WHEN MEDICATION FAILS: NEUROSTIMULATION THERAPIES FOR DEPRESSION

Linda L. Carpenter, James L. Megna,
Mariela Herrera-Rojas, and Umar A. Siddiqui

Abstract

Sometimes, psychopharmacologists will implement evidence-based treatments and still not observe ideal clinical outcomes. Despite accurate diagnostics, use of rational polypharmacy, and objective assessment with standardized rating scales, full symptom remission will not occur. Referral to a psychiatrist who specializes in neurostimulation therapies may be an appropriate next step. The greatest evidence base for neuromodulation therapies at present is in the treatment of mood disorders, and these device-based treatments are typically reserved for patients who are intolerant or resistant to pharmacotherapy interventions. This paper describes the most common neurostimulation techniques available in psychiatry and thoroughly reviews the literature about existing and future techniques that may become available to treat patients.

Key Words: pharmacotherapy interventions, resistant, neurostimulation techniques

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Linda L. Carpenter, M.D. [1], James L. Megna, M.D., Ph.D. [2],
Mariela Herrera-Rojas, M.D [2] and Umar A.Siddiqui, M.D. [2]

[1] Mood Disorders Research Program, Butler Hospital, Department of Psychiatry and Human Behavior, Warren Alpert Medical School at Brown University, Providence, RI

[2] Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY

Corresponding author
Linda L. Carpenter, M.D., Associate Professor, Brown Department of Psychiatry and Human Behavior, Butler Hospital, 345 Blackstone Blvd, Providence RI 02906, USA
Email: Linda_Carpenter_MD@Brown.edu

Introduction

Major depression is a common and debilitating disorder. It has been estimated that half of depressed patients treated with standard antidepressant medications do not show evidence of adequate response (Fava et al. 2003). A recent large multicenter clinical trial examined the effectiveness of serial antidepressant treatment interventions in (n=3671) depressed outpatients [STAR*D; (Sequenced Treatment Alternatives to Relieve Depression); www.star-d.org]. Through a stepwise progression through multiple, serially administered, adequate antidepressant treatment trials, this study demonstrated a cumulative remission rate of only 67% (Rush et al. 2006). Non-pharmacological neurostimulation therapies may offer additional options for depressed patients who have failed to respond to standard psychotherapy and pharmacological therapies.

Electroconvulsive therapy (ECT) is the oldest and most widely used neurostimulation technique for depression. Vagus nerve stimulation (VNS) was approved by the US Food and Drug Administration (FDA) in 2005 as an adjunctive treatment for treatment-resistant major depression, and a device for the delivery of transcranial magnetic stimulation (TMS) therapy for depression was cleared by the FDA in late 2008. Deep brain stimulation (DBS) has shown promise in preliminary, pilot studies of treatment resistant unipolar depression, and large controlled trials are now underway. Several newer and novel techniques include magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS) and epidural prefrontal cortical stimulation (EpCS). This chapter will review each of these neurostimulation techniques in detail and discuss their evidence base.

Electroconvulsive therapy (ECT)

ECT has been in use since the 1930s, and is still widely considered the most effective treatment for se-

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vere forms of depression in hospitalized patients. While ECT remission rates may be highest for psychotic subtypes (Petrides et al. 2001), the treatment has also proven useful for atypical depression Husain et al. 2008 and bipolar disorder (Medda et al. 2010, Mohan et al. 2009). ECT has also been used to treat various other severe psychiatric disorders, including mania, schizophrenia, and catatonic states (Weiner and Coffey 1988).

ECT involves the unilateral or bilateral application of a brief electrical impulse directly to the scalp to induce a seizure-like pattern of neuronal depolarization. Many believe that the ECT stimulus must produce a tonic–clonic movement of the patient's limbs in addition to a characteristic tracing on a scalp electroencephalograph (EEG) recording for at least twenty seconds to produce a therapeutic effect. Patients receive general anesthesia during modern ECT, and anesthesia-induced muscle relaxation prevents generalized convulsive body movements during the course of each ECT session. A typical acute course of ECT consists of between six and twelve treatments at a frequency of two to three treatments per week, and some patients require maintenance treatment consisting of weekly or monthly treatments. A specially trained psychiatrist in an inpatient or outpatient hospital setting generally administers ECT.

The putative mechanism of action for ECT efficacy in depression is not known, but several biological correlates have been identified (see review by Merkl et al. 2009). The "anticonvulsive hypothesis" postulates that the antidepressant effect of ECT is due to a compensatory increase in the function of inhibitory neurotransmitters [such as γ-amino butyric acid, (GABA)] in brain circuits. This hypothesis is consistent with findings that point to a relative deficit in GABA neurotransmission in the cortical network of depressed patients (Sanacora et al. 2000) and ECT-associated increases in occipital cortex GABA concentrations (Sanacora et al. 2004). A significant increase in cortical inhibition following ECT suggests enhancement of cortical GABA activity with the treatment (Bajbouj et al. 2006). Serum GABA levels, assessed as an index of brain GABA activity, were found to be significantly lower in depressed patients than healthy controls before ECT treatment, surged immediately after the first ECT, and increased significantly from pre-treatment baseline to the end of ECT course (Esel et al. 2008). Measurements of ECT-associated change in peripheral growth hormone response to baclofen challenge suggested an enhancement in hypothalamic GABA B receptor activity with ECT treatment (Esel et al. 2008). Preclinical evidence in support of the role of GABA in the etiopathology of mood disorders includes findings from a learned helplessness model, where rats treated with imipramine or Electroconvulsive Shock (ECS) showed a decreased glutamate/GABA ratio in the hippocampus and prefrontal cortex (PFC), compared to an increase in the same ratio in both brain regions in placebo-treated rats (Sartorius et al. 2007).

Other biological correlates of ECT described in the literature include changes in regional brain metabolism. Nobler and colleagues found the degree of prefrontal and medial frontal deactivation immediately after ECT treatment correlated with later clinical improvement and persisting until 2 months after ECT (Nobler et al. 2001). While studies using positron emission tomography (PET) scan data obtained pre- and post-ECT have produced variable results, researchers have suggested an ECT mechanism of action mediated via anterior cingulate, medial frontal cortex and thalamus (Takano et al. 2007), and speculated that ECT's effects on prefrontal cortex and amygdala occur through the limbic-cortical-striatal-pallidal-thalamic circuit (Segawa et al. 2006). Rodent ECS data suggest that the effectiveness of electroconvulsive therapy in mood disorders may be a consequence of changes in striatal synaptic plasticity (De Murtas et al. 2004), and may be mediated by transcription factor cyclic adenosine monophosphate response element binding protein (CREB) (Tanis et al. 2008).

A number of studies suggest monoamine neurotransmitter systems are possible mediators for treatment response in ECT. In humans, ECT-related changes in serotoninergic function are suggested by a variety of preclinical investigations (see review by Lisanby et al. 2000), including reduced 5-HT2 receptors in key brain regions after treatment (Yatham et al. 2010). Dopaminergic mechanisms have also been identified. Cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA) have been observed to increase following ECT (Rudorfer et al. 1992), while peripheral plasma HVA levels of were found in another study to be significantly reduced after ECT in a manner that correlated with symptom improvement (Okamoto et al. 2008). A related finding was a decrease in D2 receptor binding in the right rostral anterior cingulate associated with ECT (Saijo et al. 2010). A genotype including two combined functional polymorphisms associated with lower dopaminergic activity in prefrontal cortex was associated with clinical remission following ECT (Huuhka et al. 2008), and several investigations into the functional catechol-O-methyltransferase (COMT) val158met polymorphism have demonstrated that patients with the COMT 158val allele (i.e., with higher activity of the enzyme and thus greater metabolic degradation of synaptic dopamine) had greater baseline depressive symptom severity and better treatment responses to ECT (Anttila et al. 2008, Domschke et al. 2010).

As with other antidepressant agents, neurogenesis has been implicated as a mechanism for ECT's effect on depression. Serum BDNF levels were found to be low in depressed patients, relative to a group of health controls, but then increased to control levels following ECT (Hu et al. 2010), with magnitude of change correlated with degree of clinical improvement. Increased hippocampal volume after ECT also supports the notion of ECT-induced cell proliferation (Nordanskog et al. 2010). Peripheral cortisol measures have reflected changes in functioning of the hypothalamus-pituitary-adrenal (HPA) axis that accompany the antidepressant actions of ECT (Yuuki et al. 2005), perhaps reflecting a parallel reduction of glucocorticoid exposure to the brain.

Owing to the inherent challenges in conducting large-scale, randomized, sham-controlled and medication-controlled standardized ECT clinical trials, efficacy has been examined with meta-analyses. Two

analyses incorporating data from both controlled and observational studies confirmed the efficacy of ECT for depressive disorders (Pagnin et al. 2004, UK ECT review Group 2003). In the first, ECT was more effective than sham treatment (n=256 from 6 trials), as evidenced by a standardized effect size (SES) of 0.91 (95% confidence interval (CI) 0.54 to 1.27); ECT was also found to be more effective than pharmacotherapy (n=1144 from 18 trials; SES 0.80, 95% CI 0.29 to 1.29), and bilateral ECT was proven superior in efficacy to unipolar ECT (22 trials, n=1408; SES 0.32, 95% CI 0.19 to 0.46)(UK ECT review Group 2003). The second meta-analysis, which included data from both randomized and non-randomized controlled trials published from 1956 to 2003, also confirmed the superiority of ECT in comparisons with simulated (sham) ECT, placebo, antidepressants in general, tricyclic antidepressants, and monoamine oxidase inhibitors (Pagnin et al. 2004).

Optimization of ECT has been the focus of much research. In early work on ECT parameters, Sackeim and colleagues reported that the clinical efficacy of ECT depended on electrode placement (i.e., bilateral treatment superior to unilateral) and stimulus intensity as a function of an individual's seizure threshold (i.e., higher doses superior to lower doses), while the absolute electrical stimulus intensity appeared unrelated to clinical efficacy (Sackeim et al. 1993). Subsequent refinement of right-sided unilateral stimulation parameters, specifically the use of a narrower stimulus pulse width at an electrical intensity that adequately exceeds the seizure threshold, was shown to produce a response equivalent to that achieved with standard bilateral ECT. In a prospective, double-masked trial, 90 patients with major depression were randomly assigned to receive right-sided unilateral (RUL) ECT at 6 times seizure threshold or bilateral ECT (2.5 times seizure threshold), using either a traditional pulse (1.5 ms) or an "ultra-brief" pulse (0.3 ms). Patients in the ultra-brief pulse RUL group had a higher final remission rate (73%) compared to the remission rates of 35%, 65% and 59% for the groups who got ECT with ultra-brief bilateral, standard pulse bilateral, and standard pulse RUL, respectively (Sackeim et al. 2008). In that trial, ultra-brief pulse/high dose RUL ECT was also associated with superior outcomes on short- and longer-term cognitive measures. Comparable efficacy was demonstrated for bifrontal (1.5x seizure threshold) and RUL electrode placements (6x seizure threshold) with ultra-brief pulse ECT (Sienaert et al. 2009) and also for RUL ultra-brief pulse ECT at three different high-dose stimulation intensities: 4x, 7x, and 10x seizure threshold (Quante et al. 2011). However, questions about the relative advantage of ultra-brief RUL stimulus were raised by a naturalistic, retrospective chart review study that found that compared with standard bilateral ECT at 2.5 times the seizure threshold, patients who started with ultra-brief RUL ECT at 6 times the seizure threshold intensity required significantly more total treatments (McCormick et al. 2009). While more treatments may add to overall cost and risk of potential side effects or complications, the relative merits of ultra-brief RUL ECT may be particularly important for patients who depend on their intellect and cognitive function for their livelihood.

ECT electrode placement appears related to both efficacy and safety (Kellner et al. 2010a). A large, randomized, double blind, controlled trial (n=230) showed no significant difference in remission between bifrontal (1.5 times seizure threshold), bitemporal (1.5 times seizure threshold), and RUL placement (6 times seizure threshold), and no group differences emerged on changes in overall global cognitive and executive function (Kellner et al. 2010b). When ECT electrode placement was examined in a recent trial that included concomitant antidepressants, remission rates were higher for patients randomized to right unilateral (RUL) placement, as compared to those who received bilateral ECT (Sackeim et al. 2009).

Published efficacy data from ECT research protocols have generated impressive response rates in the 70–90% range, but treatment in community settings has revealed significantly lower remission rates, from 30–47% depending on the specific remission criteria applied (Prudic et al. 2004). The effect of concomitant pharmacotherapy on acute ECT outcomes was examined in a multisite, randomized, placebo-controlled, triple-masked trial in which patients received nortriptyline, venlafaxine, or placebo (initiated after the first ECT treatment) (Sackeim et al. 2009). Relative to placebo, remission rates were significantly higher, and cognitive side effects lower, for those receiving concurrent nortriptyline; concurrent venlafaxine was associated with a lesser degree of improvement and worse cognitive adverse effects.

Sustaining antidepressant benefits achieved with ECT remains a significant challenge. In a naturalistic 6-month follow-up study, comorbid personality disorders, depressive episode chronicity, and schizoaffective disorder were associated with poorer outcomes; among those who did achieve remission with ECT, 64% relapsed despite maintenance ECT or pharmacotherapy (Prudic et al. 2004). A naturalistic study with up to 8 years of follow-up data found 42% of initial ECT responders developed a new depressive episode requiring antidepressant medication, readmission to the hospital, or a new ECT course (Van Beusekom et al. 2007). In a sample receiving continuation ECT, rehospitalization rates of 43% at 6 months and 58% at 2 years were reported (Nordenskjold et al. 2011). However, some data suggest the total number of hospital days may be diminished with "maintenance" ECT (Gupta et al. 2008), which is typically administered less frequently than "continuation" ECT. A large, multicenter, randomized, 6-month trial comparing continuation ECT with continuation pharmacotherapy following acute ECT response showed no significant difference in relapse prevention, with both treatment arms generating relapse rates greater than 30% (Kellner et al. 2006). Post-ECT relapse can be reduced by the use of optimal antidepressant pharmacotherapy (Van Beusekom et al. 2007, Yildiz et al. 2010), and by avoiding a temporal gap between cessation of ECT and initiation of continuation pharmacotherapy Yildiz et al. 2010). While 67% of patients randomized to placebo continuation therapy (following response to acute ECT) relapsed during 18 weeks of follow-up, those randomized to continuation sertraline therapy fared better (Yildiz et al. 2010). Naturalistic data also suggest that a

combination of maintenance ECT plus antidepressant medication is superior to medication alone for preventing relapse (Gagne et al. 2000).

Despite the robust efficacy data associated with ECT, several factors other than the high relapse rate limit the use of ECT. Patient enthusiasm is limited because of the required hospital setting, high cost, exposure to anesthesia, and risk of side effects, most notably cognitive side effects (Prudic et al. 2000, Sackeim et al. 2007a). While many patients show short-tem improvements in cognitive function with resolution of their severe depressive illness (Bayless et al. 2010), concerns about memory deficits remain a central issue in the risk/benefit analysis for ECT. Immediate post-ECT side effects include short-term memory loss and cognitive impairment, specifically with impaired selective attention and executive function (Moscrip et al. 2006, Calev et al. 1991). Adverse cognitive side effects persist six months after ECT in many patients though the extent and duration of longer-term cognitive side effects appear variable, as several aspects of ECT treatment may have a potential effect on cognition: persistent retrograde amnesia was more common with bilateral electrode placement, and sine-wave stimulation was associated with slowing of reaction time; older age, lower premorbid intellectual function, and female gender were also linked to greater cognitive deficits from ECT (Sackeim et al. 2007b). Some investigators have reported substantial improvement in memory function relative to depressed baseline at 6-month follow-up (Calev et al. 1991), and post-ECT improvements in overall memory function are particularly apparent when clinical benefits are marked (Criado et al. 2007). A small naturalistic study found slightly subnormal performance on working memory and verbal and visual episodic memory tasks at 2 year follow-up after ECT, despite sustained remission of depression (Johanson et al. 2005). One author proposed that ECT treatment is effective by virtue of its ability to *restore* specific memory functions that are deficient during a severe depressive episode (Frais et al. 2010).

While objective cognitive function measures may generate data reflecting only transient side effects that resolve or improve over time during ECT (Semkovska and McLoughlin 2010), patients' self-characterizations, when directly questioned about global impact of ECT, have revealed more negative views about its effects on memory (Berman et al. 2008,Vamos et al. 2008, Sienaert et al. 2005). Patients' self-reports of cognitive difficulties have been found to persist even when depression symptoms have remitted (Feliu et al. 2008), yet satisfaction with the treatment is not necessarily related to complaints about ECT's adverse impact on memory (Sienaert et al. 2005). Several promising techniques have been explored for prevention or reduction of ECT-induced cognitive impairment from ECT including hyperventilation (Mayur et al. 2010), and concurrent treatment with oral galantamine (Matthews et al. 2008).

Psychiatrists have been using one particular neuromodulation techniques-ECT for several decades already. In the future, it is unikely ECT will become neuromodulation treatments, an office-based procedure like some of the never owing to it's requirement for anesthesia and ricovery in a medically sophisticated setting. However, clinicians should keep ECT in mind and refer more readily, particularly in resistant depression cases. As will be discussed next, the future psychopharmacologist may choose to employ some office-based neurostimulation techniques.

Transcranial magnetic stimulation (TMS)

The basic physical principle underlying TMS dates back to the work of Michael Faraday, who in 1839 discovered that a pulsed magnetic field can produce an electrical current in a conductive substance, later described as the principle of electromagnetism (Faraday 1839). In 1985, Barker and Cain (Barker and Chain 1985, George et al. 2002) developed the first TMS device that was capable of stimulating the human cortex, although at that time their goal was stimulation of spinal roots rather than the brain. Shortly thereafter, TMS was postulated as a possible treatment for depression Bickford et al. 1987), and after more than two decades of research, a TMS device was approved, in late 2008, by the FDA for treatment of depression. TMS has also been studied fairly extensively for other primary psychiatric disorders (Cohen et al. 2004, Dlabac-de Lange et al. 2010, Walpoth et al. 2008), and for neurological conditions such as tinnitus (Meeus et al. 2009), pain (Picarelli et al. 2010), migraine (Dodick et al. 2010), and movement disorders (Elahi et al. 2009).

During TMS a small, insulated electromagnetic coil is placed on the scalp. A bank of capacitors is then rapidly discharged into the coil, which converts the electrical activity into a pulsed magnetic field that then passes through the cranium with minimal impedance, unlike ECT where much electrical charge is dispersed by bone. The magnetic field induces an electrical field in the underlying cerebral cortex based on the counter-current principle (Roth et al. 1991a, Roth et al. 1991b). Upon delivery of sufficiently intense TMS to the targeted area, the cortical neurons depolarize and action potentials are generated, altering neuronal activity in the cortex. The current technology generates a magnetic field of approximately 1.5 Tesla (comparable to that in a standard MRI), which penetrates to approximately 3 cm beneath the coil surface (Demitracl et al. 2007). The pulsing frequency of the field and the excitatory or inhibitory function of the activated underlying neurons determine the ultimate effects on neural circuitry (Fierro et al. 2001). In general terms, TMS at frequencies of less than or equal to 1 Hz ("slow" TMS) are inhibitory and frequencies greater than 1 Hz ("fast" TMS) are excitatory (Chen et al. 1997, Nakamura et al. 1997). The pulses administered can be single, paired, or in a series (also called a "train"). When TMS is delivered in a series of trains, it may be called "repetitive TMS" (often abbreviated rTMS). Single and paired pulse TMS are more frequently used for neurodiagnostic purposes, whereas repetitive TMS has demonstrated therapeutic potential in psychiatric disorders. "TMS" is used in a generic sense, to refer to repetitive trains of therapeutic stimulation, throughout this chapter. Unlike ECT, which produces a widespread current distribution via a generalized seizure, a TMS device is able to induce currents in fairly specific, localized areas (Epstein et al. 1990).

Before using TMS to deliver therapeutic brain stimulation, the required amount of magnet energy is determined by calibrating the TMS with the level of excitability of cortical neurons. This is achieved with single pulse stimulation over the motor cortex. The energy delivered by the TMS device is varied until a visible twitching movement of the contralateral thumb is reliably produced. The minimal intensity required to elicit this movement represents the "motor threshold" (MT). For treatment of psychiatric disorders, the determination of MT guides one aspect of TMS stimulation dose, i.e., intensity of energy delivered in each pulse. TMS intensity is described as the percentage of MT, which for most patients is in the 80-120% range. Several studies have shown stimulus intensity of 120% or greater is associated with activation of both ipsilateral and contralateral cortices (Nahas et al. 2001, Kozel et al. 2009).

The location on the patient's scalp where MT is derived can be used to guide the placement of the magnet coil for therapeutic stimulation of targeted brain regions outside of the motor cortex. For example, to deliver TMS targeting the dorsolateral prefrontal cortex (DLPFC), the coil can be placed approximately 5 cm anteriorly (in the same parasaggital plane) relative to the spot where the MT was elicited. This "5 centimeter" technique for coil placement provides a simple and quick method for approximating an anatomical target where TMS will reach Broadmann Areas 9 and 46, regions of corticolimbic interconnections implicated in the pathophysiology of depression (Burt et al. 2002, Herwig et al. 2001a). However, brain imaging studies suggest this method of coil placement does not consistently lead to stimulation of the desired underlying anatomy (Herwig et al. 2001b), owing to widely varying brain sizes and skull morphology among patients. Placement of the TMS coil more laterally and anteriorly, relative to the target dictated by the "5 centimeter" method coordinates, was associated with better response to treatment (Herbsman et al. 2009). While functionally equivalent regions may vary across individuals, researchers have continued to explore alternative methods for determining optimal and standardizable TMS coil placement (Ahdab et al. 2010). Neuro-navigation/co-registration, a method that uses each patient's head MRI to identify the appropriate scalp position corresponding with a desired brain region, has been show to increase antidepressant effects of TMS (Rusjan et al. 2010, Fitzgerald et al. 2009a). Electroencephalogram (EEG) points have also proven useful in TMS coil placement (Fitzgerald et al. 2009b). The International 10-20 system, used for placement of EEG electrodes, takes into account individual head size and is less expensive than methods requiring brain images. A calculation "short-cut" using 3 skull measurements can be used to accurately identify the F3 position for TMS coil placement over (PFC) (Beam 2009).

In addition to intensity of energy in each pulse, there are a variety of stimulation parameters which contribute to the overall "dose" of TMS, including the time in between trains of stimulation when no stimulation is occurring (the inter-train interval), an important safety parameter used to avoid inducing seizures (Wassermann et al. 1998). Other parameters include laterality, frequency of pulsing of the magnetic field (expressed in Hz), number of trains or pulses per session, and the duration of treatment (number of daily sessions in an acute course of therapy). There is evidence supporting the treatment of depression with both right- and left-sided TMS (Fitzgerald et al. 2009c, Schutter et al. 2009, Pallanti et al. 2010). Generally, only a single session is conducted per treatment day, with 5 sessions per treatment week given for a course of acute treatment, but recent work has begun to examine the potential benefit of a more accelerated treatment schedule (Holtzheimer et al. 2004). In several recent large, controlled trials, daily treatment sessions were each comprised of 3,000 total magnetic pulses, but safety has been demonstrated in a small sample of healthy subjects that got over 12,000 pulses per day and over 38,000 pulses in one week (Anderson et al. 2006). The duration of treatment has varied across published clinical TMS trials, with longer trials generating larger sized effects; the total number of treatment sessions in early TMS trials was approximately 10-20 delivered over 3 to 4 weeks, but more recent research in this area describes an acute treatment phase duration of 6 or more weeks (Gross et al. 2007).

Similar to other available neurostimulation treatments in psychiatry, the specific biological mechanism of antidepressant action of TMS is not known. However, TMS has demonstrated effects in animal models that act as standard assays for antidepressant efficacy. For example, daily TMS reduces immobility in rats during the forced-swim test, a model of learned helplessness and depression (Sachdev et al. 2002, Hargreaves et al. 2005), perhaps through effects on synaptic plasticity (Kim et al. 2006). Rodent TMS studies have reported enhanced forebrain serotonin output and serotonin receptor function modulation (Ben-Shachar et al. 1997, Juckel et al. 1999) as well as dopamine release in the hippocampus, striatum, and in the nucleus accumbens septi, the latter being associated with a simultaneous increase in extracellular glutamate (Zangen and Hyodo 2002). The induction of kf-1, a common functional molecule known to increase after antidepressant medication and ECT, was also demonstrated after TMS in rat frontal cortex and hippocampus (Kudo et al. 2005), and TMS was found to impact synaptic plasticity in hippocampal CA1 area in a rat model with vascular dementia (Wang et al. 2010).

In human studies, positron emission tomography (PET) scans have demonstrated release of endogenous dopamine in the ventral striatum following TMS over the motor cortex (Ohnishi et al. 2004), and single photon emission computed tomography (SPECT) imaging has shown endogenous striatal dopamine release induced by prefrontal (10 Hz) TMS (Pogarell et al. 2006 and Pogarell et al. 2007). Functional MRI imaging of 1 Hz TMS over the left DLPFC produced activation of deeper structures, including the insula, putamen, hippocampus, and thalamus, via frontal-subcortical neuronal circuits (Li et al. 2004). TMS to the left DLPFC induced changes in prefrontal and paralimbic blood flow (Teneback et al. 1999); patients with the greatest changes in inferior frontal lobe activity also showed the best clinical response to TMS. Positive antidepressant response to low-frequency, right-sided prefrontal TMS was

associated with pre-treatment cerebral blood flow in left-sided medial temporal regions, including hippocampus and amygdala (Kito et al. 2008). Pre-treatment anterior cingulate activity was also identified as a predictor of TMS clinical outcome (Langguth et al. 2007). Changes in glutamate concentrations have correlated with both TMS stimulation intensity and with clinical response in a magnetic resonance spectroscopy study (Luborzewski et al. 2007).

In addition to finding a significant negative correlation between pretreatment TSH levels and therapeutic efficacy of TMS, significant elevations of thyroid stimulating hormone (TSH) have been associated with prefrontal TMS (Kito et al. 2010, Szuba et al. 2001). Neuroendocrine correlates of successful TMS include "normalization" of cortisol secretion as measured by the dexamethasone suppression test (Pridmore 1999), and a moderating role for steroid hormones has been proposed for the antidepressant efficacy of TMS in women (Schutter and Honk 2010). Other peripheral measures in clinical samples have shown increased levels of brain-derived neurotropic factor (BDNF) (Zanardini et al. 2006), and reduced concentration of plasma catecholamine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), but not homovanillic acid (HVA), after TMS treatment (Yukimasa et al. 2006). Patients responding to TMS showed resistance to mood symptom emergence following rapid tryptophan depletion (O'Reardon et al. 2007a) suggesting the therapeutic benefit of TMS is not dependent on the central availability of serotonin.

Findings from a collection of studies demonstrate frequency-dependent, at-times opposite, effects of high and low frequency TMS on local and regional brain activity (Fitzgerald et al. 2007, Knoch et al. 2006). Two weeks of daily 20-Hz TMS over the left PFC at 100% MT intensity induced persistent increases in regional cerebral blood flow (rCBF) in bilateral frontal, limbic, and paralimbic regions implicated in depression, whereas 1-Hz TMS produced more circumscribed decreases, including in the left amygdala (Loo et al. 2003). Changes in mood following the two different TMS frequencies appear inversely related, such that depressed patients with prominent anxiety tend to do better with low frequency TMS (Rossini et al. 2010). It remains unclear whether an intermediate frequency (5 Hz) TMS offers distinct clinical benefits or invokes a distinct mechanism or region of action (Fitzgerald et al. 2009c).

Although TMS was first suggested as a possible treatment for depression in 1987 (Bickford et al. 1987), and initial case reports in the early 1990s described favorable response (Hoflich et al. 1993, George et al. 1995), it was nearly ten years before TMS was first systematically examined as a treatment for depression (George et al. 1997). After a study of 10 Hz TMS administered to different sites on the scalp identified the left dorsolateral prefrontal cortex (DLPFC) as the site associated with best antidepressant efficacy (Pascual and Rubio 1996), the majority of studies that found TMS efficacy used this site. An expanded therapeutic potential was revealed when low-frequency (1Hz), right-sided TMS also demonstrated anti-depressant efficacy in a controlled trial (Klein et al. 1999). Over the last 10 years there have been nearly 40 controlled trials of TMS in depression, as a monotherapy or adjunctive treatment (Bretlau et al. 2008, Rumi et al. 2005), for both bipolar (Nahas et al. 2003) and unipolar depressed patients. Early results were mixed with regard to efficacy, but more recent studies, using greater "doses" of TMS, have demonstrated significant effects (Gross et al. 2007). An analysis of treatment parameters associated with optimal TMS outcomes in patients with depression revealed that generally longer courses (≥10 days), higher-intensity stimulation (percentage of energy relative to MT) and a greater number of pulses per day yield superior results (Gershon et al. 2003) In light of the expanding evidence base regarding optimal TMS stimulation parameters, and the incorporation of increasingly sophisticated clinical trial design features over the last decade of TMS treatment development, meta-analytic strategies have proven particularly useful for summarizing efficacy data for depression (Schutter 2009, Gross et al. 2007, Slotema et al. 2010). A recent meta-analysis that included data from 34 studies with parallel, double-blind, sham-controlled designs of TMS for depression (n=751 TMS and n=632 sham) generated a mean weighted effect size of 0.55 for active versus sham TMS ($p<.001$) Slotema et al. 2010). TMS monotherapy emerged as more effective than adjunctive TMS with antidepressant medications, perhaps owing to degree of treatment resistance in the study samples.

Results of a large, randomized, double-blind, multicenter industry-sponsored trial of high-frequency left-sided TMS monotherapy of 325 medication-free patients with major depression (O'Reardon et al. 2007b) were used for FDA review and approval of a device in 2008. In this study, TMS was delivered to left DLPFC 5 times per week for 4–6 weeks at 10 pulses/second, 120% of MT, for a total of 3000 pulses/session. Patients were minimally to moderately treatment-resistant, having failed to respond to at least one but no more than four antidepressant medication trials during the current depressive episode. In the evaluable sample (n=301), active TMS was superior to sham on the primary outcome measure at week 4, and on the secondary outcome measure at weeks 4 and 6. The initial blinded phase of this study resulted in a 24.5% response rate for TMS compared with 13.7% for the sham group. The effect size of TMS treatment in this blinded phase was similar to that seen for currently available antidepressant medications (0.55 and 0.49, respectively) (Demitrack and Thase 2009). At the end of the acute-phase portion of this trial, patients who did not respond to stimulation were invited to cross over to an open-label TMS trial with a similarly designed 6-week period of treatment (Avery et al. 2006). Patients remained blinded to their original treatment to generate data for comparing acute TMS responders (i.e. patients originally assigned to sham stimulation) to late responders (i.e. those initially assigned to active treatment who did not respond). A third phase of the study allowed for the transition of TMS into a 24-week continuation phase, with antidepressants initiated for maintenance and TMS re-introduction sessions given if symptoms worsened (Janicak et al. 2010). Patients showing 25% improvement from baseline during active treatment were tapered off TMS over 3 weeks while simultaneously initiating maintenance antidepressant

pharmacotherapy. During 6 months in a naturalistic follow-up study, TMS was readministered if patients met pre-specified criteria for sub-threshold symptom worsening; 38% of the sample met this criterion and received "booster" TMS sessions. For patients who started to slip and got reintroduction TMS, 84% re-achieved symptomatic benefit with the adjunctive stimulation. Of the original sample entering this durability study, 10% relapsed, i.e., met full threshold diagnostic criteria for major depressive episode (Kaplan-Meier survival estimate=12.9%) (Janicak et al. 2010). Safety and tolerability of TMS delivered as adjunctive therapy to medications appeared similar to that reported for acute TMS monotherapy (Janicak et al. 2008). Results from the open crossover study showed somewhat better outcomes than those observed in the blinded acute phase, especially in the sham-to-TMS group (42–43% response and 20–27% remission) (Avery et al. 2008). Of the group who had received, but not responded to active TMS in the preceding randomized controlled trial, 26% became "late responders" (during weeks 6 to 12 of TMS 5 times/week), indicating that some patients may benefit from extended courses of TMS therapy.

In a subsequent analysis of data from this same clinical trial, shorter duration of current depressive episode, lack of co-morbid anxiety, higher baseline depression severity and less severe treatment resistance (as measured by number of past failed adequate antidepressant trials) predicted superior antidepressant response to TMS (Lisanby et al. 2009). Ultimately, data describing outcomes for a subset (n=164) of this larger clinical trial were submitted to the FDA, resulting in approval of the Neuronetics' device for TMS therapy for treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior medication, at or above the minimum effective dose and duration in the current episode. For this smaller clinical study population, separation of active TMS from sham on the primary efficacy measure was highly significant at four weeks (p=.0006) (Demitrack and Thase 2009).

Results of the previously-described industry trial were subsequently replicated by a similarly designed, 4-site, randomized, controlled trial sponsored by the National Institutes of Health that evaluated the efficacy of daily (5x/week) high-dose left LPFC TMS, using the same stimulation parameters, in 190 patients with MDD (George et al. 2010). The initial blinded acute phase of 3 weeks (15 sessions, 3000 pulses per session) could be extended for up to 3 more weeks for clinical improvers, but daily TMS ended when subjects didn't show progressive improvement or when they met remission criteria. For this phase, the remission rate of 14% for active TMS was statistically superior to 5% remission in the sham group; response rates were very similar to remission rates (15% for active TMS and 5% for sham). The number needed to treat was 12. As in the previous study, most remitters had lower antidepressant treatment resistance. The design for the NIMH-sponsored trial also allowed patients who failed to respond after the first 3 weeks to cross over to an open-label, non-controlled phase in which they continued blinded to the original treatment. In the open label phase, the remission rate was 30%, which is less than desired from a treatment that requires daily intervention for at least 3 weeks. However, the 30% remission rate for TMS compares favorably with the outcomes reported for patients with similar levels of pharmacoresistance randomized to undertake a new antidepressant medication trial (George et al. 2010). Also akin to the findings from previous study, George and colleagues found a subset of patients who appear to require a longer course of daily acute TMS therapy, as 30% of the patients who initially received 3-weeks of active treatment went on to achieve remission during 3-week open extension phase. Active TMS was again extremely safe and well tolerated, leading the authors to suggest that future studies consider higher doses of stimulation in their efforts to further optimize the therapy.

Laterality and frequency have emerged as important TMS efficacy parameters. Both right- and left-sided cortical regions have been investigated as therapeutic targets in TMS research. Low frequency, right-sided TMS demonstrated comparable efficacy with high frequency left-sided treatment in a randomized trial (Fitzgerald et al. 2009d), and nonresponders to right-sided TMS subsequently achieved clinical benefits when exposure to a course of left-sided treatment (Fitzgerald et al. 2009c). A meta-analysis measuring the efficacy of slow-frequency TMS comprising nine double-blind, controlled studies (n=252) generated an overall weighted moderate mean effect size (d=0.63, 95% confidence interval=0.03–1.24), suggesting low-frequency TMS, at least when delivered over the right cortex, may be equally effective as high-frequency TMS for MDD (Schutter et al. 2010).

Researchers continue to explore ways to enhance TMS efficacy for depression through manipulation of pulse frequency and coil position. Fitzgerald and colleagues investigated the sequenced, combination application of TMS with bilateral/multi-frequency stimulation in a 6-week, sham-controlled protocol that delivered slow TMS over the right DLPFC followed by fast TMS over the left during each treatment session. The sequenced/bilateral TMS group achieved a 44% response and 36% remission rate, compared with 8% and 0%, respectively, for the sham group (Fitzgerald et al. 2006). Another study of sequenced bilateral/multi-frequency TMS, using 20 Hz on the left and 1-Hz stimulation on the right side, also demonstrated efficacy superior to sham in a randomized trial (Garcia-Toro et al. 2006). When a contralateral sham was introduced to evaluate the potential additive effect of bilateral/sequential TMS relative to unilateral stimulation (Pallanti et al. 2010), the investigators found only unilateral (right, 1-Hz) TMS emerged as superior to sham stimulation (30% versus 5% remitters), and the bilateral/sequenced TMS delivery was not statistically effective (10% remitters) compared with sham. The use of a brief course of low-intensity, 6-Hz stimulation for "priming" immediately before delivery of low-frequency, right-sided TMS treatment was found to produce a significantly greater reduction in depression scores, relative to a sham condition (Fitzgerald et al. 2008). Other novel TMS stimulation techniques currently under investigation for their therapeutic potential for depression include theta-burst stimulation (TBS) (Chistyakov et al. 2010), and deep (20-Hz)

stimulation of prefrontal cortex with a novel "H-coil" device (Levkovitz et al. 2009). TBS consists of short bursts at 50–100 Hz stimulation frequency that are repeated at 5 Hz ("theta frequency"), applied in a continuous or intermittent delivery protocol (Grossheinrich et al. 2009, Lefaucheur et al. 2008).

The literature presents conflicting evidence on the antidepressant efficacy of TMS versus ECT. A meta-analysis including 6 studies (n=215) found more favorable results with ECT compared with TMS, with a weighed effect size of 0.47 (P=.004); heterogeneity was moderately low, raising some concern regarding the validity of the pooled estimate of effect size (Slotema et al. 2010). One study reported low response and remission rates for both TMS (50% and 10%, respectively) and ECT (40% and 20%, respectively) in a medication-free, non-psychotic sample of patients with refractory depression (Rosa et al. 2006), and another produced similar response rates for the two treatments when analyses were limited to non-psychotic patients (55% with TMS and 60% with ECT) (Grunhaus et al. 2003). Six-month relapse rates did not differ between TMS and ECT in a study where both groups transitioned to maintenance antidepressant medication (Dannon et al. 2002). The only investigation to date comparing ECT with right-sided low-frequency TMS showed TMS was less effective, but also produced fewer adverse effects on cognitive function, than ECT (Hansen et al. 2010). More studies will be needed to evaluate the relative efficacy of TMS and ECT and to optimally position TMS in a treatment algorithm for depression. Treatment of depression in the pregnant or post-partum woman may be a particularly compelling indication for TMS, owing to the lack of systemic side effects and promising pilot study results (Kim et al. 2009, Garcia et al. 2010).

In general, TMS is safe and well tolerated. Common side effects from the Neuronetics' clinical trial, such as application site pain, muscle twitching, toothache, and discomfort in the facial/eye area, generally were mild-to-moderate and rapidly accommodated by patients (Janicak et al. 2008). The most significant potential risk associated with the therapy is inadvertent seizure induction. Remaining within the recommended stimulation parameters, however, confers a margin of safety that should be combined with careful screening for underlying organic brain disease (Wassermann et al. 1998). Overall, the risk of an unwanted seizure appears to be less than 1 per 1000 TMS sessions, and compares favorably to the risk of seizures with marketed antidepressant drugs such as bupropion and tricyclic antidepressants (Janicak et al. 2008). Because the TMS device emits clicking sounds with each train of magnetic pulses, there is the potential for adverse effects on hearing, and mild but generally transient and clinically insignificant shifts in auditory thresholds have occurred (Pascual-Leone et al. 1992). To minimize auditory risks patients often wear earplugs or headphone earbuds during the procedure. Induction of mania is not a widely recognized side effect of TMS, but case reports of switching into mania have been described (Dolberg et al. 2001, Xia et al. 2008). The only absolute contraindication for TMS is the presence of metallic hardware in close contact to the discharging coil, such as cochlear implants, internal generators that are physiologically controlled, or medication pumps (Rossi et al. 2009).

TMS is non-invasive, does not require anesthesia or surgery, and is typically performed on an outpatient basis. Patients are not sedated during a TMS treatment and can usually leave and drive a car immediately afterward without a recovery period. Overall, due to its ease of use, favorable tolerability profile and benign cognitive profile, TMS offers a potential viable alternative for patients who are unable to tolerate antidepressant treatment or who would otherwise have no treatment option besides ECT.

Vagus nerve stimulation (VNS)

In 1938, Bailey and Bremer (Bailey and Bremer 1938) described the synchronized activity of the orbital cortex produced by stimulation of the vagus nerve in cats in one of the first published reports suggesting that vagus nerve stimulation (VNS) directly affected central function. Dell and Olson also noted slow-wave response to VNS in the anterior rhinal sulcus and amygdala in awake cats with high cervical spinal section (Dell and Olson 1951). Primate studies provided evidence of VNS effects on basal limbic structures, thalamus, and cingulate (MacLean 1990). Based on these findings, and applying standard electrical engineering principles, Zabara hypothesized that VNS would have anticonvulsant actions (Zabara 1985a, Zabara 1985b). Observations of VNS-induced cortical EEG changes and seizure cessation in dogs suggested mechanisms impacting both direct termination of an ongoing seizure as well as seizure prevention (Zabara 1992). Following this basic pilot work, VNS was further developed as an adjunct treatment for seizure disorders, leading to approval by the FDA for the treatment of pharmacoresistant epilepsy in 1997. VNS therapy consists of repetitive, cyclical electrical stimulation applied to the vagus nerve (cranial nerve X) in the left cervical region, by a surgically implanted device that looks similar to a cardiac pacemaker.

Mood elevations serendipitously observed in epilepsy patients initially prompted VNS researchers to more systematically examine possible effects of VNS on emotional health (Handforth et al. 1998, Elger et al. 2000, Ben-Menachem et al. 1994, Harden et al. 2000). In turn, prospective clinical trials were conducted to evaluate the efficacy of VNS in depressed patients who had not benefitted from multiple standard antidepressant treatments. The prospective investigation of VMS effects in depressed patients generated data (reviewed below) that resulted in the FDA approval of VNS as an adjunct therapy for treatment-resistant major depression in July of 2005.

In addition to observed mood-elevating effects of VNS in patients with epilepsy, the rationale for investigating VNS as a possible treatment for depression is based on preclinical investigation of VNS in animal models demonstrating the direct effects of VNS on central cortical function (Naritoku et al. 1995), and on human neuroimaging data demonstrating that VNS affects the function of various important limbic structures (Henry et al. 1999, Ko et al. 1996). Furthermore, the established efficacy of anticonvulsant

medications as mood stabilizers in mood disorders (Ballenger and Post 1980, Calabrese et al. 1999, Post et al. 1998) provides an additional link between the two therapeutic areas. Investigations in both animals and humans show that VNS alters concentrations of neurotransmitters implicated in mood disorders (i.e. serotonin, norepinephrine, gamma aminobutyric acid, and glutamate) within the central nervous system (reviewed in detail below). VNS is thought to improve mood via ascending projections through the nucleus tractus solitarius to the parabrachial nucleus and the locus coeruleus (Krahl et al. 1998). This is the site of many norepinephrine-containing neurons that have important connections to the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions linked to mood and anxiety regulation (Van Bockstaele et al. 1999).

The effects of VNS on the brain have been studied using a variety of neuroimaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) (Chae et al. 2003, Conway et al. 2006, Nahas et al. 2007). Garnett and colleagues (Garnett et al. 1992) showed that left VNS in epilepsy patients caused increased rCBF in the ipsilateral anterior thalamus and the cingulate gyrus. Others (Ko et al. 1996) found VNS increased blood flow in the contralateral thalamus and posterior temporal cortex, and in ipsilateral putamen and inferior cerebellum. Both acute and chronic effects of VNS have been demonstrated in the brain (Henry et al. 1999, Henry et al. 2000, Henry et al. 1998a, Henry et al. 1998b). High level (500 ms, 30 Hz, 30 s on, 5 min off, mean 0.5 mA) left VNS stimulation increased the blood flow to rostral and dorsal medulla oblongata as well as to bilateral orbitofrontal gyri, right entorhinal cortex and right temporal pole in epilepsy patients, whereas both high and low level (130 ms, 1 Hz, 30 s on, 180 min off, mean 0.85 mA) stimulation increased blood flow to the right thalamus, right postcentral gyrus, bilateral inferior cerebellum as well as to bilateral hypothalamus and anterior insula. Decreased blood flow was observed to the bilateral amygdala, hippocampus, and posterior cingulate gyrus (Henry et al. 1998a, Henry et al. 1998b). In patients with depression, acute VNS-induced rCBF changes were also seen in brain regions and structures associated with depression and with the afferent pathways of the vagus nerve (Conway et al. 2006), and blood oxygenation level dependent (BOLD) signal showed a pattern of deactivation in ventro-medial prefrontal cortex that correlated with antidepressant response to VNS therapy (Nahas et al. 2007).

Various SPECT studies (Ring et al. 2000, Van Laere et al. 2000, Vonck et al. 2000) have demonstrated a role for VNS in thalamic activity, with limbic hyper-perfusion and chronic thalamic hypo-perfusion correlating with positive clinical efficacy in an epilepsy sample (Vonck et al. 2008). Researchers have also reported rCBF changes in multiple limbic structures following 4 weeks of VNS in patients with depression (Zobel et al. 2005). Decreased activity in cingulate gyrus, an area implicated in the pathoetiology of depression, has been associated with symptom relief in various studies (Bremner et al. 1997, Ebert et al. 1994, Mayberg et al. 1997). Therefore, modulation of activity in the cingulate gyrus by VNS, along with VNS effects on the activities of the brainstem, limbic system and other central nervous system areas, implicates a similar mechanism for VNS antidepressant activity (George et al. 2000).

Both clinical and animal studies have shown that VNS induces cellular and neurochemical changes in the central nervous system, suggesting additional possible mechanisms of antiseizure and neuropsychiatric effects of VNS (reviewed by Nemeroff et al. 2006). Studies in rats undergoing VNS reveal increases in cellular activity, as measured through the oncogene C-fos level, in amygdala, cingulate, locus coeruleus (LC), and hypothalamus (Naritoku et al. 1995). An investigation into the modulatory effect of VNS on the development of long-term potentiation (LTP) in the dentate gyrus found VNS modulates synaptic plasticity in the hippocampus (Zuo et al. 2007). VNS induced an increase in the number of available progenitor cells in the adult rat dentate gyrus by a mechanism presumably involving increased progenitor proliferation. Preclinical work has also demonstrated modulation of serotonin (Dorr and Debonnel 2006), norepinephrine (Krahlet al. 1998), g-aminobutyric acid (GABA), and glutamate (Walker et al. 1999). Results from a study of sleep and EEG activity in cats revealed VNS-associated effects on sleep architecture changed during different stages of the sleep-wakefulness cycle (Valdes-Cruz et al. 2008). A study of lumbar cerebrospinal fluid (CSF) analytes in epilepsy patients sampled before and after 3 months of VNS showed significant increases in CSF concentrations of GABA and trend-level decreases in glutamate (Ben-Menachem et al. 1995). Other provocative findings from CSF studies are VNS-induced increases in levels of the major metabolite of dopamine, homovanillic acid (Carpenter et al. 2004), and the major metabolite of serotonin, 5-hydroxyindoleacetic acid (Ben-Menachem et al. 1995), although no changes were observed in CSF levels of the peptide Substance P (Carpenter et al. 2008) when a 3-month course of VNS was administered to patients with treatment resistant depression.

Additional data on the mechanisms by which VNS impacts brain come from a rodent electrophysiology study showing increased basal firing rates of dorsal raphe nucleus and LC following long-term VNS treatment (Dorr et al. 2006). In a related line of research, responders to VNS exhibited enhanced P300 response to auditory evoked potentials (Neuhaus et al. 2007). Several studies have identified an impact of VNS on inflammatory processes (Li and Olshansky 2010, Majoie et al. 2010). While these and other data appear to provide converging lines of evidence that VNS exerts measurable effects in brain regions and neurotransmitter systems implicated in mood disorders, a putative VNS antidepressant mechanism of action remains obscure (Nemeroff et al. 2006), as it does for other neuro-modulation therapies.

VNS surgery is considered a procedure of low complexity and is typically performed in an outpatient surgical setting with general anesthesia. A pulse generator (pacemaker-like device) is implanted subcutaneously into the left wall of the chest, posteriorly towards the axilla and is connected to bipolar electrodes, which are attached to the left vagus nerve within the

neck. Two small incisions are made, one in the left neck and one in the left chest wall. A tunneling tool is used to connect the lead wires deep subcutaneously between the pulse generator site in the chest and the place of attachment on the vagus nerve. After a 2-week post-surgical recovery period, the device is turned on and stimulation is titrated to optimal treatment levels. Stimulus "dosing" – including selection of intensity, frequency, pulse width, duration "on" per cycle, and duration of "off interval" – is non-invasive and adjusted by an external telemetric wand. A typical programming cycle consists of 30 seconds of stimulation followed by a 5-min off-period (Labiner and Ahern 2007). VNS "dose" adjustments occur in the outpatient office setting, which allows the patient and physician to observe and address stimulation-related side effects prior to the patient returning home.

The safety of VNS is well established from its use in the treatment of epilepsy (Ben-Menachem 2010). In total, >80,000 patients have been implanted with the VNS device worldwide since the 1990s (Cyberonics, Houston, TX, USA; personal communication). The side effects of VNS are generally mild and are associated with stimulation (i.e. the "on" phase of the cycle). Voice alteration/hoarseness, dyspnea, and neck pain were the most frequently reported adverse events in a long-term follow-up study of VNS in patients with depression (Rush et al. 2005a). One study reported two cases of persistent vocal cord palsy (Corcoran et al. 2006) and other VNS-induced vocal cord movement abnormalities could increase risk for aspiration in some cases (Fahy 2010). Patients with sleep apnea may require additional monitoring (Papacostas et al. 2007) with VNS, though adjustments in stimulation pulse width and frequency can be performed to manage many side effects and to optimize therapy (Labiner and Ahern 2007). VNS has been safely combined with ECT (Burke and Husain 2006), and does not appear to cause cognitive impairment.

Published data supporting the antidepressant efficacy of VNS come from open-label and naturalistic studies where the neuromodulation therapy was added to ongoing regimens of psychotropic medication. In an open-label pilot study, 60 patients with treatment-resistant major depressive episodes who had not responded to at least two trials of medication from different antidepressant classes received 12 weeks of adjunctive VNS (Sackeim et al. 2001). Response rates ranged from 31–37%, depending on the scale used. The most common side effect was voice alteration or hoarseness, which was generally mild and related to output current intensity. A naturalistic follow-up study was conducted to determine whether the initial promising effects were sustained in a subgroup (n=30) following exit from the 3-month acute study (Marangell et al. 2002). At 1-year follow-up, response rates for the subgroup were sustained (40–46%) and remission rates significantly increased (17–29%), although psychotropic medications and VNS stimulus parameters varied during the follow-up interval. Subsequent follow-up data from a larger number (i.e., 59 patients from the original pilot study cohort who completed the acute phase study and continued with adjunctive VNS) demonstrated a response rate of 44% at 1-year, which was largely sustained (42%) after 2 years of active treatment (Nahas et al. 2005). Remission rates demonstrated a similar pattern, rising from 15% at 3 months to 27% at 1-year follow-up, then holding fairly steady at 22% after 2 years of stimulation. Following these promising open-label pilot study results, a larger controlled trial was undertaken.

The large (n=235), randomized, sham-controlled, multicenter study of adjunctive VNS did not find a significant difference in acute-phase response between active and sham groups (15% and 10%, respectively) at the 12-week endpoint (Rush et al. 2005b). However, open-label follow-up observations of this cohort over the subsequent year suggested a cumulative beneficial effect of treatment over time (Rush et al. 2005a), leading to speculation that positive VNS response requires more time than that typically seen with antidepressant medications and ECT. While the patients initially receiving active VNS continued with ongoing active stimulation for another 9 months after the blinded acute phase, those who had been randomized to the sham group crossed over to receive 12 months of active VNS. All participants received antidepressant treatments and active VNS, both of which could be adjusted. Data from this open-label study revealed response rates of 27–34% and an open-label remission rate of 16% at one year (Rush et al. 2005a).

Since the short-term/acute study results were negative, and the extended/long term open-label study results were promising, investigators set out to better understand the long-term effects of VNS when combined with community treatment-as-usual (TAU) over 12 months (n=205). These outcomes were compared with those measured in a demographically and clinically similar group of patients with treatment-resistant depression who received TAU only (without VNS; n=124) in a non-randomized, naturalistic cohort study (George et al. 2005). An analysis comparing the VNS+TAU group (monthly data) with the TAU only group (quarterly data) on scores from a standard self-report depression symptom scale showed adjunctive VNS to be associated with significantly greater improvement per month than TAU across 12 months; 1-year response rates were 27% for VNS+TAU and 13% for TAU, suggesting greater antidepressant benefit in VNS patients (George et al. 2005). Review of these (nonrandomized) data led to FDA approval of adjunct VNS in 2005, with an indication for treatment of chronic or recurrent depressive episodes in both bipolar and unipolar types of affective disorder.

Subsequent 24-month follow-up data from study patients treated with adjunct VNS therapy found a decline in suicide attempts, diminished levels of suicidal ideation, and fewer hospitalizations for worsening depression over time (Burke and Moreno 2006). 77% of VNS recipients identified as early responders (i.e. by 3 months) and 65% of late responders (i.e. by 12 months) maintained their response at the 24-month assessment (Sackeim et al. 2007), with data confirming sustained response in a subsequent 2-year naturalistic VNS study in Europe (Bajbouj et al. 2010) . In the European study, 74 with therapy-resistant depression (Bajbouj et al. 2010) were assessed after 3, 12, and 24 months, yielding a 53% response and 39% remission rate at study endpoint. Thus, while modest response and remission rates appear to accompany VNS therapy

for depression, available data suggest a high level of durability of response for those who experience clinical benefits. Widespread access to VNS for patients with treatment resistant depression has been limited by lack of coverage by third party payers, despite FDA approval and data suggesting that potential reductions in healthcare costs with VNS for some patients with severe depression may be substantial (Warnell and Elahi 2007).

A double-blind, randomized, multisite controlled trial ("D-21") designed to further evaluate VNS antidepressant efficacy and relationships between clinical response and stimulation parameters (n=331) was requested by FDA at the time of device approval, sponsored by the manufacturer and recently completed. While the data had not been subjected to peer-review and published at the time of this writing, the company made preliminary results public though a press release (Cyberonics' May 27, 2010). Patients were randomized to receive one of three stimulation levels (low, medium or high) of adjunct VNS during a 22-week acute phase, after which stimulation levels could be increased. There was no differentiation of efficacy outcomes across the three dose groups at 22 weeks, but the response and remission rates after 50 weeks of treatment were generally consistent with those generated by previous naturalistic studies of VNS,48% and 21%, respectively. Durability of the benefits was confirmed by data showing that 81% of patients achieving response by 22 weeks maintained response at 50 weeks.

One recent effort to explore the potential benefits without the risks related to surgery and implantation of hardware was described by investigators who used a non-invasive, transcutaneous method to stimulate vagal afferents via electrical stimulation of the nerves in the left outer auditory canal in healthy subjects (Kraus et al. 2007) in a feasibility study. Compared with earlobe stimulation as a sham comparator, fMRI revealed BOLD-signal decreases in limbic brain areas induced by transcutaneous VNS (t-VNS), while increased activation was seen in the insula, precentral gyrus and thalamus. Psychometric assessment revealed significant improvement of well-being after t-VNS, and earlobe stimulation as a sham control intervention did not show similar effects on fMRI or mood ratings (Kraus et al. 2007). Once VNS device implantation surgery has occurred, programming the stimulation parameters for the therapy is a simple, office-based procedure that could be readily incorporated into a psychopharmacologist's routine practice.

Deep brain stimulation (DBS)

DBS is an FDA-approved treatment for tremor in Parkinson's disease, essential tremor and dystonia. While it is estimated that over 60,000 patients worldwide have received DBS for movement disorders since 1997 (Medtronic website http://www.medtronic.com/your-health/obsessive-compulsive-disorder-ocd/getting-therapy/index.htm), the treatment remains investigational for all psychiatric disorders except Obsessive-Compulsive Disorder (OCD). The FDA approved a Humanitarian Device Exemption (HDE) for DBS therapy in patients with chronic, severe, treatment-resistant OCD in February of 2009. Since it requires invasive neurosurgery and associated risks, and does not have the requisite data establishing efficacy and safety for mood disorders, DBS is currently reserved for patients with the most severe and treatment refractory depression in research protocols. Pilot studies of DBS for depression have typically included patients who have failed multiple antidepressant treatment courses from multiple pharmacological classes, psychotherapy, and ECT.

Surgery to implant DBS devices occurs in two phases, which may or may not take place on the same day. First, electrodes are inserted through burr holes in the skull under general anesthesia. These electrodes are placed into targeted subcortical areas, often guided by sterotactic positioning and brain imaging. After implantation and successful testing, the electrodes are connected with lead wires that are tunneled subdermally under the scalp, neck, and chest wall areas to pacemaker-like pulse generators bilaterally. As with VNS, adjustment of DBS parameters is performed via computer-controlled telemetric wand.

To date, several anatomical targets have been investigated with DBS for depression. The rationale for DBS delivered to the subgenual cingulate gyrus (SCG) stemmed from the influential neurocircuitry model of depression that has been advanced by Mayberg (Mayberg et al. 1997). This is based on functional neuroimaging studies of regional brain metabolic activity in the depressed mood state and changes in the activity of Brodmann Area 25 (BA25) following successful antidepressant response (Mayberg 2002, Mayberg 2003, Giacobbe and Kennedy 2006). A pilot study of chronic DBS to BA25 in six patients with refractory depression revealed robust remission in four (67%), corresponding with PET reductions in rCBF locally and rCBF changes in downstream limbic and cortical sites (Mayberg et al. 2005). An extension study, with sample expansion beyond this initial cohort of depressed patients (n=20) showed 60% response and 35% remission at six months (Lozano et al. 2008).

Based in part on mood improvements observed in a pilot study of OCD patients receiving DBS applied to the ventral portion of the anterior limb of the internal capsule and adjacent dorsal ventral striatum (Greenberg et al. 2004), this ventral capsule/ventral striatum (VC/VS) target has also been investigated for DBS treatment in refractory depression (Greenberg and Rezai 2003, Greenberg 2003). Data from 15 depressed patients receiving continuous open DBS to the VC/VS (6 months to 4 years of follow up) showed significant improvements in depressive symptoms and global functioning and tolerated the treatment well; 40% of patients met criteria for response at 6 months, and 53% at last follow up, with corresponding remission rates of 20% at 6 months and 40% at last visit (Malone et al. 2008).

Treatment of OCD with DBS to the VC/VS is supported by data from several studies in patients with severe and disabling obsessive-compulsive symptoms that were not responsive to pharmacotherapy (Greenberg et al. 2006, Gabriels et al. 2003, Greenberg et al. 2008). Neuroimaging studies have shown dysfunction in the orbitofrontal and anterior cingulate cortex, striatum, and thalamus in such patients, and acute DBS at the VC/VS target is associated with

activation of this circuitry (Rauch et al. 2006). Pilot study data describing 36-month outcomes in 8 OCD patients revealed four of them had positive response (35% or greater decrease on OCD symptom scale scores) to DBS of the VC/VS, while two more showed less robust (i.e., between 25 and 35% drop from baseline scores) improvement (Greenberg et al. 2006).

Data from both clinical investigations and studies of the neurophysiological effects of DBS are supportive of the notion that chronic electrical stimulation of the brain exerts both immediate and long-term effects on neuronal firing rates and patterns (Johnson et al. 2008). Arising from the clinical observation that the effects of DBS in Parkinson's disease mimicked those of ablative neurosurgical procedures (Benabid et al. 1987), it has been hypothesized that DBS created a reversible lesion by inhibiting the neurons being stimulated, perhaps through its effects on voltage-gated sodium (Beurrier et al. 2001) and potassium channels (Shin and Chetkovich 2007). Alternatively, it has been suggested that DBS may exert its effects via "jamming" pathological neuronal signals thereby preventing such activity from being propagated to other parts of the brain (Grill et al. 2004).

A strong preclinical rationale supports the nucleus accumbens (NAcc) as target for DBS in depression. The NAcc is uniquely situated; its shell projects to limbic brain areas, including the SCG, while the NAcc core is connected to the extrapyramidal motor system, so modulating NAcc activity may thus serve to improve both the hedonic and motoric symptoms of depression (Giacobbe and Kennedy 2006). In animal models, stimulation of the NAcc generates hedonic properties, resulting in increased exploratory behavior and food intake. Animals readily learn operant tasks to increase the rate of electrical pulses delivered to the NAcc (van Kuyck et al. 2007). As emphasized in several reviews (Kopell and Greenberg 2008, Nestler and Carlezon 2006), its rich dopaminergic projections make NAcc a focus of both human and animal studies linking dysfunction in this brain region with impaired reward processing seen in depression (Tremblay et al. 2005). Accordingly, a double-blind pilot study of DBS to rostral area of NAcc (n=3) showed immediate depressive symptom improvement when stimulation was active and subsequent worsening when the stimulation was turned off; PET images demonstrated significant changes in brain metabolism as a function of the stimulation in fronto-striatal networks (Schlaepfer et al. 2007). Five (50%) of 10 patients receiving bilateral DBS to NAcc responded at 12 months, with no cognitive impairment and notable improvements observed in hedonic drive and anxiety (Bewernick et al. 2010). PET scans for this sample showed decreased activity in prefrontal subregions and an isolated increase in the precentral gyrus.

A case report of a patient with long-standing treatment-resistant depression showing robust response after 4 months of DBS of the lateral habenula, a juncture of the monoaminergic systems and limbic regulatory cortex that has been found to be overactive during depressive states, suggests this target may also hold promise for future treatment protocols (Sartorius 2010).

There are several major limitations of DBS. The risks for neurosurgery are high and include intraoperative seizure, intracranial hemorrhage, edema, infection and death (Greenberg et al. 2004, Greenberg et al. 2006). Hardware malfunctions either during or post-implantation may also be a limiting factor, and batteries require replacement every 1-3 years (Abosch and Lozano 2003). As in VNS, implanting the generator may be disfiguring, depending on the location of the generator and body habitus. Common transient side effects of DBS may include dose-dependent lightheadedness, insomnia, hypomania, and psychomotor changes, but DBS trials thus far do not suggest adverse cognitive side effects (McNeely et al. 2008). There are very limited data on long-term DBS outcomes, a particularly salient issue given the permanence of the implanted device and the relatively young age of some patients with pharmacoresistant depression. While the available pilot study results suggest a fairly benign profile and promising outcomes in open-label treatment research settings, the small numbers of patients enrolled in these early studies preclude definitive statements about the appropriate placement of DBS therapy in the treatment algorithm for depression.

In addition to the lack of solid evidence base, DBS carries more surgical risk than VNS. However, following implantation of the DBS device, programming procedures to adjust dose and monitor the functioning of the system can be done as office-based procedures.

Magnetic seizure therapy (MST)

MST consists of the noninvasive administration of high-frequency, high-intensity magnetic fields, under a general anesthetic with a coil placed on the head, to induce electrical currents confined to the superficial cortex. Using a device similar to those used for TMS therapy, the goal of MST is to produce a therapeutic focal seizure targeting brain circuits involved in the pathogenesis of depression, while sparing cortical regions implicated in the cognitive adverse side effects observed with ECT (Lisanby et al. 2003, Lisanby et al. 2003, Hoy and Fitzgerald 2010,). MST requires stimulation at a frequency greater than 40 Hz, delivered in trains of relatively long duration (2 and 6 seconds), which is not possible with standard TMS therapy coils. A new device was developed to provide magnetic energy for MST at a dose of 100 Hz, in 10-second duration trains, after earlier work with the technology suggested that a more limited stimulus output might compromise efficacy, and that the higher "dose" would be needed to overcome the anticonvulsant effect of anesthesia (Rowny et al. 2009a).

Neurophysiological characterization of nonhuman primates with EEG tracings showed that relative to shock with ECS, MST produced less robust postictal power and ictal expression patterns associated with shorter time to complete an orientation task after seizure (Cycowicz et al. 2009). The differential physiological response observed with MST suggests it has a more superficial cortical site of action, relative to ECT, indicating that MST-induced seizures are less generalized to deep brain structures (Rowny et al. 2009b).

Treatment depression in the first human subject with MST revealed shorter seizures and faster

orientation recovery times, compared with that typically produced by ECT (Kirov et al. 2008), and a double-masked controlled trial of MST (50 Hz, 100% MT, 8 seconds duration), comparing different coil types and scalp locations demonstrated different seizure thresholds for the coils, and vertex was superior to prefrontal coil position. Depression scores significantly improved, and 53% had at least a 50% improvement. Also, MST was associated with a better cognitive side effect profile and with a smaller dose of anesthetic required, when compared with simultaneously treated patients receiving ECT (Lisanby et al. 2003a). Clinical trials are being conducted around the world to compare the efficacy of MST with ECT for the treatment of depression, as well as to investigate optimal coil position.

Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a noninvasive method of brain stimulation that involves the application of a low amplitude (1-2 mA) direct current to the brain via two small electrodes (size between 25 and 35 cm^2) placed on the scalp for up to 20 minutes. Some of this current passes through the scalp and induces changes in cortical excitability, with an increase in excitability produced under the anode, due to neuronal depolarization, and a decrease in excitability under the cathode, due to a local hyperpolarization (Murphy et al. 2009). Modulation of neuronal resting membrane potential appears to be the primary antidepressant mechanism of action of tDCS, while the after effects might be explained by alterations of NMDA receptor efficacy initiated by the membrane potential shift, and probably by the accompanying cortical activity modification (Nitsche et al. 2009). Four out of five patients receiving active tDCS had a decrease in depressive symptoms in a pilot study (mean 60% improvement), while there was no response in patients treated with sham stimulation (Fregni et al. 2006). In an expanded cohort of 40 patients with major depressive disorder, active left prefrontal tDCS resulted in a greater average clinical response (40% average reduction in HDRS, versus 21% for occipital stimulation and 10% for sham treatment); there was no worsening in cognitive function, and benefits were stable 30 days after the last stimulation (Boggio et al. 2008). Relative to observations made in patients receiving fluoxetine, clinical outcomes with tDCS were estimated to be equally robust, yet rDCS is associated with faster onset of antidepressant effect (Rigonatti et al. 2008). A recent randomized trial comparing tDCS with sham in 40 depressed patients found no adverse cognitive effects, improvement in depressive symptoms after 10 treatments in the active treatment group, but no significant difference between groups (Loo et al. 2003). Similar to TMS and DBS, future development of this neurostimulation modality will address issues such as optimal target and areas stimulation protocols, and durability of response in long-term follow up, but preliminary work suggests tDCS is safe, with the most common side effects being burning, tingling, and itching sensations at the site of the electrodes (Murphy et al. 2009, Loo et al. 2003). One case of hypomania has been reported (Arul-Anandam et al. 2010). Less common side effects include nausea, headache, concentration difficulties, visual disturbance (phosphenes), and dizziness, and safety guidelines regarding current density and electrode composition have been developed to avoid these side effects (Murphy et al. 2009). Enthusiasm for this neuromodulation therapy comes from the fact that it is inexpensive, and easy to use.

Epidural prefrontal cortical stimulation

Another neuromodulation technique in the early stages of exploration as a potential antidepressant therapy is epidural prefrontal cortical stimulation (EpCS), a system of stimulation over the prefrontal cortex with electrodes placed under the skull bone but outside the dura mater (Nahas et al. 2010). This approach is more invasive than therapies that use energy transversing scalp/skull tissues, but potentially more direct in targeting specific brain regions. Further, EpCS may be safer than DBS because electrodes don't puncture dura and penetrate brain tissue. Four of five patients with treatment resistant depression who got bilateral/prefrontal EpCS improved, and 3 reached remission by 7 month followup. One patient underwent removal of the electrodes on one side due to a scalp infection, but the rest tolerated the surgical procedure and chronic stimulation well, with no worsening of cognition (Nahas et al. 2010).

Conclusion

ECT, the first neuromodulation treatment in psychiatry, was once considered the "gold standard" therapy for pharmacoresistant depression, but cognitive side effects and limited durability of response limit its widespread use and acceptance. The emergence of alternative neuromodulation therapies with safer and potentially more durable benefits reflect a burgeoning area of research in mental health treatments. In the past decade, devices for delivery of VNS and TMS were approved. Other treatments (DBS, MST, tDCS, and EpCS) are in earlier stages of developments and testing. Clearly, refinements in device technology and further elucidation of optimal targets, stimulation parameters, and mechanisms of action are needed. Given the promising preliminary data, this specialty area of psychiatry appears to hold considerable promise and potential for the foreseeable future.

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