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New Psychiatric Surgeries Tread a Fine Line Between Research and Therapy

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Brain surgery for severe depression, obsessive-compulsive disorder, and Tourette's syndrome offers new forms of relief for desperate patients. But professors from several universities who are developing these experimental treatments worry that their ability to investigate them is tangled in a complex net of federal regulations, insurance requirements, and demands from medical-device manufacturers that make it hard to do the basic science that will ultimately improve therapies.

They are also concerned that the pressures, and the eagerness from patients themselves for help, may compromise patient safety. "This is brain surgery. It isn't going out to get your nails done," said Helen S. Mayberg, a professor of psychiatry and neurology at Emory University. She aired her concerns, as did her colleagues, at a symposium at the 2011 meeting of the American Association for the Advancement of Science here on Friday.

The notion of opening up the brain to relieve something like depression is startling, but the candidates for this operation—which involves implanting electrodes into brain areas thought to produce errant signals involved in these disorders—have not been helped by any kind of drug or talk therapy. And they are existing in remarkable pain, unable to function, said Benjamin D. Greenberg, an associate professor of psychiatry at Brown University who works with patients with obsessive-compulsive disorder. "I worked with one man who took eight hours to eat breakfast. He moves so slowly because he has to do everything over so many times," Dr. Greenberg said at the meeting. Michael S. Okun, an associate professor of neurology at the University of Florida, described people with extreme Tourette's as practically paralyzed by tics. Patients often talk of feeling like they are going to die.

There are not huge numbers of patients like this, Dr. Greenberg said. In any given year, for instance, about 1 percent of the U.S. population has OCD, and less than 40 of those patients get some

kind of brain surgery. But low numbers do not mean they should be ignored, he said.

The operation now being tested on these psychiatric patients was originally developed for people with movement disorders like Parkinson's disease. It is called deep-brain stimulation. Neurologists identified an area deep inside the brain that seemed to be misfiring in Parkinson's patients, and tried implanting electrodes in it rather than destroying it surgically, as had been done earlier. The device "is like a cardiac pacemaker," said Mahlon R. DeLong, a professor of neurology at Emory who first identified the problem regions. A thin wire (the electrode) is inserted through the skull and into that region, then connected to a controller and battery implanted under a patient's skin. The results can be "dramatic and transformative," he said at the AAAS meeting. About 70,000 patients now have these devices.

During the past five or so years, neurologists identified other circuits in the brain that seem to be misfiring in psychiatric disorders like depression. But applying brain-stimulation surgery to those problems should be handled very carefully, Dr. DeLong said. He learned with Parkinson's that "poor outcomes can happen," if the wrong patients are selected, or patients are not given the extensive postoperative support that is required. Some of those poor outcomes included brain hemorrhages, which can be deadly, and failure of the patient to improve.

Dr. Mayberg has identified part of the brain called "area 25," in a region associated with emotions called the cingulate, that appears to be misfiring in patients with treatment-resistant depression. They have not been helped by antidepressants, nor by electroconvulsive therapy. Or if they did benefit, the improvement was short-lived, followed by a relapse. Dr. Mayberg, along with colleagues at the University of Toronto, implanted devices in 20 patients. Fourteen remained in the trial and were still using the devices three to four years later, she said at the meeting. Of the six who were not, two had committed suicide, two had decided to have the devices removed, and the others had died of unrelated causes. The 14 who remained in the trial had experienced no relapse. One told her that before surgery "I was pretty convinced I was going to die. I had no friends. I couldn't work. I couldn't eat. I would go to bed for days. [Now] I am working again. I am planning things." They are still depressed, Dr. Mayberg noted, but it is not extreme, and they are able to get further help from regular therapy.

Other researchers told similar stories. Dr. Greenberg inserted brain stimulators into brain regions called the ventral capsule and ventral striatum in 26 intractable OCD patients. "Afterward, many

looked like patients who do improve on medication," he said. Their symptoms were reduced by 25 percent. Dr. Okun found similar success with a small group of Tourette's patients.

But all three scientists urged extreme caution. Dr. Mayberg noted that the research was actually hindered by the manufacturers of the devices, on whom she depends for the device supply. (She is listed as an inventor on a patent application by one electrode maker, St. Jude Medical Inc.) Because the companies are trying to develop a therapy, she said, they only provide devices for tests in one brain area—exploring takes more time and might give an edge to a competitor—while the scientists would like to compare different possible targets. "I don't blame companies, because they need to make money, " she said, "but university trials are best suited to do comparisons."

The electrodes are approved for use in these trials by the U.S. Food and Drug Administration under a "humanitarian device exemption," but several researchers say that rule carries its own burdens. Dr. Greenberg noted that it covered electrodes that were bigger than the ones scientists would like to use to refine brain targets. But if they didn't use the larger electrodes, they couldn't conduct experiments. He also noted that his trials were restricted in scope by private insurance. Patients need the insurance to pay for the continuing therapy after the operation, but insurance will not pay for tests that use devices not covered by the humanitarian exemption.

That exemption may actually be too loose for proper clinical trials with patient safety as a priority, said Joseph J. Fins, chief of the division of medical ethics at Weill Cornell Medical College, in New York City. "Just because a device works in one situation doesn't mean it is absolutely safe in another," he said. And because the exemption is currently the only way to get these devices, it also hampers the basic science, he said. The limited supply, and restrictions on use, prevents true scientific rigor in these trials. "The exemption may be therapeutic in the short term, but you might be compromising development of better therapies in the long term," he said.

Dr. Fins called for a new kind of federal regulation requiring companies to place devices used in early safety trials into a general pool available to all investigators. "This would allow negative results to surface, along with positive ones," he said, because no one would own the rights to such results. It would move the science along more quickly and allow trials with careful safeguards for patients.

Current trials do inform patients of the dangers and safety measures available, said Dr. Greenberg. "OCD patients go over the test protocols very carefully, again and again, and know exactly what their risks are." But he endorsed the idea of a device pool for basic scientific work. And Dr. Mayberg noted that much of the pressure to use devices in these trials came from patients. "My office got 1,500 phone calls about the 20 places in my small trial," she said.

Dr. Mayberg agreed that changes to produce better studies and better science would only help patients. "Maybe that will let us get closer to the core of depression," she said. "I personally hope that the science, and not the clinical trials, will let us replace ourselves," she said. "Not with more surgeries but with other therapies."

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Everything old is new again. So we now revisit "psychosurgery" and again approach lesion making in the brain to reorder behavior. Unfortunately, there is SO little known about the actual mechanistic scientific underpinnings of depression, affective disorders, and other psychiatric disorders that the field has advanced very little from the original hypothesis of Bunney and Schildkraut 50 years ago that norepinephrine and serotonin were involved in depression. Big pharma has been turning out the meds, including antidepressant and anti-anxiety meds, making up new syndromes to increase sales, and carefully avoiding the discouraging data that often show the meds have only marginal effects on behavior greater than placebos. And, of course, we know how wonderfully honest many of the psychiatric shills have been in revealing their COIs as they cash in on big pharma's "thought leader" payoffs. So these are the folks who now want to move forward with a new round of psychosurgery.

There is virtually no information about how brain plasticity and reorganization will effect behavior after such lesions, and no real scientific hypotheses that make sense. Virtually all such approaches end up with disastrous consequences that soon replace the initial optimism. Even a procedure as straightforward as brain cell transplantation for Parkinson's disease turned out to be disappointingly ineffectual, in part because the proponents did not do the appropriate CAREFUL preclinical work that was needed before proceeding with humans. But those careful preclinical studies do not fit into the scramble for nobel prizes.

The issue of informed consent is not a small one. These procedures are clearly research, and do not fall under any coverage by insurance, not should they. It is difficult to understand how a patient can make an objective informed consent decision regarding a procedure being endorsed and featured by the surgeon in question.

Before anyone gets too excited about this "new frontier" of psychosurgery, they need to go back and review the sorry history of prefrontal lobotomies and other procedures for severing longitudinal association pathways in the brain. And it also would be refreshing to see someone come up with better mechanistic understanding of the behavior disorders that now appear to be a grab bag of symptoms taken from the DSM bibles to justify throwing one drug after another at them to see if something sticks to the wall. Psychiatry needs to become part of the solution rather than part of the problem.

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