

Neuromodulation for treatment-resistant depression

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Abstract

Treatment-resistant depression affects at least 1-3% of the US population. This article reviews the current state of focal neuromodulation therapies for treatment-resistant depression, focusing on those treatments with published clinical data. These include transcranial magnetic stimulation, transcranial direct current stimulation, magnetic seizure therapy, vagus nerve stimulation, direct cortical stimulation, and deep brain stimulation among others. Of these, only two (transcranial magnetic stimulation and vagus nerve stimulation) currently have US Food and Drug Administration approval for the treatment of depression.

Introduction

Major depression is one of the most prevalent and costly medical conditions worldwide [1,2]. Antidepressant medications and psychotherapy, the most common first-line therapies for depression, are effective for many patients, though a sizable minority (10-40%) remain significantly treatment resistant [3,4]. Treatment-resistant depression therefore affects at least 1-3% of the US population.

Historically, electroconvulsive therapy and ablative neurosurgery have been the treatments available for patients with varying degrees of severe, treatment-resistant depression. Ablative neurosurgery (including, anterior capsulotomy, dorsal cingulotomy, and subcaudate tractotomy) evolved from early anatomical theories of mood regulation and has been consistently used for the most severely ill and treatment-resistant depressed patients. Although efficacy has been suggested, side effects are common, thus limiting use [5-8]. Electroconvulsive therapy, first introduced in 1938, also predates medications as a treatment for depression [9] and remains the most effective antidepressant treatment available, with acute remission rates around 60%, even in treatment-resistant patients [10,11]. Electroconvulsive therapy is administered by delivering electricity directly to the brain via scalp electrodes to induce a generalized seizure. A series of

seizures (typically 9-12) are given over several weeks. Cognitive side effects, including post-ictal confusion, anterograde amnesia (difficulty encoding new memories during the course of electroconvulsive therapy) and retrograde amnesia (loss of memory for events that occurred prior to electroconvulsive therapy) can occur and are typically transient and well-tolerated. Changes in electroconvulsive therapy methods, such as the use of right unilateral electrode placement and the introduction of ultrabrief pulse stimulation, have attempted to minimize cognitive side effects without sacrificing efficacy. However, cognitive side effects, stigma and practical concerns (e.g. needing to take time off work) continue to limit the utility of electroconvulsive therapy. Further attempts to optimize electroconvulsive therapy or electroconvulsive therapy-like treatments include magnetic seizure therapy (discussed below) and focal electrically-administered seizure therapy ([12] FEAST), which is now in clinical trials (clinicaltrials.gov identifier NCT01589315).

Focal neuromodulation offers a potential alternative, non-pharmacologic approach for treatment-resistant depression. Broadly defined, neuromodulation involves directly altering the function of a specific neural structure with the intent of modulating activity throughout a neural network of brain regions implicated in depression. Current neuromodulation therapies have largely emerged

from electroconvulsive therapy and ablative neurosurgery, coupled with neuroimaging data from studies of depression and antidepressant treatment response. Together, electroconvulsive therapy and ablative neurosurgery represent early attempts at “neuromodulation”. Although medications and psychotherapy likely alter the function of the neural networks involved in depression, the targets of these treatments are not specific neural structures. Alternatively, developing neuromodulation strategies aim to primarily affect activity of a specific brain region with the expectation of unique, secondary alterations of function throughout the “depression network”.

This article will review the current state of focal neuromodulation treatments for depression, with the scope limited to those treatments with published clinical data. Specific treatments to be reviewed include transcranial magnetic stimulation, transcranial direct current stimulation, magnetic seizure therapy, vagus nerve stimulation, direct cortical stimulation, and deep brain stimulation among others. Of these, only two (transcranial magnetic stimulation and vagus nerve stimulation) have US Food and Drug Administration (FDA) approval for the treatment of depression.

The rationale for neuromodulation for depression is based on a neural network theory that posits a specific set of structurally and functionally connected brain regions that work together to maintain normal mood regulation [13,14]. Depression is hypothesized to arise from dysfunctional communication between nodes within this network. For all of the techniques discussed below, the general mechanism of action is presumed to be modulation of the “depression” network, often through “downstream” effects on brain regions remote from the actual target of stimulation. However, which nodes and/or connections must be affected for an adequate antidepressant effect may differ between methods, resulting in different initial targets of stimulation. Additionally, different targets for neuromodulation may be chosen in an effort to improve the safety of the intervention while maintaining antidepressant benefit (e.g. developing focal magnetic seizure therapy as an alternative to electroconvulsive therapy).

Transcranial magnetic stimulation

Transcranial magnetic stimulation uses a rapidly alternating magnetic field to induce an electric current in underlying cortex, depolarizing cortical neurons [15]. Transcranial magnetic stimulation is non-invasive and requires no anesthesia. Each treatment involves delivery of multiple stimuli in a series of trains over about an hour. Treatments are typically given daily, five times per week, for three to six weeks (most of the treatment trials described below used 10-20 treatments). Transcranial magnetic

stimulation is generally very well-tolerated, though scalp pain and headaches may be associated with stimulation, and seizure is a rare potential adverse effect. [16-18]. Transcranial magnetic stimulation is FDA-approved for the treatment of depression that has not responded to one antidepressant medication.

Transcranial magnetic stimulation has been studied as a treatment for depression for nearly 20 years, and a number of meta-analyses and two large sham-controlled trials have confirmed that transcranial magnetic stimulation is associated with statistically significant antidepressant effects [16,17,19-24]. Although stimulation parameters have differed across studies, the most common settings include 5-20 Hz (high frequency) transcranial magnetic stimulation applied to the left dorsolateral prefrontal cortex at 80%-120% motor threshold (intensity needed to cause movement in a muscle group in half of 10 or more trials). Treatment courses have generally included 10 to 30 sessions (over 2-6 weeks). A few studies have used low-frequency (≤ 1 Hz) transcranial magnetic stimulation delivered over the right dorsolateral prefrontal cortex with evidence of efficacy [25]. Targeting the dorsolateral prefrontal cortex was based on this region consistently showing abnormal activity in depressed patients versus controls [26,27] as well as empirical data [28]. Additional studies have demonstrated that dorsolateral prefrontal cortex transcranial magnetic stimulation can alter activity in more distant brain regions implicated in the “depression” network (e.g. [29,30]).

Response and remission rates with transcranial magnetic stimulation for treatment-resistant depression, while statistically significant, have often been relatively low in sham-controlled studies (20-40% and 10-20% respectively). However, these are not dissimilar from response/remission rates seen for other antidepressant treatments in patients failing at least one prior treatment [3]. Transcranial magnetic stimulation is probably not more effective than optimally dosed electroconvulsive therapy [31-40], and likely has a role for the treatment of depression that is somewhat, but not extremely, treatment resistant.

Transcranial magnetic stimulation may also be appropriate for patients who do not tolerate or cannot take adequate doses of standard antidepressant medications (opening up the possibility for benefit in specific populations such as pregnant women [41-45], children [46-51] and the medically ill and/or elderly [52-57]).

Relapse rate following successful transcranial magnetic stimulation is not clear. To date, studies addressing this have had the following: inconsistent definitions of relapse vs. symptom worsening; different samples

(e.g. responders vs. remitters); small sample size; and high loss to follow-up. That said, data to date are somewhat encouraging, and suggest relapse following transcranial magnetic stimulation may not be different from other acute treatments, such as electroconvulsive therapy. In one head-to-head study, the six-month relapse rates following electroconvulsive therapy vs. transcranial magnetic stimulation were identical (20%) [58]. In another study, the six-month maintenance of response following an acute course was 44% [59] – not dissimilar from that seen following electroconvulsive therapy [11]. In one large, multi-center trial, 58% of remitters to an acute course of transcranial magnetic stimulation maintained remission after an additional three months following the acute course [60]. In another large trial, 48% of patients either relapsed or had significant symptom worsening within the six months following successful transcranial magnetic stimulation [61]; of those patients with worsening symptoms, 84% achieved benefit from another course of transcranial magnetic stimulation. Repeated transcranial magnetic stimulation courses may help maintain initial benefit [62], suggesting that maintenance transcranial magnetic stimulation may have a role in the management of patients with depression similar to maintenance electroconvulsive therapy.

Attempts to optimize transcranial magnetic stimulation as a treatment for depression are underway and include combining high- with low-frequency treatments [63-68], developing “deep” transcranial magnetic stimulation systems that can stimulate structures below superficial cortex [69-73] and developing novel dosing strategies typically aimed at increasing the overall dose or shortening the treatment time for a given dose [74-78].

Transcranial direct current stimulation

Transcranial direct current stimulation delivers a low intensity direct current to the cortex via scalp electrodes. Unlike transcranial magnetic stimulation, transcranial direct current stimulation does not depolarize cortical neurons but may affect their excitability [79]. However, like transcranial magnetic stimulation, the mechanism of action is presumed to involve modulation of function of the regions stimulated with the potential for “downstream” effects throughout the depression neural network. Stimulation is non-invasive, requires no anesthesia and is very well-tolerated [80,81]. Treatments are provided about five times per week over several weeks (similar to transcranial magnetic stimulation). As an alternative to transcranial magnetic stimulation, transcranial direct current stimulation may have fewer acute side effects, though it is based on the same rationale of directly altering dorsolateral prefrontal cortex function. Based on a small number of open- and sham-controlled studies, transcranial direct current

stimulation may have antidepressant effects in depressed patients [79,82-87]. Response and remission rates have not been consistently reported in the literature (and in one study did not differ between the active and sham group despite a statistically significant difference in change in depression severity [85]). Relapse rate following successful treatment has not been reported. A multi-site study of transcranial direct current stimulation compared to sertraline is ongoing [88], but, to date, transcranial direct current stimulation has not been compared to other brain stimulation therapies, such as transcranial magnetic stimulation.

Transcranial low voltage pulsed electromagnetic fields

Transcranial low voltage pulsed electromagnetic fields stimulation involves applying low intensity electromagnetic fields to the brain via a series of scalp coils. Targeted pulsed electromagnetic fields are non-invasive and require no anesthesia. Unlike transcranial direct current stimulation, targeted pulsed electromagnetic uses electromagnetic fields rather than direct electrical current to stimulate cortical neurons. Unlike transcranial magnetic stimulation, the electromagnetic fields are relatively static and not strong enough to actually depolarize cortical neurons. A 5-week sham-controlled study (N = 50) reported statistically significant antidepressant effects for targeted pulsed electromagnetic [89], and it appears to be relatively safe and well-tolerated. It has not been compared to other brain stimulation therapies, and the potential mechanism of action is unknown.

Magnetic seizure therapy

Magnetic seizure therapy involves inducing a series of generalized seizures (similar to electroconvulsive therapy) using a transcranial magnetic stimulation device focused on the prefrontal cortex. To date, magnetic seizure therapy has shown open-label antidepressant efficacy (i.e. there are no data with patients blinded to treatment), though its relative efficacy/safety (including cognitive safety) compared to electroconvulsive therapy is not clear. Some studies have shown equivalent efficacy while others show that electroconvulsive therapy is superior; cognitive safety has either been equivalent or slightly better than electroconvulsive therapy [90-94]. There are currently no sham-controlled studies of magnetic seizure therapy for treatment-resistant depression. As with electroconvulsive therapy, the potential mechanism of action of magnetic seizure therapy is unknown.

Vagus nerve stimulation

Vagus nerve stimulation involves surgically attaching an electrode to a vagus nerve (typically the left) with electrical stimulation controlled by an implanted pulse

generator. Vagus nerve stimulation was approved by the FDA for medication-refractory epilepsy in 1997 and for medication-refractory depression in 2005; however, in the US, the Center for Medicare and Medicaid Services, and most other insurers, do not cover the costs of vagus nerve stimulation for treatment-resistant depression. The rationale for vagus nerve stimulation as a treatment for depression was initially based on mood-elevating effects in implanted epilepsy patients without depression [95,96]. Additional justification was provided by several human and animal studies highlighting the ability of vagus nerve stimulation to alter activity in brain regions and neurotransmitter systems implicated in depression [97].

Open-label studies have shown a 30-40% antidepressant response rate (defined as a >50% decrease depression severity) and a 15-17% remission rate after 3-24 months of vagus nerve stimulation in treatment-resistant depression patients [98-103]. A large, sham-controlled study of vagus nerve stimulation for treatment-resistant depression showed no statistically significant benefit for 10 weeks of active vagus nerve stimulation [104], though open-label response/remission rates went up with more chronic, open-label treatment [100] and were higher than those seen with treatment-as-usual (without vagus nerve stimulation) in a non-randomized comparison group [105]. Sustained response over 12-24 months may occur in 44-77% of patients [106,107].

Vagus nerve stimulation surgery is relatively minor with few significant risks. Chronic stimulation also appears to be safe and well-tolerated. Potential stimulation-related side effects are only present during active stimulation and typically include mild voice changes, hoarseness, coughing and dysphagia. Chronic vagus nerve stimulation has generally not been associated with negative neuropsychological effects [108], though modest cognitive impairments may occur with higher stimulation parameters [109].

Direct cortical stimulation

With direct cortical stimulation, electrodes are surgically implanted directly onto the surface of the brain (usually epidurally) and stimulation is controlled through an implanted pulse generator. The rationale for direct cortical stimulation is similar to that for transcranial magnetic stimulation and transcranial direct current stimulation with the potentially added value that stimulation can potentially be given chronically, more focally and at higher intensities. Two small pilot studies have suggested potential benefit from direct cortical stimulation applied to the dorsolateral and/or medial prefrontal cortices in treatment-resistant depression patients, though relapse

rates have not been reported [110,111]. Prefrontal direct cortical stimulation appears to be well-tolerated, though there are risks of bleeding and infection associated with surgery.

Deep brain stimulation

Deep brain stimulation involves implanting one or more electrodes into specific brain regions using stereotactic neurosurgical techniques; stimulation is controlled through an implantable pulse generator. Deep brain stimulation is an established treatment for many patients with medication-refractory movement disorders. Deep brain stimulation of the ventral anterior internal capsule and ventral striatum is FDA approved for patients with treatment-refractory obsessive-compulsive disorder under an FDA Humanitarian Device Exception (HDE); this was based on available open-label data since a definitive sham-controlled trial was not performed [112]. The main risks of deep brain stimulation are associated with the implantation surgery (bleeding, infection, complications from anesthesia). Effects of acute and chronic stimulation largely depend on the brain site of stimulation.

A number of small, mostly open-label studies have examined the safety and efficacy of deep brain stimulation of various brain regions for treatment-resistant depression. The largest dataset exists for subcallosal cingulate white matter deep brain stimulation with targeting based on a converging database implicating this region and its connections in the neurobiology of the antidepressant response [113]. Remission rates with six months to several years of subcallosal cingulate stimulation are approximately 40-60% [114-120]. For patients who remit, relapse has been uncommon. To date, there appear to be no adverse effects of acute or chronic subcallosal cingulate deep brain stimulation, including no neurocognitive impairments [118,121], and an industry-sponsored pivotal trial of subcallosal cingulate deep brain stimulation for depression is currently underway. Subcallosal cingulate deep brain stimulation may operate through modulation of a mood regulation network such that patients are able to regulate mood appropriately and not remain "stuck" in the depressed state [4].

Small trials have shown similar efficacy for deep brain stimulation of the ventral anterior internal capsule and ventral striatum and nucleus accumbens for treatment-resistant depression [122-124]. The rationale for the first target came primarily from observations of antidepressant effects of ventral anterior internal capsule and ventral striatum deep brain stimulation in patients with obsessive compulsive disorder and comorbid depression [122]. The latter target was similarly justified with additional rationale provided by the prominence of anhedonia

(the inability to feel pleasure) as a symptom of depression and the role of the nucleus accumbens in reward processing [125]. With both of these targets, acute stimulation was associated with a number of side effects including hypomania (a mild degree of mania), anxiety, perseverative speech (the persistent repetition of a word or phrase), autonomic symptoms and involuntary facial movements. These effects were reversible with changes in stimulation parameters, and there were no adverse effects of chronic deep brain stimulation, including no neuropsychological impairments. An industry-sponsored pivotal trial of ventral anterior internal capsule and ventral striatum deep brain stimulation for depression is currently underway.

Case reports have described potential antidepressant efficacy for deep brain stimulation of the inferior thalamic peduncle [126] and the habenula [127]. The inferior thalamic peduncle target was chosen based on its role in conveying thalamo-cortical information (an early rationale for ablative neurosurgical procedures). The habenula target was chosen based on its role in monoaminergic neurotransmission.

Summary

Electroconvulsive therapy and ablative neurosurgery are among the oldest neuromodulation techniques and are still the considered reasonable treatments for severe and treatment-resistant depression. Over the past two decades, neuromodulation, primarily in the form of focal brain stimulation, has re-emerged as a potential treatment option for depression. Transcranial magnetic stimulation, transcranial direct current stimulation, transcranial low voltage pulsed electromagnetic fields and magnetic seizure therapy are non-invasive and well-tolerated and may have a role in treating patients with a limited degree of treatment resistance (and perhaps as an alternative to medications or psychotherapy in certain patient populations). Vagus nerve stimulation, direct cortical stimulation and deep brain stimulation are more invasive with greater associated risks and will therefore likely play a role in treating more severely ill and treatment-resistant patients, presuming safety and efficacy are established in larger trials.

As the neurobiology of depression is still largely unknown, it is difficult to presume how various treatments for depression might work. The general rationale for neuromodulation in depression is that focal intervention in the neural network involved in mood regulation may have therapeutic effects by regulating the function of this network. With all of the above treatments, it is presumed that, if effective, modulation of network function occurs in a beneficial way. It remains an open question which nodes or pathways in the network must be affected for

beneficial effect or whether different depressed patients may need different types of neuromodulation.

Going forward, it will be critically important to evaluate the acute versus long-term efficacy of these various treatments. As with electroconvulsive therapy, several of the above therapies (transcranial magnetic stimulation, transcranial direct current stimulation, transcranial low voltage pulsed electromagnetic fields, magnetic seizure therapy) are designed to provide acute treatment of the depressive episode. It is not yet clear how long the beneficial effects of these treatments last and whether they can successfully be used as "maintenance" treatments over time. Of the newer "acute" neuromodulation therapies, only transcranial magnetic stimulation has been subjected to a large number of sham-controlled studies, including two, large pivotal trials, with these trials demonstrating statistically significant acute efficacy. However, the long-term efficacy of transcranial magnetic stimulation and other "acute" neuromodulation therapies is not yet clear. Vagus nerve stimulation has not demonstrated acute antidepressant efficacy, but may have benefits over months to years; still, this has not been adequately established in the literature. For the other invasive treatments (direct current stimulation, deep brain stimulation), long-term effectiveness should be clearly demonstrated before these treatments are made available in standard clinical practice; in many ways, long-term efficacy of these treatments may be more important than acute efficacy.

Finally, it will be critically important to clarify which patients are appropriate for which treatments (e.g. based on level of treatment resistance or co-morbidities). This may be achieved through head-to-head trials comparing different neuromodulation approaches and through the use of well-constructed registries (for FDA-approved treatments). By investigating specific and shared mechanisms of action for these diverse treatments, biological factors predicting differential treatment response may be identified. These data may also identify new targets for treatment. Neuromodulation for depression is at an exciting and promising stage of development, and continued well-conducted research will help clarify and realize its potential.

Abbreviation

FDA, US Food and Drug Administration.

Competing interests

Dr. Holtzheimer receives consulting fees from St. Jude Medical Neuromodulation, a company engaged in a large-scale, multi-center trial of a deep brain stimulation system for treatment-resistant depression. He also receives

consulting fees from Cervel Neurotech, a company that is testing a transcranial magnetic stimulation system that may be able to stimulate deeper cortical structures.



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