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Neurotherapeutic Interventions for Psychiatric Illness

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Abstract

Many patients with mental illness do not respond to common evidence-based treatments such as psychopharmacology and psychotherapy. We increasingly understand these illnesses as disorders of brain circuits, suggesting that otherwise treatment-refractory patients might be helped by direct intervention in those circuits. Non-invasive techniques for circuit intervention include electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). Circuits can also be targeted more directly and focally through neurosurgical intervention, including through vagus nerve stimulation (VNS), ablative neurosurgery (cingulotomy and capsulotomy), cortical brain stimulation (EpCS), or deep brain stimulation (DBS). Each of these approaches has evidence supporting its use in a major psychiatric disorder, although many have yet to demonstrate a strong clinical signal in a randomized controlled trial. New technologies that may aid in that demonstration include non-invasive techniques that can focus energy more precisely in the deep brain and invasive devices that respond in real time to changes in brain activity (closed-loop stimulation). In this article, we review the modalities and evidence base for these neurotherapeutics, with an emphasis on their clinical readiness and relative advantages.

Keywords

Brain stimulation; psychosurgery; mood disorders; obsessive-compulsive disorder; neuromodulation

Introduction

The advent of psychotropic medications over half of a century ago heralded a sea change in the treatment of psychiatric illness. Psychopharmacologic and psychotherapeutic interventions have improved outcomes for millions of patients. However, despite this armamentarium of treatments, many patients do not achieve adequate benefit from these interventions. The brain is, of course, an electrochemical organ. While the “chemical” properties of the brain have been leveraged via psychopharmacology, we have barely scratched the surface in the exploitation of the “electrical” properties of the brain for therapeutic benefit. Neurotherapeutics are defined as device and/or surgical interventions for psychiatric illness. These interventions are circuit-based and utilize the electrical properties of the brain as their mechanism of action. Until relatively recently, only electroconvulsive therapy (ECT) has been commonly used to treat psychiatric illness. In the past decades,

however, a growing number of neurotherapeutic interventions have been studied as potential treatment for psychiatric illness. In this review, we will describe these interventions and discuss future directions in the field.

Neurotherapeutic Interventions

Electroconvulsive Therapy (ECT)

The longest utilized neurotherapeutic intervention, ECT, has been available for almost a century and remains the gold standard intervention for treatment resistant depression (TRD). ECT is noninvasive and uses electrodes to deliver electrical charge to the brain through the skull. ECT is usually administered 3-5 times per week for a total of 8-16 treatments. Multiple clinical trials and meta-analyses demonstrate that ECT is more effective than sham or continued pharmacological treatments for TRD. ECT does require general anesthesia and muscle relaxants and involves induction of a grand mal seizure so it is highly nonfocal (i.e., affects most, if not all, of the brain). Additionally, ECT is commonly associated with transient cognitive side effects although new approaches such as ultra brief stimulation may mitigate some of these effects. Newer approaches such as theta-burst stimulation and magnetic seizure therapy are also being studied. Lastly, in addition to TRD, ECT may be useful for the treatment of mania, psychosis, and catatonia.

Transcranial Magnetic Stimulation (TMS)

TMS applies a noninvasive external magnetic field to generate electrical current on the brain surface. Because it does not require induction of a seizure, no anesthesia is required. Additionally, the electrical stimulation is delivered in a focal manner at a chosen cortical target rather than affecting the entire brain like ECT. For psychiatric indications, TMS is delivered in a rapid and/or repetitive manner (rTMS), often involving thousands of pulses per session (~40-50 minutes), usually 5 times per week for a total of 20-30 treatments. An industry sponsored trial resulted in the FDA approval of rTMS of the left dorsolateral prefrontal cortex (DLPFC) for major depressive disorder (MDD) in 2008. A subsequent, independent, NIH-sponsored study also demonstrated the efficacy of rTMS of the left DLPFC for MDD¹. While the first TMS devices could only stimulate the cortical surface, more recent coil designs appear able to stimulate deeper brain structures. In 2013, the FDA approved the first so-called “deep TMS” system for the treatment of MDD. Lastly, other noninvasive devices designed to stimulate the brain are under study (although none currently have FDA approval for psychiatric indications) including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and cranial electrical stimulation (CES)². Studies of TMS for OCD and other psychiatric disorders are ongoing.

Vagus Nerve Stimulation (VNS)

VNS is currently an invasive procedure, requiring accessing the left vagus nerve (the right vagus nerve is not used due to its parasympathetic branches to the heart) in the neck and wrapping stimulating electrodes around the nerve. These electrodes are then subcutaneously attached by wire to a subcutaneous implantable pulse generator (IPG), similar to those used for cardiac pacemakers, in the chest wall. The clinician communicates transcutaneously with the IPG, using a transducer and computer to program the desired stimulation parameters.

These parameters include current amplitude, pulse frequency, pulse width, and duty cycle. Typically, the duty cycle is 30 seconds of stimulation followed by 5 minutes off for a 10% duty cycle (30 seconds/300 seconds). Duty cycles higher than 50% are not recommended as they may be neurotoxic. In 2005, the FDA approved VNS for the treatment of TRD (in this case, defined as lack of response to four or more adequate treatments). However, this approval was based on secondary outcome data from the pivotal trials, as the change in the primary outcome measure in the trial was not statistically significant ($p=0.06$). Therefore, most third party payers do not currently reimburse for the procedure. Recent data from a 5-year, prospective, open-label, nonrandomized, observational registry study of VNS involving 795 patients showed significantly higher response (67.6% for VNS compared to 40.9% for treatment as usual) and remission (43.3% for VNS compared to 25.7% for treatment as usual)³. This may help change the reimbursement landscape. VNS is not currently approved for the treatment of any other psychiatric disorders.

Epidural Cortical Stimulation (EpCS)

EpCS is an invasive procedure involving placing a flat stimulating electrode on the brain surface via craniotomy and using subcutaneous wires to connect to a subcutaneous IPG placed on the chest wall. In this manner, it is similar to VNS, except that the electrode is on the brain surface instead of the vagus nerve. As with VNS, transcutaneous communication with the device uses a transducer and parameter settings are adjusted using an attached small handheld computer. One EpCS trial for psychiatric illness, in this case TRD, has been published⁴. This randomized, single-blind, sham-controlled study examined chronic, continuous stimulation of the left DLPFC (the FDA approved target for rTMS) in 12 patients with TRD. The hypothesis was that continuous stimulation of the left DLPFC (EpCS) might be more efficacious than intermittent stimulation (rTMS). While there was no statistically significant difference between active versus sham stimulation during the blinded phase of the study, subsequent open label results demonstrated significant improvement of depressive symptoms for the cohort. Future studies, likely involving a larger number of patients and perhaps with a longer blinded phase, are needed.

Ablative Limbic System Surgery

Ablative limbic system procedures have typically involved a craniotomy followed by radiofrequency ablation of stereotactically targeted brain tissue. Newer neurosurgical techniques such as gamma knife and high intensity focused ultrasound may eventually obviate the need for a craniotomy as they can create stereotactic lesions noninvasively⁵. Nonetheless, the targets for these interventions are the same. They include the dorsal anterior cingulate cortex (anterior cingulotomy), the anterior limb of the internal capsule (anterior capsulotomy), and the white matter tracts below the head of the caudate nucleus (subcaudate tractotomy). The combination of an anterior cingulotomy and subcaudate tractotomy is described as a limbic leukotomy. These procedures have been performed in patients with highly treatment refractory MDD and obsessive compulsive disorder (OCD) since the 1960s. Patients are awake during the procedure, adverse events are minimal (see references for full details), and patients are usually discharged within 48 hours after the procedure. For the open procedures, active versus sham comparisons of outcome are not feasible. However, unblinded, long-term, prospective studies have demonstrated response rates as high as 69%

for intractable OCD⁶ and 75% for TRD⁷ for anterior cingulotomy and/or subcaudate tractotomy and 54% for anterior capsulotomy for intractable OCD⁸. Ablative limbic system surgery is not currently typically used to treat any other psychiatric disorders.

Deep Brain Stimulation (DBS)

DBS involves performing a craniotomy to stereotactically place electrodes in deep brain regions (as opposed to on the brain surface like EpCS). Otherwise, the subcutaneous wires, subcutaneous IPG, and transcutaneous communication and control are comparable to EpCS and VNS. DBS has been used for movement disorders, particularly Parkinson disease, since the 1980s; over 130,000 Parkinson patients in the US have been treated with DBS. In 1999, the first report of using DBS to treat psychiatric illness, in this case OCD, was published.⁹ Since then, in 2008 the FDA approved DBS at the ventral capsule/ventral striatum (VC/VS) target (near the region of ablation for anterior capsulotomy) for intractable OCD. Subsequent pivotal trials of DBS at the VC/VS target and in the subgenual cingulate cortex (SCC) for TRD were negative,^{10,11} although one more recent VC/VS TRD trial reached its desired endpoint using a novel design¹². DBS is also currently being studied for dementia, PTSD, and substance use disorders.

Future Directions

While efforts are underway to increase the clinical uptake of currently available neurotherapeutic interventions, the neurotherapeutic toolkit is rapidly growing. Continued development of noninvasive interventions (e.g., low intensity focused ultrasound) and advanced targeting will likely lead to improved outcomes and more widespread use. Animal neuroscience is identifying new circuits that could be targeted with existing devices. Additionally, while current use of DBS is so-called “open loop” (continuous stimulation), work is underway to develop “closed loop”, or responsive stimulation.^{13,14} Such strategies may be necessary to adequately affect the complex circuitopathies associated with psychiatric illness.

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