Therapeutic Neuromodulation: Overview of a Novel Treatment Platform

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ABSTRACT

There is an increasing interest in the development of novel nonpharmacological options for the treatment of major psychiatric illnesses, especially major depressive disorder. This is understandable, given that a majority of patients with major depression experience difficulty achieving disease remission with currently available treatments. Therapeutic neuromodulation defines a group of technologies that effect changes in the brain by exploiting both (1) the electrochemical nature of neurons, and (2) that the pathophysiology of psychiatric diseases, including depression, can be described as a disruption in the functional connections of neuronal networks. These emerging treatment options include technologies cleared by the U.S. Food and Drug Administration—electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS)—as well several experimental methods. This article provides a general overview for understanding these various technologies and places them within a framework to help differentiate the mechanisms by which they influence the behavior of neurons. [Psychiatr Ann. 2014; 44(6):274–278.]
The current treatment reality of major depression underscores that unmet needs in treatment still exist, even more than 20 years after the availability of the first modern selective serotonin reuptake inhibitor (SSRI) antidepressant. The information reported from the replication study of the National Comorbidity Survey (NCS-R) is the most up-to-date estimate of the prevalence and morbid consequences of major psychiatric disorders in the U.S. population. This study has estimated that in any 1-year period of time, 14 million U.S. adults meet formal diagnostic criteria for major depressive disorder (MDD). Of these, only half (approximately 7.2 million individuals) seek treatment within the health care system. Of these 7.2 million treated patients, the NCS-R estimated that approximately 4 million people remain poorly served by existing treatments.

Approximately 50% of patients who do receive treatment for their depression will not adequately respond to acute phase treatment. The acute outcomes reported in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study clearly demonstrate the complicated issues patients face when they fail to achieve remission with initial pharmacotherapy. At Level 2 of the study, which included patients who had failed to receive adequate clinical benefit from only one prior antidepressant treatment, those who were offered a switch to another antidepressant of the same or a different class already demonstrate a reduction in their likelihood of achieving remission to approximately 21%.

Patients experiencing treatment resistance represent a complex population with a disease that is difficult to manage and who generate significantly greater direct and indirect medical costs than patients with major depression who benefit from initial treatment. These issues have led to a considerable research interest in the development of alternative treatment strategies for this group of patients. Among the most promising new options for patients who fail pharmacotherapy is the burgeoning field of therapeutic neuromodulation.

**THERAPEUTIC NEUROMODULATION**

Therapeutic neuromodulation methods exploit the fact that neurons are electrochemically active, and as such, their functional activity can be influenced via electrical as opposed to chemical stimuli. These approaches also build on the knowledge that the pathophysiology of psychiatric diseases, including depression, can be described as a disruption in the functional connections of neuronal networks. Neuroimaging studies of patients during and following recovery from depression have shown specific patterns of change in the metabolic activity of different brain regions, including the left dorsolateral prefrontal cortex and components of the limbic system including the cingulate cortex, amygdala, and hippocampus.

As of this writing, three neuromodulation techniques are approved by the U.S. Food and Drug Administration (FDA) for use in adult patients with MDD: electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS). Experimental neuromodulation approaches that are currently being studied for treatment of MDD include deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS). Two other experimental forms of therapeutic neuromodulation—magnetic seizure therapy (MST), which uses high-energy magnetic fields to generate a convulsion similar to that obtained during ECT, and synchronized TMS (sTMS), which uses low-field rotating fixed magnets to generate a small nondepolarizing induced electrical current—will be briefly addressed.

The variety of approaches to therapeutic neuromodulation reflect the various ways the electrochemistry of the brain can be influenced. All of these modalities share a common process of delivering an electrical current to nervous tissue. However, the method of delivery, the strength and pattern of the induced electrical current, and the anatomic localization of the current delivery varies considerably among the different interventions. As the field of therapeutic neuromodulation advances, it is necessary to provide a framework for organizing and differentiating these various technologies.

These different approaches may in some ways represent a continuum in the spectrum of methods to influence the behavior of neurons for therapeutic benefit. It may be instructive to define these approaches by their effect on the nervous system. When considering the various types of therapeutic neuromodulation, three broad characteristics can be used for categorization:

- Convulsive or nonconvulsive. Does the therapy by design provoke a generalized seizure in the process of producing a therapeutic effect?
- Depolarizing or nondepolarizing. Among the nonconvulsive therapies, another differentiating feature is whether the induced electrical current is of sufficient magnitude to produce neuronal depolarization
- Focal or diffuse. A specific therapeutic neuromodulation approach may have direct effects that can be precisely targeted to a limited region of cortical tissue in the immediate vicinity of the stimulation source or diffuse effects that involve activation of broad populations of cortical neurons.

Using these criteria, we can now place the different forms of therapeutic neuromodulation in relation to each other (Table 1). These criteria also allow us to understand some of the unique features of TMS in particular. In addition to placing TMS in relation to other neuromodulatory approaches, we will use these criteria to place TMS in relation to the other emerging techniques of therapeutic neuromodulation.
to the other forms of therapeutic neuromodulation, we describe critical aspects of TMS coil design that have an influence on these parameters and on treatment effects.

**COMMERCIAL AVAILABLE THERAPEUTIC NEUROMODULATION TECHNIQUES**

**Electroconvulsive Therapy**

ECT is the oldest of the therapeutic neuromodulation techniques, introduced in the 1930s. Sufficient directly applied electrical energy is required to produce a convulsive seizure, with consequent effects on dopaminergic, serotonergic, and adrenergic neurotransmission; gamma-aminobutyric acid and glutamate neurotransmission; as well as release of pituitary hormones.

The most frequent description of the applied power used for ECT is total charge applied in milli-seconds; typical applied currents are in the 800 to 900 mA range; however, there are significantly different therapeutic and safety effects based on the choice of stimulus parameters, including electrode placement location, stimulation frequency, pulse width, and waveform. A comprehensive review of the effect ECT stimulus parameters is reported by Peterchev et al. The neuromodulation effects of ECT are convulsive, depolarizing, and diffuse.

**Vagus Nerve Stimulation**

For VNS, the electrical current is applied through an electrode that is surgically implanted and attached to the left vagus nerve in the neck, some distance from the brain itself. A depolarizing signal propagates along the vagus nerve to brain stem regions distal to the site of stimulation. Afferent connections of the vagus nerve directly or indirectly affect neurons in the nucleus tractus solitarius and the locus coeruleus, which have extensive projections throughout the neuraxis including the limbic system. VNS was initially approved by the FDA in 1997 as a treatment for refractory epilepsy. In 2005, VNS was approved for patients with a history of failing to respond to at least four antidepressant trials. Typical stimulation currents are in a range from 1.0 to 1.5 mA. The cortical effects of VNS may be considered nonconvulsive, diffuse, and non-depolarizing.

**Transcranial Magnetic Stimulation**

The first TMS device, the NeuroStar® TMS Therapy System (Neuronetics, Malvern, PA), was approved by the FDA in 2008 based on a large, multisite, randomized, sham-controlled trial. The independent U.S. Agency for Healthcare Research and Quality (AHRQ) review of nonpharmacological treatments for adults with treatment-resistant depression found that TMS has the largest controlled trial data set for any of the approved therapeutic neuromodulation technologies. AHRQ found a “high strength of evidence” that TMS produces significantly greater decreases in depression severity, response rate, and remission rate when compared to a sham treatment condition in the majority of peer-reviewed published clinical trials.

For TMS, the intracerebral electrical current is generated via the application of pulsed magnetic fields generated in an insulated coil held immediately against the location on the surface of the head above the targeted brain region of interest. The pulsed magnetic fields induce an electrical current to flow in the cortical tissue beneath the location of the coil, with sufficient induced current to cause direct neuronal depolarization. TMS also produces indirect activation of other, more distant brain areas that are functionally connected to the stimulated brain region via trans-synaptic connections. So by definition, all TMS devices that activate cortical neurons will secondarily activate connected deeper brain regions, and thereby modulate the activity of an integrated brain neural network.

There are currently two main characteristics that define TMS coils designs that influence their clinical effect, which allows TMS to have a broad range of applicability in the family of therapeutic neuromodulation techniques. Coils can be classified by whether their cortical effect is focal or diffuse, and if the coil has an air-core or a ferromagnetic-core.

### Table 1.

<table>
<thead>
<tr>
<th>Neuromodulation Technique</th>
<th>Convulsive/Nonconvulsive</th>
<th>Depolarizing/Nondepolarizing</th>
<th>Focal/Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroconvulsive therapy</td>
<td>Convulsive</td>
<td>Depolarizing</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Vagus nerve stimulation</td>
<td>Nonconvulsive</td>
<td>Depolarizing</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Transcranial magnetic stimulation (TMS)</td>
<td>Nonconvulsive</td>
<td>Depolarizing</td>
<td>Focal or diffuse*</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>Nonconvulsive</td>
<td>Depolarizing</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Transcranial direct current stimulation</td>
<td>Nonconvulsive</td>
<td>Depolarizing</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Magnetic seizure therapy</td>
<td>Convulsive</td>
<td>Depolarizing</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Synchronized TMS</td>
<td>Nonconvulsive</td>
<td>Nondepolarizing</td>
<td>Diffuse</td>
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*Dependent on coil design and output power.
Extensive research modeling the effects of various TMS coil designs has been reported by Deng et al., which clearly demonstrate that for a given stimulation power level, there is a trade-off between stimulation depth and focality, with increases in depth being accompanied by losses in focality of the volume of stimulated cortical tissue. Larger coils have more spread across large areas of the cortical surface and are therefore inherently incapable of anatomically focal stimulation, whereas small coil designs (e.g., figure-8 coils) are capable of anatomically focal and precise targeting of limited volumes of cortical neurons. Importantly, Deng et al. explored the biological and clinical implications of these variations in coil design, particularly regarding depth of stimulation and safety of treatment, concluding both that “all coils can stimulate targets at 4 cm” and “direct TMS of targets at depths of ~4 cm or more results in stimulation strength in superficial cortex that exceeds the upper limit in current rTMS safety guidelines.”

TMS coil designs have a significant impact on their treatment parameter capabilities, as shown in Table 2. Focal coils have an advantage, allowing precise targeting of specific cortical structures, permitting one coil to be used for multiple cerebral targets, and are amenable to new targeting techniques such as neuronavigation. Iron-core coils have a substantially narrower pulse width relative to the pulse characteristics of air-core devices, which may allow for preferential stimulation of cortical neurons relative to sensory neurons, and are much more energy efficient than air-core designs, resulting in improved thermal performance.

Given the extensive options provided by differing coil designs and the ability to vary the induced power, TMS can be broadly adapted to cover all of our predefined treatment characteristics. TMS can be focal or diffuse, depolarizing or nondepolarizing, and is by design nonconvulsive.

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### EXPERIMENTAL THERAPEUTIC NEUROMODULATION TECHNIQUES

#### Deep Brain Stimulation

The use of DBS for depression is not currently an FDA-approved indication. DBS electrically stimulates neuronal networks by the use electrodes implanted in the brain, with a millimeter-sized area directly affected by stimulation currents. Both the tissue targets and stimulation parameters are an important considerations for DBS; for example, a specific tissue target described for MDD by some investigators is the subgenual anterior cingulate (Brodmann area 25). Treatment pulse parameters include stimulation frequency, applied voltage, and pulse width. DBS was first approved in 1997 for the suppression of medication-refractory tremor in patients with Parkinson’s disease, has received a Humanitarian Device Exemption for dystonia, and is a designated as a Humanitarian Use Device for treatment-resistant obsessive-compulsive disorder. Although the use of DBS for MDD remains an area of active research, the recent early termination of the BROADEN (BROdmann Area 25 DEep brain Neuromodulation) trial (http://www.sjm.com/broaden) has raised questions about the challenges facing study design and methodology of future studies. The direct effects of DBS be are nonconvulsive, depolarizing, and focal.

#### Transcranial Direct Current Stimulation

tDCS is a technology using low-level direct electrical currents that modify brain activity. The current is supplied by a battery-powered stimulator attached to moistened electrodes applied to the scalp. Typical applied currents are in the 1 to 3mA range, generating cortical current densities of approximately 0.090 A/m². The mechanism of action for tDCS is unclear, but the applied currents likely alter the neuronal resting membrane potentials, leading to augmentation of neurotransmission. tDCS is currently limited by U.S. federal law to investigational use only. In terms of its cortical effects, tDCS is nonconvulsive, nondepolarizing, and diffuse.
**Magnetic Seizure Therapy**

An alternative, unapproved method proposed to induce convulsions is the use of high-field magnetic impulses called MST. It is postulated that MST will allow for more precise control over seizure induction, so as to maintain the efficacy of ECT but with a better side effect profile; however, a recent open trial of MST found responder rates similar to those found with open-label use of TMS.

**Synchronized TMS**

An experimental, unapproved variant of TMS, sTMS, operates on the theory that the effect of TMS is based on entraining neurons at their native frequency. It should be noted that although this technique is currently referred to as a subset of TMS, it creates an applied electric potential that is considerably smaller than that produced by the category of TMS devices discussed above. The induced current is less than 1% of conventional TMS and therefore is clearly not capable of depolarizing neurons. A recent study found no evidence that matching the sTMS stimulation frequency to the patient’s native alpha frequency had an independent effect, but in a pooled group analysis of all active-versus-sham patients, there was a significant effect of treatment (48.5% versus 19.3%, respectively; \( P = 0.001 \)).

**CONCLUSION**

The future is promising for neuromodulation in psychiatry. Therapeutic neuromodulation should, and will, continue to play an ever-increasing role as a treatment strategy. Although many questions remain regarding optimal treatment parameters for approved therapeutic neuromodulation technologies, this should not detract from the clear therapeutic benefits of ECT, TMS, and VNS. To understand more fully the effects of therapeutic neuromodulation, it is necessary going forward for investigators and clinicians to be aware of more than simple summary metrics of treatments such as applied power.

The stimulus parameters for therapeutic neuromodulation such as pulse amplitude, pulse shape, and pulse width, as well as frequency, treatment duration, and applied power, may produce important neurobiological effects that uniquely affect treatment response and side-effect profile. Future publications in the field of therapeutic neuromodulation should include standard descriptive criteria for technical standards, including stimulation frequency, pulse width, volume of tissue affected, and induced electric current. Only by assessing these detailed stimulus parameters can we hope to gain a greater understanding of the mechanisms of action for the various forms of neuromodulation.

**REFERENCES**