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Neurotherapeutic Interventions for Psychiatric Illness

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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 an electrochemical organ. While the "chemical" properties of the brain have been leveraged via psychopharmacology, we have barely scratched the surface in exploitating the "electrical" properties of the brain for therapeutic benefit. Neurotherapeutics are defined as interventions using surgery or a device 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 treatments for psychiatric illness. In this review, we will describe these interventions and discuss future directions in the field.

NEUROTHERAPEUTIC INTERVENTIONS

Electroconvulsive Therapy

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, with the consequence that 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. Finally, in addition to being effective for TRD, ECT may be useful for mania, psychosis, and catatonia.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (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 (as with ECT). For psychiatric indications, TMS is delivered in a rapid or repetitive manner (rTMS), often involving thousands of pulses per session (~40 to 50 minutes), usually 5 times per week for a total of 20–30 treatments. An industry-sponsored trial resulted in Food and Drug Administration (FDA) approval of rTMS of the left dorsolateral prefrontal cortex (DLPFC) for major depressive disorder (MDD) in 2008. A subsequent, independent, National Institutes of Health–sponsored study also demonstrated the efficacy of rTMS of the left DLPFC for MDD.[1] While the first TMS devices could stimulate only 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 treating MDD. Finally, other noninvasive devices designed to stimulate the brain are under study (although none currently has FDA approval for psychiatric indications), including transcranial direct current stimulation, transcranial alternating current stimulation, and cranial electrical stimulation.[2] Studies of

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TMS for obsessive-compulsive disorder (OCD) and other psychiatric disorders are ongoing.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is currently an invasive procedure that requires accessing the left vagus nerve (the right vagus nerve is not used, because of 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 by 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). This approval was based, however, on secondary outcome data from the pivotal trials, as the change in the trial's primary outcome measure was not statistically significant ($p = .06$). Therefore, most third-party payers do not currently reimburse for the procedure. Recent data from a five-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), though also higher remission (43.3% for VNS compared to 25.7% for treatment as usual).[3] These results may help change the reimbursement landscape. VNS is not currently approved for the treatment of any other psychiatric disorders.

Epidural Cortical Stimulation

Epidural cortical stimulation (EpCS) is an invasive procedure that involves placing a flat stimulating electrode on the brain surface via craniotomy and that uses 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 small, attached handheld computer. One EpCS trial for psychiatric illness—in particular, TRD—has been published.[4] That 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 via EpCS might be more efficacious than intermittent stimulation via rTMS. No statistically significant difference was observed in active versus sham stimulation during the blinded phase of the study, but 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 the gamma knife and high-intensity focused ultrasound may eventually obviate the need for a craniotomy, as they can create stereotactic lesions noninvasively.[5] 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 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 OCD[6] and 75% for TRD[7] using anterior cingulotomy or subcaudate tractotomy, and 54% for intractable OCD using anterior capsulotomy.[8] At present, ablative limbic system surgery is not typically used to treat any other psychiatric disorders.

Deep Brain Stimulation

Deep brain stimulation (DBS) involves performing a craniotomy to stereotactically place electrodes in deep brain regions (as opposed to placement on the brain surface, as in 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's disease, since the 1980s; over 130,000 Parkinson's patients in the United States have been treated. In 1999, the first report of using DBS to treat psychiatric illness (OCD) was published.[9] In 2008, the FDA approved DBS at the ventral capsule/ventral striatum (VC/VS) target (near the region of ablation for anterior capulotomy) for intractable OCD. Subsequent pivotal trials of DBS at the VC/VS target and in the subgenual cingulate cortex for TRD were negative,[10,11] although one more recent VC/VS TRD trial that utilized initial open-label treatment with DBS for up to 52 weeks followed by a blinded withdrawal of DBS did show a difference between true DBS withdrawal and sham DBS withdrawal, with true DBS withdrawal resulting in statistically significant greater worsening when compared to sham DBS withdrawal.[12] DBS is also currently being studied for dementia, posttraumatic stress disorder, and substance use disorders.

FUTURE DIRECTIONS

While efforts are under way 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 under way 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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