Noninvasive Brain Stimulation for Depression — The Devil Is in the Dosing

Sarah H. Lisanby, M.D.

In this issue of the *Journal*, Brunoni and colleagues report on transcranial direct-current stimulation (tDCS) in the treatment of major depression.[1] This technique, which delivers weak electrical direct current to the scalp to modulate brain function, is one of a growing number of noninvasive brain stimulation interventions that change brain function and offer an opportunity to study brain–behavior relationships in health and disease. These tools have the potential to translate knowledge of the neural circuitry of the brain and patterns of electrical activity within those circuits (known as neural oscillatory dynamics) into treatments for psychiatric and neurologic disorders. Other related technologies that alter electrical brain activity include transcranial magnetic stimulation, transcranial alternating-current stimulation, electroconvulsive therapy, deep-brain stimulation, and focused ultrasound. Of these, only transcranial magnetic stimulation and electroconvulsive therapy are currently cleared by the Food and Drug Administration for the treatment of depression, and deep-brain stimulation has a humanitarian device exemption for the treatment of obsessive–compulsive disorder.

In contrast to the invasive nature of deep-brain stimulation, the noninvasive nature of transcranial magnetic stimulation, transcranial alternating-current stimulation, electroconvulsive therapy, and focused ultrasound makes them appealing for studying healthy volunteers with the goal of illuminating basic brain functions and testing hypotheses regarding the neural basis of psychiatric disorders. Unlike functional imaging that passively measures brain function, noninvasive brain stimulation actively changes neural function and can establish likely causal relationships between electrical patterns and mental dysfunction. Understanding these patterns is essential to the design and implementation of noninvasive electrical therapies.

The antidepressant efficacy of tDCS has been an active area of study, and a recent meta-analysis has provided support for this use.[2] A previous trial conducted by Brunoni and colleagues showed that tDCS had similar efficacy to sertraline in the treatment of depression, but that trial was not powered to test whether tDCS was noninferior to the medication.[3] The present trial provides such data.

As in the previous trial, the present trial used a double-dummy design, in which patients received the antidepressant escitalopram or placebo and tDCS or sham tDCS in order to mask the group assignment. The tDCS group and the escitalopram group both had efficacy that was greater than that observed in the group that received sham tDCS and placebo. However, a test of the noninferiority of tDCS to escitalopram failed, so the investigators could not draw a firm conclusion that tDCS was as effective as the medication. The trial has a number of limitations; most importantly, the patients in the medication group became aware of their assigned therapy presumably as a result of the side effects of the medication, which may have inflated efficacy and invalidated the noninferiority comparison. Patients in the tDCS group were unaware of the treatment they received; thus, the reported rates of response (41% in the tDCS group vs. 22% in the placebo group) and remission (24% vs. 13%) in depression can be taken as estimates of the antidepressant efficacy of tDCS. Furthermore, the use in this trial of transcranial magnetic stimulation as a probe of inhibitory tone in the brain points to this tone as an interesting potential predictor of response to tDCS (details are provided in the Supplementary Appendix of the article by Brunoni et al., available at NEJM.org).

Another limitation, one shared by most other trials of noninvasive brain stimulation, is the lack of a measure of target engagement. The experimental-therapeutics approach that has been adopted by the National Institute of Mental Health is meant to ensure that when clinical trials fail to meet efficacy end points, they are at least informative regarding the reasons for failure. For example, treatment with noninvasive brain stimulation may be ineffective because the interven-

tion did not deliver sufficient electrical current to the targeted brain region or because it did not result in the expected effect on the functioning of the targeted circuit (i.e., target engagement).

We cannot know whether the tDCS dose that was used in this trial successfully engaged the intended cerebral target circuits, but future work could provide such a test. As with all forms of noninvasive brain stimulation, the most effective tDCS dosing is not known,[4] and more is not always better.[5] Software now permits the visualization of the strength and the spatial distribution of the electrical current that is injected into the brain from each tDCS electrode configuration. This information could permit the personalization of the tDCS dose and electrode configuration to specific cortical regions that are implicated in a patient's disorder. Furthermore, functional imaging can be used to determine whether the delivered dose was sufficient to change the targeted neural circuitry. It is also possible that noninvasive brain stimulation has a synergistic effect with medications on depression.[3,6] There may also be factors that influence efficacy that were not measured in this trial; for example, polymorphisms in *BDNF* (encoding brain-derived neurotrophic factor) have been reported to influence the physiologic effects of tDCS.[7]

Although uncertainty remains regarding the antidepressant efficacy of tDCS, this trial shows key knowledge gaps in the dose–response relationship and physiologic mechanisms for tDCS and other forms of noninvasive brain stimulation that need to be addressed in order for an effective therapy to be developed. Ultimately, the more we know about the ways in which noninvasive brain stimulation influences brain activity at a mechanistic level, the closer we come to determining the clinical usefulness of these new therapies.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the National Institute of Mental Health, Bethesda, MD.

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