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Clinical overview

Neurostimulation therapies in depression: a review of new modalities

Marangell LB, Martinez M, Jurdi RA, Zboyan H. Neurostimulation therapies in depression: a review of new modalities.

Objective: In response to an increased understanding of the neurobiology of severe psychiatric disorders, new therapeutic modalities are entering clinical practice that involve the direct stimulation of the brain.
Method: We provide a review of published literature regarding the clinical use of vagus nerve stimulation (VNS) therapy, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) in psychiatric disorders, with an emphasis on treatment-resistant depression (TRD).
Results: Vagus nerve stimulation is approved for use in both the EU and US for TRD. TMS has been approved for TRD in Canada, Australia, New Zealand, the European Union and Israel, but not yet in the United States. DBS remains in the early stages of investigation.
Conclusion: While additional studies are clearly warranted, treatments that directly stimulate the brain appear to hold great therapeutic promise for severe psychiatric disorders.

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Key words: neurostimulation; vagus nerve stimulation; transcranial magnetic stimulation; deep brain stimulation; psychiatry; review

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Summations

- Long-term VNS is well tolerated and may improve the course of illness in patients with treatment-resistant depression.
- rTMS is well tolerated and likely effective in the acute treatment of TRD.
- DBS is currently in the early phases of study in psychiatry.

Considerations

- While compelling, the VNS data would be strengthened by a replication study with a randomized longer term control group. Additionally, further data are needed regarding optimal programming settings for the VNS device and predictors of response.
- Published studies of rTMS in treatment-resistant depression are limited by small sample sizes and brief durations of treatment. One fully powered 6-week trial has been presented but is not yet published and peer reviewed.

Introduction

Despite a wide variety of conventional treatment options, such as pharmacotherapies and psychotherapies, treatment-resistant psychiatric disorders are a significant source of worldwide disability (1). As a result of our increased understanding of the neural circuitry and neurobiology of major psychiatric disorders, investigators are developing new treatments that directly stimulate the brain with the goal of symptom improvement. While neurostimulation is an area of active preclinical research, this article focuses on the therapeutic aspects of neurostimulation in psychiatry, specifically vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) in treatment-resistant depression (TRD). While electroconvulsive therapy (ECT) is a brain stimulation technique with established efficacy, and is indeed the 'gold standard' for acute efficacy in TRD, we do not include ECT in this review in order to allow us to focus on newer technologies.

Aims of the study

This manuscript provides a summary of three new neurostimulation treatments in use or under investigation for TRD

Material and methods

An electronic search was conducted using PubMed and combinations of the following search terms: vagus nerve stimulation, transcranial magnetic stimulation, deep brain stimulation, treatment and major depression. Additional publications were identified from reference lists of retrieved articles. All relevant articles published in English and reporting original data were included. Small case series ($n < 5$) and individual case reports have been included only where illustrative.

Results

Each of the three technologies is presented below, including a description of the technology, rationale for use, a summary of clinical efficacy and safety data, and clinical recommendations for use.

Vagus nerve stimulation

The treatment. Vagus nerve stimulation is the first regulatory approved implanted device for the treatment of a psychiatric disorder. The treatment is administered using a pacemaker-like device that is surgically implanted in the left chest wall, where it delivers an electrical signal through an implanted lead that is wrapped around the left cervical vagus nerve (Fig. 1). The implanted pulse generator is then programmed with a telemetric wand using a laptop or handheld computer to deliver pulses to the vagus nerve, typically for 30 s every 5 min, 24 h a day or until turned off. Adjustable parameters include pulse width, signal frequency, output current, signal on time, and signal off time. Hence, the treatment itself consists of one surgical implantation procedure, typically under general anesthesia. No portion of the device is in the brain, but the intermittent stimulation of the vagus nerve provides chronic bilateral activation of brain circuits, as described below. The battery life ranges from 3 to 10 years, depending upon the parameter settings and pulse generator model (2).

Current status. In Europe and Canada, VNS has been approved for use in patients with TRD since 2001. In the United States, the FDA approved the use of VNS for TRD in July of 2005. VNS has been used since 1997 to treat epilepsy patients in the United States. Other areas of investigation in psychiatry, with only preliminary data, include anxiety disorders, rapid cycling bipolar disorder, bulimia and Alzheimer's disease.

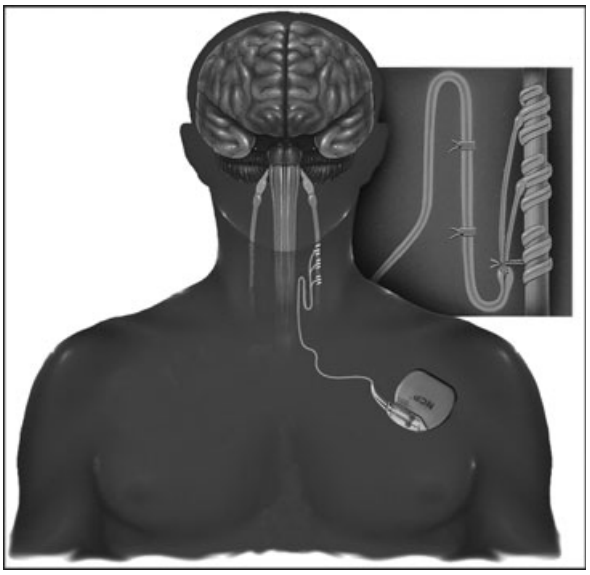

Fig. 1. The VNS generator and lead (with permission from Cyberonics, Inc.).

Rationale for use in psychiatry. The rationale for using VNS for the treatment of major affective disorders is multifactorial and our understanding of the mechanism of action is still evolving. The vagus nerve sends sensory information from the periphery to the brain, including the locus ceruleus (a major source of norepinephrine in the brain), the raphe nuclei (the main source of serotonin in the brain), and the nucleus tractus solitarious (3–5). Functional brain imaging studies indicate that VNS induces changes in regional cerebral blood flow (rCBF) that are similar to changes seen with antidepressant treatment. (6, 7).

Efficacy data. The use of VNS for TRD is based on an open pilot study ($n = 60$) (8), a randomized sham-controlled acute trial ($n = 235$) (9), and long-term follow-up of both of these cohorts (10, 11). Both the pilot study and the acute, randomized study included outpatients with chronic or recurrent depression (unipolar or bipolar) who were in a major depressive episode (MDE) and had failed adequate trials of at least two antidepressant medications from different classes in the current episode. Importantly, VNS was added to existing, stable doses of pharmacotherapy in the acute phase of the study. Following the 12 week acute treatment phase, during which both medications and

device parameters were kept stable, all eligible and consenting subjects entered long-term follow-up. Medications and stimulation parameters could be adjusted during long-term follow-up, as clinically indicated.

In the pilot study, response rates, defined as a 50% or greater reduction in the Hamilton Rating Scale for Depression score, 28-item (HRSD) (12), and remission, defined as a score of less than 10 on the HRSD, were 30.5% and 15.3%, respectively, at the end of the 12 week acute phase. After 1 year of adjunctive VNS therapy, the response rate increased to 44% and was largely sustained after 2 years of active treatment. Of note, the remission rate also improved from 15.3% after acute-phase treatment to 27% after an additional 9 months of treatment and 22% at 2 years (11).

The pivotal study was a 21-site randomized, sham-controlled study. At the end of the acute phase, the response rates on the primary outcome measure (HRSD, 24-item) were not statistically significantly different between the treatment group (15.2%) and the sham group (10.0%). However, concordant with the results seen in the epilepsy clinical trials (13), long-term follow-up of this cohort demonstrated an accrual of benefit over time. Specifically, the response rate increased from 15% at acute treatment exit to 30% after 12 months of active treatment (acute treatment phase + 9 months), and 33% after 24 months of treatment (14). Regarding durability of the clinical benefit, 70% of patients who responded to the acute treatment phase were continuing to respond to treatment at 2 years in the pilot study cohort (14). More detailed methods and study results have been published elsewhere (15–17).

Limitations of efficacy data. Few data sets exist that include longitudinal data on patients with severe treatment-resistant affective disorders, making the open long-term results difficult to interpret. Toward that end, George et al. (18) compared the outcomes of patients with very similar clinical and demographic characteristics who received treatment as usual (TAU) to those who receive VNS in the pivotal study. The investigators reported that remission and response rates were significantly higher for patients who were treated with VNS + TAU compared to patients were treated with TAU alone (response rates: 22% VNS + TAU and 12% TAU, $P = 0.029$; remission rates: 15% TAU + VNS and 4% TAU, $P = 0.006$), where response was defined as at least a 50% reduction in the Inventory of Depressive Symptomatology – Self Report (IDS-SR_{30}) (19) scores and remission was defined as an IDS-SR_{30} score of 14 or less. While these comparison data support the benefit of adjunctive VNS therapy for patients with TRD compared to TAU, it is important to note that this is a non-randomized comparison. Studies in such severely ill patients are ethically, scientifically and financially challenging. Nonetheless, an additional controlled trial, perhaps comparing VNS to best available non-VNS treatment (as opposed to community treatment or sham treatment) would be very useful.

Safety and tolerability. As described elsewhere, implantation-related adverse events in the depression trials are comparable to the larger epilepsy database and tend to be mild and short-lived (2). While rare cases of ventricular asystole have been reported when the device is tested during the implantation procedure in the operating room, no long-term negative outcomes resulted in these cases (20). The most common side-effects resulting from device stimulation of the vagus nerve are voice alteration (55%), increased cough (24%), dyspnea (19%), neck pain (16%), dysphagia (13%), laryngisimus (11%), and paresthesia (10%) (2).

Recommendations for use. Vagus nerve stimulation therapy is indicated as adjunctive treatment for adult patients with a history of recurrent or chronic depression who have failed at least four adequate antidepressant medication trials. Patients with TRD include those with both unipolar and bipolar major affective disorders. Of note, patients with rapid cycling bipolar disorder were excluded from the above studies. The effects of VNS on rapid cycling bipolar disorder are under investigation. In addition, while VNS is labeled for use in epilepsy for children 12 years of age and above, its use in children and adolescents with mood disorders has not been studied.

Data to date suggest that VNS therapy may be a viable long-term treatment option for patients with TRD. However, VNS should not be considered an emergency intervention. It is important to provide patients and families with realistic expectations regarding the potential long duration to improvement and the possibility of non-response. In addition, a thorough TRD evaluation should precede consideration of VNS in order to exclude underlying medical and/or substance use disorders that might be contributing to treatment resistance, as well as personality or psychosocial factors that might warrant a non-somatic intervention. Contraindications to VNS therapy include having a history of a bilateral or left cervical vagotomy and receiving diathermy.

Transcranial magnetic stimulation

Although initially introduced as a research instrument to assess central nerve conduction pathways, transcranial nerve stimulation was reintroduced in 1985 as a new method of noninvasive brain stimulation. The device works via the following mechanism: a rapidly alternating current passes through a small coil placed over the scalp; this generates a magnetic field that induces an electric field in underlying areas of the brain; ionic currents are generated; and neuronal depolarization occurs.

The treatment. The basic device includes a magnetic coil, a reclining chair, and a console. The coil is variously shaped depending on the TMS device, but all are fashioned to fit against the scalp. The console contains settings for the stimulus parameters, including pulse frequency (the frequency at which the magnetic field oscillates during stimulation), pulse intensity (a percentage of the motor threshold; motor threshold is currently defined as the intensity needed to elicit a motor response when the coil is placed over the motor cortex), pulse duration, inter-pulse interval, and total number of pulses per treatment session. Adjusting these parameters alters treatment effects. For example, high frequency (20 Hz) repetitive TMS (rTMS) administered over the left prefrontal cortex is associated with *increases* in rCBF in the prefrontal cortex (L > R), cingulate gyrus, (L > > R), left amygdala, bilateral insula, bilateral thalamus, bilateral hippocampus, and other limbic structures. Low frequency (1 Hz) rTMS administered in the same area is associated with *decreases* in rCBF in the right prefrontal cortex, left amygdala, left medial temporal cortex, and left basal ganglia (21).

During the treatment session the patient is awake and reclining comfortably in the chair while the magnetic coil is placed snugly against the scalp. Coil location is currently determined by identifying the motor cortex and then moving the coil 5 cm rostrally to approximate the location of the dorsolateral prefrontal cortex. Treatments can last 45 min, and can occur daily. In general, patients tolerate rTMS well and are able to resume their daily activities immediately following treatment (Fig. 2).

Current status. Transcranial magnetic stimulation has been approved for TRD in Canada, Australia, New Zealand, the European Union, and Israel, but not in the United States.

Rationale for use in psychiatry. Multiple neuroimaging studies from independent research groups have found abnormal metabolism or perfusion in prefrontal cortex of patients with major depressive disorder (MDD) (22, 23). This neuroanatomic region is easily accessible by TMS, supporting the hypothesis that TMS might modify activity in these circuits and thereby treat depression. Indeed, treatment with rTMS significantly alters rCBF in the prefrontal cortex and other brain structures involved in modulating mood, such as the anterior cingulate, thalamus, and periinsular cortex (24).

Fig. 2. TMS device (courtesy of Neuronetics, Inc., maker of the NeuroStar TMS Therapy system).

Efficacy data. Multiple blinded, sham-controlled studies evaluating the efficacy of rTMS as a treatment for depression have been completed, with many reporting that rTMS applied to the left dorsal lateral prefrontal cortex (DLPFC) significantly improves MDD symptoms (25–27). However, comparing studies is challenging because of numerous variations in how the intervention is administered. For example, while one study (26) may administer 15 daily treatment sessions each consisting of 32 (10 Hz) 5 s trains separated by 25–30 s inter-train intervals, another study (27) may deliver 10 daily sessions, each consisting of 30 (15 Hz), 2 s trains separated by 4 s inter-train intervals. Other parameters that can differ include stimulus location and intensity. Most studies examining the efficacy of rTMS as a treatment for depression focus on the left prefrontal area; however, some investigators have explored the right-hand side, and others have attempted bilateral stimulation with promising results. Stimulation of the right prefrontal cortex at 0.5–1.0 Hz yielded significant decreases in depressive symptoms in patients with MDD (28, 29). In a sham-controlled blinded trial, Fitzgerald et al. (30)

($n = 50$) explored using rTMS bilaterally in patients who suffered from MDD, and who had failed at least two antidepressants. They found a significant group by time interaction ($P = 0.005$), such that Montgomery Asberg Depression Rating Scale (MADRS) (31) scores decreased more in patients receiving active treatment (baseline: active 34 ± 5.9, sham 34.1 ± 5.2; week 6: active 8.9 ± 7.9, sham 34.5 ± 12.0). By the end of the study, 44% of the patients in the active group and 8% of patients in the sham group responded to treatment ($P < 0.05$). Thirty-six per cent of patients in the active group achieved remission, while none of the patients in the sham group achieved remission ($P = 0.005$).

Until recently, the number of subjects included in studies ranged from 2 to 71. In 2005, the largest ($n = 325$) randomized, sham-controlled trial of longest duration (6 weeks of active treatment, 3 week taper phase) was completed which explored the use of left prefrontal rTMS compared to a sham control in patients with MDD who had failed adequate treatment with one or more antidepressants. The treatment (TMS or sham) was administered for 5 days during the active treatment phase. Although the data are not published, a presentation at the 2006 American Psychiatric Association meeting (32) indicated that results are promising.

Limitations of efficacy data. The current 'placebo' for TMS studies typically entails angling the coil so the magnetic field stimulates the scalp muscles without affecting neural tissue. Clinical trials suggest that sham manipulations can affect cerebral glucose metabolism (33) and motor-evoked potentials (34, 35), which may confound results. In addition, active TMS stimulates the scalp more directly than sham TMS, and therefore, is felt more strongly by the patient, which may confound blinding.

Safety and tolerability. Transcranial magnetic stimulation is generally considered safe and without lasting adverse effects (36). Specifically, no significant cognitive (37, 38) or cardiovascular sequelae have resulted from rTMS treatment. Based on a review of papers published from January 1998 until December 2003, the most common adverse event reported with rTMS was headache, occurring in 23.6 ± 16.0% of patients (39). Of note, headaches were also reported in sham-stimulation conditions. The second most common frequent complaint was neck pain.

The primary safety concern with TMS is seizures. Although this adverse event rarely occurs, at least eight seizures have resulted from rTMS therapy. Most occurred with stimulation of the primary motor cortex using parameter settings outside of currently published guidelines, or in the presence of medications that could have potentially lowered the seizure threshold. Seizure thresholds vary from person to person and the best indicator of sensitivity is the 'motor evoked potential' or 'motor threshold', the stimulus intensity at which stimulation over the motor cortex produces a muscle twitch. Current guidelines adjust the train and inter-train interval parameters based on stimulation frequency and motor threshold (i.e., increasing the inter-train interval for higher frequencies and higher motor thresholds) (36). Although changes have been made to increase the safety of this procedure, seizures still remain a small risk and seizure precautions must be in place at treatment centers.

Recommendations for use. The most consistently successful results are from studies where the treatment is used as monotherapy, but combination treatment may be useful yet understudied. Use of TMS as an acute intervention appears reasonable in countries where it is approved. The choice of TMS as opposed to oral medications for acute MDE, including TRD, depends mostly on patient preference and treatment availability. TMS has the advantage of not being associated with systemic side-effects (e.g., sexual dysfunction, weight gain), but is less convenient as the patient must come to the device location multiple times a week. TMS may be preferred to ECT because it does not involve anesthesia and is not associated with cognitive impairment; however, it remains unclear if TMS is as effective as ECT in TRD. Finally, TMS is currently viewed as an acute treatment, as opposed to VNS and pharmacotherapy, which are more realistic long-term treatments for TRD at this time.

Deep brain stimulation

Introduction. Although it has been mostly used in patients with Parkinson's disease (PD) and essential tremor (ET), DBS has recently been gaining momentum as an alternative treatment modality for TRD. DBS has provoked depressive and manic states in individuals without psychiatric illness (40) and has improved symptoms of obsessive–compulsive disorder (41). Early theories suggested that the antidepressant effect of DBS was related to repeated stimulation leading to inactivation of overactive voltage dependent ion channels and thus reduction in impulse generation (42). However, some recent studies suggest that excitatory axonal response adds to its therapeutic effect (43).

The treatment. Several models of DBS have been developed since its emergence in the late 1980s. The device consists of a battery-powered pulse generator (IPG) implanted near the clavicle similar to pacemakers or VNS devices. One or two leads (unilateral or bilateral) are tunneled from the device(s) under the scalp along the skull. Neuroimaging and brain stimulation recording during the implantation procedure facilitate exact placement of the lead in the targeted brain area.

The tip of each lead is composed of up to five contact areas that usually spread sequentially to cover additional parts of the intended anatomic site. The generator delivers brief repeated pulses of current, which is adjusted based on individual tissue impedance. Side-effects and therapeutic response often determine the administered 'dose'. DBS parameters are often adjusted over a period of weeks as any initial response may be a reaction to the surgical placement of the lead, general anesthesia, high patient expectation and post-surgical cerebral edema.

The anatomic target of DBS differs depending on the underlying disease. The ipsilateral ventro-posterior hypothalamus is targeted in cluster headache, the anterior limb of the capsula interna in obsessive compulsive disorder, subthalamic nucleus in PD internal globus pallidus in dystonia (44–46), subthalamic nucleus, internal globus pallidus, ventral internal capsule/ventral striatum, and the subgenual cingulated region in depression (47–50) (Fig. 3).

Current status. Deep brain stimulation is still in its early investigational state for all psychiatric indications including TRD.

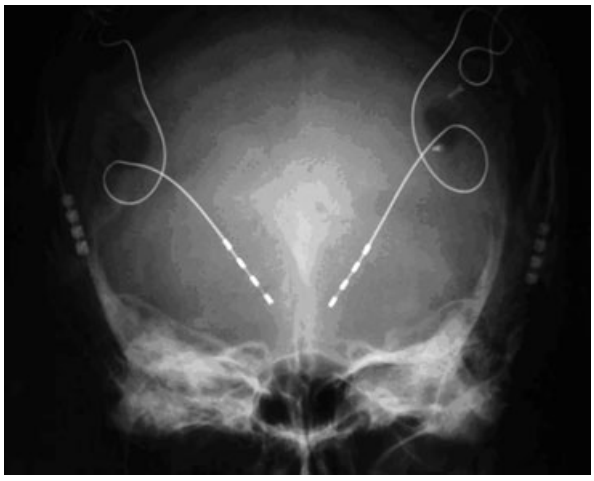

Fig. 3. DBS electrodes positioned in the ventral capsule/ventral striatum of a patient with treatment-resistant depression (courtesy of Ali Rezai, Cleveland Clinic).

Rationale for use in psychiatry. As noted above, MDD involves multiple limbic-cortical pathways. Stimulation of the subthalamic nucleus and internal globus pallidus have been targeted in several studies, mostly in subjects with movement disorders, which have resulted in improvement in depression symptoms. Mandat et al. (51) reported two cases of hypomania after subthalamic nucleus stimulation. However, the subgenual cingulated region (Cg25) has been the recent focus of DBS in depressed patients, mostly due to its connections to the brainstem, hypothalamus, insula, orbitofrontal, medial prefrontal and cingulate cortices, all of which have been implicated in leading to various depressive symptoms (49). In addition, decreased activity in Cg25 has been reported in responders to ECT, selective serotonin reuptake inhibitors, rTMS, and ablation surgeries. Consequently, DBS aims to decrease metabolic hyperactivity in Cg25 which may lead to alleviation of depression symptoms.

Efficacy data. Most of the data related to efficacy of DBS in TRD comes from case reports and secondary analysis of mood in studies involving DBS in subjects with movement disorders. A 62-year-old female had a 50% improvement in HRSD score after bilateral stimulation of the globus pallidus internus for tardive dyskinesia over an 18-month period (48). In a single case study, Jimenez et al. (47) reported remission of depression after bilateral stimulation of thalamic peduncle. In a study involving 60 patients with PD undergoing bilateral DBS of sub-thalamic nuclei, Castelli et al. (52) reported a statistically significant decrease in scores on the Beck Depression Inventory ($P = 0.008$) (53).

The most compelling data for DBS as a TRD treatment come from the work of Mayberg et al. in six patients with a primary diagnosis of TRD (49). All six patients reported acute improvement following stimulation of Cg25. All subjects reported 'sudden calmness' or 'disappearance of void'. These findings were reproducible and reversible with sham or subtherapeutic stimulation. Within 2 months, two out of six subjects (33%) showed $>50\%$ decrease in HRSD (17 item). At 6 months, response was reported in four subjects (66%) with three out of four achieving complete remission with an HRSD score less than <8. Marked improvement in middle insomnia, decrease in energy, decrease interest, psychomotor retardation, anhedonia, apathy, and social isolation were reported. This study also showed that at 1 month after stimulation, rCBF was decreased in Cg25 and adjacent orbital frontal cortex. Responders showed additional reduction in rCBF medial frontal

cortex, increase in CBF to dorsal prefrontal, anterior cingulate and parietal cortexes that were not seen in responders (49).

Safety and tolerability. With advances in medical technology, adverse events from the DBS procedure are minimal. The most common side-effects reported are from the procedure itself. They include infection of IPG site, skin erosion, subcutaneaous seroma, intercerbral hematoma, and extension cable discomfort (48, 51).

Emerging data have raised concern about possible increases in suicide rates after DBS in patients with movement disorders. Following 140 patients over 9 years, Burkhard et al. (54) reported six cases of completed suicide. Five had a history of severe depression and four were on medication or being seen by a psychiatrist at the time of death. Additionally, Foncke et al. (45) reported two cases of suicide in a cohort of 16 patients with dystonia; one of which committed suicide 3 weeks after surgery. Caution should be taken in extrapolating such data to patients with depression undergoing DBS. Nonetheless, this will be of crucial importance to evaluate as studies of DBS in TRD move forward.

Limitations of efficacy data/recommendations for use. The current but limited data on the role of DBS in TRD are encouraging. Remission rates of 50% are very uncommon in such populations. However, randomized studies with higher statistical power are needed to establish efficacy.

Declaration of interests

Dr Marangell has served as a consultant to Cyberonics and Medtronics, received grant support from Cyberonics and Neuronetics and honoraria from Cyberonics. Dr Martinez receives grant support from Cyberonics.

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