigger uncharacteristic predilections, including gambling, obsessive housecleaning, overeating, compulsive tinkering with electrical components, and a robust increase in sex.

Similar clinical observations are beginning to be discussed in the DBS world, Dr. Frank said. "There are some reports of impulsive behavior with DBS, including gambling — just not to the same extent as the dopamine agonists," he explained. But still, he said, these problems are rare, and the benefits of the technology far outweigh any of these risks.



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'**If this is confirmed** by other groups, the next step is to determine whether stimulation settings can be altered to prevent these cognitive problems while maintaining effective motor treatment.'

"We are in no way advocating that patients stop either of these treatments, which are often quite effective," he explained. But he said the investigators would want patients to be aware of the associated, though rare, risks for impulsivity with DBS so they can discuss it with their doctors should any of these problems arise during the treatment. As the medication studies show, stopping the medicine eliminates these obsessive and impulsive behaviors.

Study Protocols

Dr. Frank and his colleagues decided to test for impulsive tendencies on and off the electrical device to determine what the treatment is doing in the brain to bring out impulsivity. They tested two groups of patients — 17 who had DBS and 15 taking dopamine medications — and age-matched healthy controls. Patients were tested on an off medication and with DBS on and off.

The investigators designed a computer game, training the patient to choose a symbol associated with positive feedback. They used Japanese symbols in lieu of English letters so the patients would not figure out a system based on letters they know. Instead, they were shown two symbols — one paired with

Continued on page 12

THE ROLE OF DBS AND DOPAMINE IN REWARDS AND DECISION-MAKING

Dopamine wears many hats in the brain. In the 1950s, Swedish scientist Arvid Carlsson discovered the neurotransmitter dopamine and described the depletion in Parkinson disease. He and others noted the loss in substantia nigra and that more than 80 percent had to be wiped out before symptoms appeared. For decades, doctors focused on the motor symptoms. Over time, scientists also found that dopamine circulates in major cerebral reward circuits, and these deficits affected cognitive and mood changes as well.

To be a good king of rewards, dopamine in the system must go up when the rewards are high and go down when they are not. If things are good, dopamine goes up, and the reward — the good feeling — strengthens the learning that took place on the road to the experience. But medicines keep dopamine levels artificially high all the time, and thus the reward systems are bound to go slightly off center. And that is precisely what Dr. Frank and his colleagues have found.

"Normally, when you make a decision that is not rewarding, dopamine goes down," Dr. Frank explained. "And that should drive learning to avoid actions preceding the negative stimulus so that they are not likely to do that behavior again. Medication continuously releases dopamine and doesn't allow the brain to experience low dopamine levels when it should, when the chips are down," he added.

Unlike medications that keep dopamine levels artificially high all the time, DBS has a different effect, the scientists discovered, supporting the idea that the subthalamic nucleus is required to "hold your horses."

The dopamine levels lost in the disease trigger overactivity of the subthalamic nucleus and lower the ability of the basal ganglia to function properly in motor actions.

DBS disrupts the overactivity of subthalamic function, but in truth scientists still don't understand exactly why it works so well. What they can say is that DBS does not act on the dopamine system itself, but addresses the "effects" of the depleted dopamine in the basal ganglia by counteracting these effects in a different way.

PFO, Stroke

Continued from page 1

ARTICLE IN BRIEF:

✔ The prevalence of patent foramen ovale was significantly greater in the general population among those with stroke of unknown cause, including both younger and older patients.

director of the Stroke Center at Hartford Hospital in Connecticut. When someone has an ASA, it means that flap moves to and fro between the left and right chambers. That movement can increase the risk of a cryptogenic stroke.

It's unclear exactly why those with PFO, and particularly those with ASA, have more strokes. But researchers believe that if a clot forms, the opening allows the clot to go from the right side of the heart to the left and then up to the brain.

"The hypermobility of the ASA probably contributes to the physics of the blood flowing across," said Dr. Silverman. In cardiac ultrasound studies, you can "see the shunting of the bubbles across the walls of the PFO with patients with ASAs — the walls of the flap may then act to literally guide bloodflow through the PFO."

Study Protocols, Results

Investigators compared data on 503 patients who had had a stroke — 227 with an unknown cause and 276 patients with a known cause, including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and other known causes. They also compared data between the 131 patients younger than 55 years old and 372 patients older than 55.

The findings: 13.4 percent of younger patients and 15.2 percent of older patients with cryptogenic stroke also had a PFO and an ASA. And 44 percent of younger patients with unexplained stroke had a PFO versus 14 percent of younger patients with a known cause of stroke; in older patients the prevalence of PFO was 28 percent (for cryptogenic stroke) versus 12 percent for those with a known cause of stroke.

Implications for Treatment

But while doctors, who were not involved with the trial, say the study was strong, particularly since transesophageal echocardiography (TEE) was done on all the participants, it leaves them without answers about treatment.

"It's the gray area," said Steven R. Messé, MD, a neurologist in the division of Stroke and Neurocritical Care at the Hospital of the University of Pennsylvania. "We're not sure what's best for these patients."

There are two main paths: medical management and surgery to close the PFO. "With medical management you can give them aspirin, or possibly warfarin [Coumadin]," said Dr. Messé. "But then you run a higher risk of bleeding complications over time, a major concern with younger patients."

The risk of recurrent stroke in patients who are found to have a PFO after the first one is about 1 percent a year, said Dr. Messé. This risk is about the same in patients with unexplained stroke and no PFO. But for those patients with both PFO and ASA, the risk of recurrent stroke is probably higher, about 3 percent, he said.

There are procedures to close the PFO, but surgery is not 100 percent effective, and there is a risk — around 1 percent — of a major complication.

Dr. Harloff, the study author, said the goal was not to evaluate secondary prevention. He noted that although several ongoing trials are comparing PFO closure with medical management, there are no clear guidelines based on randomized trials.

Decisions for the patients in the study were made individually and following the recommendations of the German Neurological Society. Those with PFO and first transient ischemic attack/stroke were given aspirin 300 mg a day after coagulation disorders and deep vein thrombosis were excluded. Those with PFO and ASA, or those with relapsing stroke while taking aspirin, were treated with warfarin for at least two years, he said.

Those who had a stroke despite warfarin treatment or those with contraindications against oral anticoagulant therapy had surgical closure of the PFO. To close the PFO, doctors use a cardiac catheterization procedure, in which a catheter is inserted in the groin and an occluder device — slightly larger than the defect — is placed around the PFO. Over time, usually three to six months, the patient's tissue grows around the device to seal the area. Howard S. Kirshner, MD, professor and vice chair of the department of neurology for Vanderbilt University in Nashville, TN, said that it is often unclear what to do. "I just had a 65-year-old patient with a TIA," he said. "He has a PFO, and he had a heart transplant; the PFO was in the transplanted heart. We do not want to give him warfarin because they need to get cardiac biopsies to check on the transplant."

Although the 2001 WARSS trial — reported in the *New England Journal of Medicine* — comparing the use of warfarin and aspirin showed that there were no significant differences between the treatment groups, Dr. Kirshner said larger clinical trials are needed to establish clearer guidelines for treatment: medical therapy versus closure of the PFO, particularly for those with ASA. Current guidelines do not recommend either routine warfarin anticoagulation or closure.

Dr. Silverman said his standard practice is that if a PFO is found in someone with a cryptogenic stroke, he gives warfarin for three or four months, and then switches to low-dose aspirin.

"One initially treats with warfarin for the concept of a hidden clot on the venous side of the body to prevent that clot from going into the bloodstream, through a PFO and into the brain," he said.

In addition to the concerns about bleeding, taking warfarin is harder on the patient because they need bloodwork every one to four weeks to be certain they remain within the therapeutic range, he said.

The study's finding that PFO is often found in older patients throws a further wrench into treatment, doctors said. "We should be looking for PFO in older patients, because we always assumed that with older patients there were other causes, especially atherosclerosis of large arteries in the neck or cardiac sources, high blood pressure, and diabetes," said Dr. Silverman. "We need to study these patients more, especially with TEE, and maybe the next generation of studies will address treatment."

Dr. Messé said part of the problem is getting patients to join the studies. "Having a stroke is stressful, and to some people, being told that there is a hole in their heart demonizes it, and it's psychologically difficult to imagine not closing the PFO," he said. "And then for some people, they say, 'You are not going near me with that device.'"

"The bottom line is — what should we do for the patient? And we honestly do not know right now." ■

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DBS & Impulsivity

Continued from page 10

positive feedback 80 percent of the time, the other one with negative feedback 80 percent of the time. Then, they presented new combinations of symbols so that the positive and negative feedback symbols were each presented together with other more neutral symbols.

They defined "win-win" conflict situations as those in which one symbol was rewarding 80 percent of the time and another was rewarding 70 percent of the time, and lose-lose situations where there was little reward for choosing either symbol.

Decision-Making Results

Patients off medicine were good at avoiding the most negative symbol but did not do well when forced to choose a more rewarding symbol. When they were on medicine, the opposite occurred: they were poor at avoiding the most negative symbol.

To see whether patients on DBS had changes in impulsive behavior, they designed a slightly different model to test whether stimulation leads to impulsive decision-making. DBS patients chose the more rewarding symbol and avoided the less rewarding symbol when their devices were shut off.

But the results were different when the patients had to make high-conflict choices where there was little reward for choosing either symbol. Whereas healthy participants and patients on and off medication slowed down for high-conflict choices, DBS patients did not, the study team showed. In the high conflict choices, they even sped up their responses, and the more they sped up, the less likely they were to make the best choice. In other words, they were more impulsive when the stimulators were turned on. When the device was turned off, they had no problems slowing down for high conflict situations relative to low conflict decisions.

"If this is confirmed by other groups, the next step is to determine whether stimulation settings can be altered to prevent these cognitive problems while maintaining effective motor treatment," Dr. Frank said.

Another problem is that most DBS patients have had the disease much longer than patients taking medication and this could also factor in for some side effects.

The Arizona researchers are now studying the effects of other stimulator settings — lowering the voltage and frequency to see whether that would reduce the cognitive side effects of treatment. Indeed, the Mount Sinai group is heading in the same direction to figure out what can be done to avoid these side effects without giving up the benefits of DBS. ■

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