Well into the 1970s, we psychiatrists believed that depression came from anger turned inward—and we acted on this notion. Psychiatrists spent countless hours trying to get depressed patients to talk about their anger. Enterprising psychologists and psychiatrists devised schemes to make such patients angry. As a medical student, I watched from behind a one-way mirror as a hospitalized depressed man built a tower of small blocks. When he had almost completed the tower, the "therapist" knocked it down. Undeterred, the man persisted and, as I recall, he never got angry. He continued to start the tower and seemed unconcerned when the psychiatrist whacked it down. But the anger theory captivated us—it came straight from Freud's paper "Mourning and Melancholia"—and the total lack of evidence that any of these therapies actually worked seemed trivial, barely worth mentioning. So patients endured our attempts to get at their anger until, for one reason or another, their depressions lifted. Gradually, drugs took over, and by the end of the 1970s, depression was a biochemical disturbance in the brain. Now a new paradigm for depression is coming into view. Fueled by 2 decades of brain imaging findings and, more recently, by brain stimulation therapies, neural circuits seem about to displace serotonin and norepinephrine as the source of melancholia. The brain imaging results, plentiful as they are, are difficult to interpret. If depressed patients are shown to have small hippocampi or reduced prefrontal cortical blood flow, does this cause the depression or result from it? Few of the neuroanatomic findings have been consistently replicated or are specific to depressive illness. But if a depressed patient gets relief from stimulation of a part of the prefrontal or cingulate cortex, not only is it fair to implicate that structure—or something connected to it—in the pathophysiology of depression, but also we may have a new and better treatment. At least this is what we're hearing from the advocates of the new stimulation therapies: vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS).

ROOTED IN NEUROLOGY These stimulation techniques have more in common with the anger-turned-inward theory than it appears. First, both are firmly rooted in neurology: the anger-turned-inward theory was devised by a neurologist with a background in neuropathology and, likewise, the brain stimulation techniques were developed by neurologists and neurosurgeons. Second, as with the anger-turned-inward theory, more than a few psychiatrists are convinced that the stimulation procedures work—particularly VNS, to date the only stimulation technique that is FDA-approved for depression—despite the dearth of evidence in support of their effectiveness. VNS had an auspicious beginning. As Linda Carpenter, MD, associate professor of psychiatry at Brown Medical School and a VNS researcher, tells it, some patients with epilepsy who were participating in a clinical trial of VNS stayed at the same Gainesville, FL, hotel whenever they came into town for the study. A hotel clerk mentioned to one of the researchers, "I don't know what you're doing, but every time I see them, they get happier." This sort of serendipitous observation not uncommonly lies behind important treatment innovations: the discovery of the antidepressant properties of monoamine oxidase inhibitors (MAOIs), for example, arose from an observation not very different from the hotel clerk's; some patients being treated for tuberculosis with iproniazid, an MAOI, were noted to have elevated mood. But not all chance observations end in an effective treatment. Prompted by the hotel clerk's observation, 2 studies systematically addressed mood changes in epileptic patients treated with VNS. Mood rating scale scores did improve somewhat over a 12-week period.1,2 Then, an open clinical trial in treatment-resistant depressed patients showed that after 10 weeks of VNS, 30.5% improved.3 From then on, however, the evidence began to unravel. The only randomized controlled trial of VNS failed. This 12-week pivotal study compared VNS with sham VNS (stimulator not turned on) in patients with treatment-resistant depression (TRD), unresponsive to at least 2 treatment trials. VNS had no significant advantage over sham treatment.4 Then in a long-term follow-up study, patients with TRD received 1 year of VNS and were compared with a
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Clinically similar group of patients who had been evaluated for VNS but for a variety of reasons did not receive it. After 1 year, 27% of the VNS-treated patients met standard criteria for treatment response (50% improvement), whereas in the comparison group, 13% responded.5 The VNS-treated patients sustained their improvement during a second year of treatment.6 On the basis of the pivotal study, the FDA had decided not to approve VNS, but the agency changed its mind when presented with the longitudinal data. In July 2005, it approved VNS as a treatment for TRD. Ziad Nahas, MD, an associate professor of psychiatry at the Medical University of South Carolina and a VNS researcher, thinks the FDA did the right thing. He readily acknowledges that VNS is "not for every depressed patient," but he thinks it's a useful option for patients who continue to be depressed after trying several antidepressants. He points out that in the long-term study (in which he was an investigator), adding VNS to ongoing treatment doubled the chance that a patient would get better. Others, like Michael Thase, MD, a depression researcher from the University of Pittsburgh, find the same data unconvincing. The long-term study wasn't randomized, and the control group and only 27% of the VNS-treated patients improved after 2 years. As in all the VNS trials, patients were treated with antidepressant medication as well as VNS, which complicates the inferences that can be drawn about the reason for improvement. There was "simply not a good-enough basis in evidence" for FDA approval, Thase says. "The shaky state of the evidence means we have to be very cautious with this and prepare for the possibility that the hoped-for benefit isn't there."7 When used as a treatment for depression, VNS is applied in the same manner as it is when used as an adjunctive treatment for epilepsy. (VNS was approved for treatment-refractory, partial-onset seizures in 1997.) Under general anesthesia, a pulse generator is implanted in the left chest wall and a wire threaded into the neck and around the left vagus nerve. The stimulator-similar to a cardiac pacemaker-is programmed through an external handheld device. Stimulus parameters include pulse width, signal frequency, and signal on-and-off time. This procedure is safe, and the only common adverse effect is hoarseness. Clearly, VNS poses no more risk and causes fewer side effects than some of the antidepressant medications and electroconvulsive therapy (ECT) commonly used to treat patients for depression. Nonetheless, the idea of performing a surgical procedure under general anesthesia to heal an illness that is conventionally treated with medication or ECT, seems, to some, a bit over the top. But John Rush, MD, professor of psychiatry at the University of Texas Southwestern Medical School, is enthusiastic about VNS as a treatment option. He has been researching the use of VNS for the treatment of depression from the outset of VNS studies and has "no doubt" that the treatment works. He thinks it has value as long-term maintenance therapy for people who are chronically depressed and who quickly relapse after they improve with conventional antidepressant therapy. Rush has seen patients get better and stay better with VNS who, he is convinced, would not have done so without it. He is undaunted by the limited evidence in support of it. About the failed pivotal trial, he said, "If they had used my scale they would have seen a significant effect." The Inventory of Depressive Symptomatology Self Report, a depression rating scale developed by Rush, was a secondary outcome measure in that trial; unlike the primary outcome measure, it showed a small but statistically significant advantage for VNS. Despite the considerable media attention given to VNS as a new treatment for depression, and although Cyberonics, which makes the VNS device, is pushing it hard, one practicing psychiatrist is not about to latch on to VNS just yet. George Kolodner, MD, a psychiatrist in Silver Spring, MD, said, "It's an interesting thing, but I plan to watch it from a distance." MAGNETIC STIMULATION Unlike VNS, which evolved from a chance observation, rTMS is rooted in the known mood effects of brain stimulation and theories about the brain circuitry involved in depression. Transcranial magnetic stimulation (TMS) is based on the principle that you create a magnetic field when you pass electricity through a coil. In TMS, the magnetic field creates electrical impulses in neurons lying beneath the coil. Depending on the intensity of the magnetic field, those impulses can either stimulate or inhibit neuronal activity. For more than 2 decades, single-pulse magnetic stimulation has been used as both a research probe to examine the functions of discrete brain sites and as a diagnostic tool to assess neuronal function and isolate lesions. Given that direct brain stimulation can evoke elevated mood and discrete brain lesions can relieve depressive symptoms, researchers reasoned that a noninvasive procedure that stimulates discrete brain areas might be therapeutic. Accordingly, studies of rTMS as a treatment for depression have been under way since the early 1990s. At last count, 62 such studies have been published. Most are small and uncontrolled; some have compared rTMS to sham TMS. The sorts of patients treated, length of treatment, stimulus parameters, and location of the coil vary from study to study. Generally, patients are somewhat treatment-resistant and undergo 10 or fewer rTMS sessions, and the target is the left dorsolateral prefrontal cortex. Despite a considerable number of studies and the substantial number of patients treated-about 1000 (far more than have been treated with VNS)-the effectiveness of rTMS...
remains in doubt. Paul Holtzheimer, MD, assistant professor in the Department of Psychiatry at Emory University, began studying rTMS as a treatment for depression during his residency and has been at it for more than 5 years. He pointed out that 5 meta-analyses of rTMS have been conducted, and even the most stringent shows rTMS to have a statistically significant, albeit a small, antidepressant effect. In the meta-analysis conducted by Holtzheimer and colleagues, for example, 13.7% of patients with TRD treated with rTMS improved, compared with 7.9% treated with sham TMS.8 The question remains whether this effect, although statistically significant, is clinically meaningful. Holtzheimer said he is “confident that rTMS has an antidepressant effect,” but he acknowledges that the data so far are not overwhelmingly convincing. Nahas, who also has been involved in rTMS research for several years, conceded that if rTMS has an antidepressant effect, it is not a “robust” one. So far, the data on rTMS are not definitive one way or another. The intensity and frequency of stimulation used may not be ideal, and it’s devilishly difficult to devise a credible sham treatment. Patients undergoing rTMS experience a unique tingling sensation under the coil and often get a headache. It’s difficult to reproduce these sensations with a sham procedure, so most of the sham treatments to date have simply involved placing a coil on the scalp and assuming that the patient is not aware of the sensations that accompany rTMS. Two multicenter trials of rTMS, each involving several hundred patients, are now under way. One is sponsored by the National Institute of Mental Health and the other by Neuronetics, the company that makes the TMS device. The protocols stipulate, based on previous research, that stimulus parameters, duration of treatment, and coil placement are most likely to be effective. rTMS will be compared with a credible sham treatment—the coil placed at a 90-degree angle to the scalp. Nahas characterized these as make-or-break studies. In light of the ambiguities in the data so far, if the studies don’t show rTMS to have a clear advantage over the sham treatment, rTMS may end up in the well-populated dustbin of treatments that hold theoretic appeal but don’t actually work. A DBS SUCCESS STORY A limitation of rTMS is that only brain regions close to the scalp can be stimulated. However, brain imaging studies suggest, as do the “vegetative” symptoms of depression, that subcortical structures play a central role in the illness. Helen Mayberg, MD, a neurologist at Emory University School of Medicine, has been brain-imaging depressed patients for 20 years. She has consistently found a pattern of increased activity in a neuronal circuit that includes a central role for the subgenual cingulated region. Based on these observations, she began a study to determine the therapeutic effects of direct subgenual stimulation. Although the brain target differs, the direct subgenual stimulation technique applied by Mayberg and her surgical collaborators is similar to that developed for movement disorders. Electrodes are introduced through a scalp burr hole and under MRI visualization directed to the subgenual region. High-frequency stimulation inhibits neuronal activity. Patients selected for this procedure, both by Mayberg and the few other investigators studying direct subgenual stimulation, are severely and chronically ill and have not responded to any of the available treatment modalities including, in most instances, ECT. Mayberg and colleagues published the results from their first 6 patients in March 2005.9 The report garnered considerable media attention and interest from the medical community—and rightly so. Five of the 6 patients experienced substantial respite from their depressive symptoms, and 4 remained well after 6 months of treatment. Mayberg emphasizes that in the patients who responded, depressive symptoms lifted as soon as the stimulator was turned on. She pointed out that the depression relief had a distinctive quality. One patient reported having a greater sense of awareness of his surroundings, as if a veil had been lifted. Mayberg found it interesting that with subgenual stimulation, “we seem to be not adding something good but removing something bad.” Taking a different approach to DBS, Benjamin Greenberg, MD, and colleagues are among the handful of investigators who are targeting the anterior limb of the internal capsule, a region that contains the nucleus accumbens. This area is part of the pleasure and reward circuit and may well be linked to the anhedonia characteristic of depressive illness. Greenberg, an associate professor of psychiatry at Brown Medical School, chose the anterior limb of the internal capsule as the target for DBS because, in his work with patients suffering from severe obsessive-compulsive disorder and depression, he found that stimulation of that region relieved depression as well as obsessive-compulsive symptoms. He has carried out DBS in 8 severely depressed patients thus far and said that although it’s still “early days,” the results are promising.10 Several of Greenberg's patients have become transiently hypomanic, which suggests both that this brain area does have a substantial impact on mood and that hypomania may be an adverse effect. None of the investigators involved in DBS envision it as anything other than a last resort for severely ill, treatment-refractory patients. So far, fewer than 20 depressed patients worldwide have undergone DBS. Although Mayberg and others have found that positive effects on mood are reversed when they turn off the stimulator, these procedures have not yet been formally tested.
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