The Current Status of Transcranial Direct Current Stimulation as a Treatment for Depression

May 07, 2014
By William K. Silverstein, BMSc [1], Zafiris J. Daskalakis, MD, PhD [2], and Daniel M. Blumberger, MD, MSc [3]

Evidence has accumulated on the efficacy of transcranial direct current stimulation in major depression. The authors review its potential mechanism of action, findings from recent clinical trials, and potential role in the treatment of depressive disorders.

Major depressive disorder is a leading cause of disability worldwide, affecting an estimated 120 million people; the lifelong prevalence is 10% to 15%.1,2 Depression leads to severe morbidity and is the leading cause of suicide. An emerging problem in the treatment of depression is the development of treatment resistance. Treatment-resistant depression (TRD) occurs in 15% to 35% of depressed patients.3 In addition, TRD is associated with serious economic burden: the cost of treating TRD is 6 times higher than that of treating nonresistant depression.4

In response to the emergence of TRD, novel therapies have been developed as alternatives to pharmacotherapy and psychotherapy. These include brain stimulation therapies. Currently, ECT is the most effective: 50% to 70% of patients respond to treatment. ECT is a first-line therapy for severe or psychotic depression. Despite its efficacy, however, many patients avoid ECT because of the negative public perception associated with it and the potential cognitive adverse effects. In recent years, evidence has accumulated on the efficacy of transcranial direct current stimulation (tDCS). This article describes the history of its use for treating major depression and its potential antidepressant mechanism of action. In addition, we review findings from recent clinical trials and discuss the potential role of tDCS in the treatment of depressive disorders.

Antecedents and mechanisms

tDCS is a minimally invasive form of brain stimulation that does not induce seizures. During tDCS, a weak, direct electrical current (1 to 2 mA) is applied using 2 scalp surface electrodes that are covered by sponges and soaked in saline. Findings from preclinical studies suggest that tDCS may cause polarity-dependent alterations in cortical excitability and activity. Anodal stimulation increases cortical excitability and cathodal stimulation decreases cortical excitability.5 The changes in cortical excitability are probably through respective depolarization and hyper-polarization of neurons. It appears that this effect can be attributed to a subthreshold modulation of resting membrane potential, and it can persist even after stimulation stops.5,6

As a result of its ability to alter cortical activity, scientists began investigating the utility of tDCS as a treatment for depression in the 1960s. The results from these studies were mixed, and methodological variability between studies confounded the findings; as a result, interest in tDCS waned after the 1960s. However, beginning in the 1990s, research into the use of brain stimulation therapies for depression grew exponentially. Renewed interest in tDCS as a treatment for depression has led to multiple studies that examined optimal treatment protocols and efficacy of tDCS. In addition to its potential clinical utility and minimal adverse-effect profile, tDCS appears to improve cognitive performance.

MDD is a complicated disorder: its pathophysiology and etiology are not completely understood. However, one hypothesis asserts that in depression, there is a pathological abnormality and imbalance in the activity of the left and right prefrontal cortices: the left dorsolateral prefrontal cortex is hypoactive and the right dorsolateral prefrontal cortex is overactive.7-9 tDCS may produce electrode-dependent changes in regional brain activity by ameliorating the pathological imbalance between the two hemispheres of the dorsolateral prefrontal cortex by enhancing the excitability of the left and reducing the activity of the right.

By applying anodal tDCS to the left hemisphere to augment activity and cathodal tDCS to the right hemisphere to reduce activity, the pathological imbalance of activity in the brain may be restored to resolve the depression. While the protocol of stimulating both the left and right dorsolateral...
prefrontal cortices has been used in some studies, in others, anodal tDCS was applied to the left dorsolateral prefrontal cortex and cathodal tDCS was applied to a neutral region, such as the right supraorbital region, the contralateral orbit, or the contralateral cortical area. One of the hypothesized rationales for use of these protocols is to restore the physiological intrahemispheric and interhemispheric balance.

Recent clinical trials
Several open-label studies and randomized controlled trials have been conducted to examine the efficacy of tDCS in treating depression. Most of these studies demonstrate that active tDCS is effective in reducing depressive symptoms. The efficacy of tDCS alone was shown to be similar to that of a relatively low average dosage (50 mg/d) of sertraline. In this factorial study, the combination of sertraline and tDCS led to an additive response that was superior to sham tDCS and placebo, to tDCS alone, and to sertraline alone. This suggests that combining tDCS with other antidepressant treatments may be a method of enhancing outcomes and that the efficacy of tDCS may be comparable to that of first-line antidepressants, which may reduce the burden of TRD. Findings also indicate that tDCS is effective in patients with mild to moderate depression that is not treatment-resistant. The adverse effects associated with tDCS appear to be mostly limited to headaches and itchiness and redness at the site of stimulation, which are significantly less severe than the cognitive effects associated with other brain stimulation treatments, such as ECT. In addition to its potential clinical utility and minimal adverse-effect profile, tDCS appears to improve cognitive performance.

There is much discussion as to what the optimal time and stimulation frequency for tDCS treatment should be. Earlier studies used lower-amplitude stimulation (1 mA), but larger amplitudes (2 mA) are now being used. Higher stimulation amplitudes elicit a larger cognitive effect than do lower amplitudes. The effects of tDCS were also shown to be cumulative, which led to an increase in the number of treatments in various protocols. Earlier studies used once-daily tDCS for 5 alternate days; more recent studies used tDCS twice daily for 5 consecutive days or once daily for 10 consecutive weekdays. The next generation of studies administered treatments for up to 20 consecutive days. Still more recent studies have extended the treatment course to 6 weeks or 30 treatments. The extended duration of treatment led to enhanced efficacy, with remission of symptoms for at least 1 month. While replication is needed on the duration and number of treatments, it appears that enhanced treatment outcomes are associated with more intense stimulation and an increased number of treatment sessions. Although the aforementioned trials have shown positive results, other findings suggest that multiple treatment failures, use of higher doses of benzodiazepines, and a failed course of ECT herald a worse response to tDCS. No differences were seen in comparison studies of tDCS and sham stimulation. The lack of multicenter, randomized, controlled data limits the ability to advocate the treatment to the broad population of patients with depression. In addition, there are no studies that compare tDCS with other brain stimulation treatments (eg, repetitive transcranial magnetic stimulation and ECT).

The heterogeneity of patients in the various trials of tDCS makes it difficult to come to a definitive conclusion on the value of tDCS as a treatment for depression. Because the sample size was relatively small in many of the studies, the results of these trials need to be treated with caution. In addition to the small sample sizes used, few trials have looked at whether the antidepressant effects persist after the acute phase of treatment. Thus, it is not known if the antidepressant effects exerted by tDCS are lasting or if maintenance treatments are necessary.

There is still a lack of consensus on the placement of electrodes that leads to optimal treatment outcomes, although there have been reductions in depressive symptoms with anodal stimulation of the left dorsolateral prefrontal cortex and cathodal stimulation of the right dorsolateral prefrontal cortex, or anodal stimulation of the left dorsolateral prefrontal cortex with a neutral region. Although study results overall have been promising, additional research is needed before tDCS can be adopted in the broader clinical context. Research should focus on establishing the optimal stimulation parameters for tDCS. Adequately powered, randomized, controlled trials with longer follow-up times are needed to establish the long-term antidepressant effects of tDCS. Studies that examine biomarkers of treatment response to tDCS are necessary to gauge which patients will respond to treatment.

Conclusion

tDCS is an appealing treatment for depression because of its relative safety and efficacy profiles coupled with the fact that it is relatively inexpensive. This has spurred interest in the do-it-yourself (DIY) community, leading to the proliferation of DIY tDCS devices being sold on the Internet. Many of
the Web sites offer either inexpensive tDCS devices or instructions on how to assemble a device using a 9V battery and $50 worth of basic electronic parts. The proliferation of these DIY devices is worrisome because unsupervised tDCS use can impair cognitive function, interfere with concomitant treatments, and result in long-lasting unintended and undesirable effects. Scientists, treatment providers, and regulators need to collaborate on drafting policy that ensures the safety of tDCS for users while simultaneously not discouraging use of DIY or relatively inexpensive devices. tDCS appears to have tangible antidepressant effects. It is a promising therapy because of its minimally invasive nature and relatively benign adverse-effect profile. That said, its use appears to be limited to patients with mild to moderate depression; it is not for patients with higher degrees of treatment resistance. It could also be effectively used as an add-on therapy to pharmacotherapy and psychotherapy to optimize treatment outcomes. Further research is needed to examine the utility of tDCS as a front-line treatment for more severe forms of depression. Currently, we would not recommend using tDCS as a first-line brain stimulation therapy for severe and treatment-resistant forms of depression. However, for now, it seems reasonable to consider tDCS as a treatment for patients with mild to moderate depression without treatment resistance, or to use it to enhance the first-line response rates when combined with pharmacotherapy or psychotherapy. This article was originally posted online on 2/27/2014.

More on This Topic
Deep Brain Stimulation for Depression and Alzheimer Disease: An Emerging Therapy
November 11, 2013
by Nir Lipsman, MD and Andres M. Lozano, MD, PhD
Demographic shifts and rising life expectancies will lead to an epidemic of chronic neuropsychiatric disease, and societal and public health costs will be enormous. Deep brain stimulation—a procedure that interfaces directly with the neural elements that drive pathological behavior—could be useful. http://www.psychiatrictimes.com/neuropsychiatry/deep-brain-stimulation-depression-and-alzheimer-disease-emerging-therapy

Neurostimulation Treatments in Psychiatry: An Overview and Recent Advances
October 9, 2013
by Charles R. Conway, MD, Pilar Cristancho, MD, and Thomas E. Schlaepfer, MD
Several brain structures play a role in the development and maintenance of depression. Repetitive transcranial magnetic stimulation studies are targeting the anterior cingulate cortex, the anterior limb of the capsula interna, the nucleus accumbens, and the medial forebrain bundle. http://www.psychiatrictimes.com/neuropsychiatry/neurostimulation-treatments-psychiatry-overview-and-recent-advances/

Disclosures:
Mr Silverstein is a medical student in the Faculty of Medicine, University of Toronto, Toronto, and summer research student at the Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health (CAMH), Toronto. Dr Daskalakis is the Chair of the Temerty Centre for Therapeutic Brain Intervention and a clinician scientist at the Campbell Family Mental Health Research Institute, CAMH; he is Professor in the department of psychiatry, University of Toronto. Dr Blumberger is Medical Head at the Temerty Centre for Therapeutic Brain Intervention and clinician scientist at the Campbell Family Mental Health Research Institute, CAMH; he is Assistant Professor in the department of psychiatry, University of Toronto.

Mr Silverstein has no financial disclosures. In the past 5 years, Dr Daskalakis has received research and equipment in-kind support for an investigator-initiated study from Brainsway Ltd and a travel allowance through Merck; he has also received speaker funding through Sepracor Inc and AstraZeneca, and served on the advisory board for Hoffmann-La Roche Ltd. This work was supported by the Ontario Mental Health Foundation, the Canadian Institutes of Health Research (CIHR), the Brain and Behaviour Research Foundation, and the Temerty Family and Grant Family and through the CAMH Foundation and the Campbell Institute. Dr Blumberger receives research support from CIHR, the Brain and Behaviour Research Foundation (formerly NARSAD), and the Temerty Family and through the CAMH Foundation and the Campbell Research Institute, and equipment in-kind support for an investigator-initiated study from MagVenture/Tonika and research and equipment in-kind
support for an investigator-initiated study from Brainsway Ltd.

References:


Links:
[1] [http://www.physicianspractice.com/authors/william-k-silverstein-bmsc](http://www.physicianspractice.com/authors/william-k-silverstein-bmsc)
[2] [http://www.physicianspractice.com/authors/zafiris-j-daskalakis-md-phd](http://www.physicianspractice.com/authors/zafiris-j-daskalakis-md-phd)
[3] [http://www.physicianspractice.com/authors/daniel-m-blumberger-md-msc](http://www.physicianspractice.com/authors/daniel-m-blumberger-md-msc)