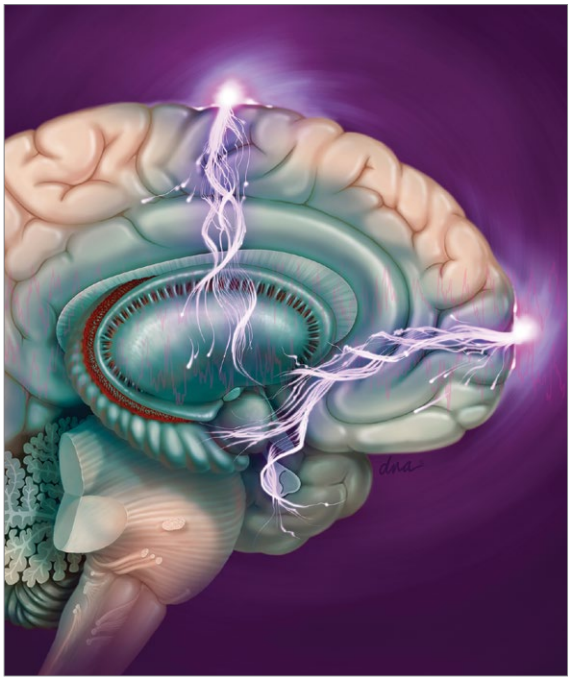
Current PSYCHIATRY

Neuromodulatory options for treatment-resistant depression



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Evidence is strongest for ECT and rTMS, but other modalities show promise

The emergence of treatment-resistant depression (TRD) poses a great clinical and public health challenge. There is no clear consensus on criteria to define TRD. The criteria range from failure to respond to 4 weeks of a single antidepressant to failure to respond to a single trial of electroconvulsive therapy (ECT).[1]

Neuromodulatory treatments for depression involve electrical stimulation of the brain through invasive or noninvasive methods. In this article, we discuss criteria for defining TRD, and compare the advantages and disadvantages of 4 neuromodulatory treatment options—ECT, vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS)—for patients with depression who fail to respond to appropriate pharmacologic interventions (***Table 1, page 27***). Most of the studies we discuss selected patients who had severe depression and had not responded to numerous treatment trials.

Defining treatment resistance

Thase and Rush[2] suggested progressive stages for categorizing TRD, ranging from Stage I (failure of at least 1 adequate trial of antidepressants) to Stage V (failure of adequate treatment with 2 selective serotonin reuptake inhibitors [SSRIs], a tricyclic antidepressant, a monoamine oxidase inhibitor, and a course of bilateral ECT). The Massachusetts General

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Table 1

Neuromodulatory treatments: A comparison

Treatment	Advantages	Disadvantages
Electroconvulsive therapy	Oldest established treatment for treatment-resistant depression. Noninvasive. High remission rates	Cognitive deficits; requires anesthesia
Vagus nerve stimulation	Improves sleep patterns and executive functioning. No adverse effects on cognitive functioning	Invasive; requires surgery. Effectiveness based on observational studies; poor evidence from RCTs
Repetitive transcranial magnetic stimulation	Noninvasive. Good evidence of physiologic effects on imaging studies	Low remission rates. Uncertainty about long-term maintenance of effects. Possibility of inducing seizures with high-frequency rTMS
Deep brain stimulation	Surgery is reversible (non-ablative). Stimulation can easily be adjusted, stopped, or restarted. Shows promise in early studies	Invasive; requires surgery. No consensus about the site for electrode implantation

RCTs: randomized controlled trials; rTMS: repetitive transcranial magnetic stimulation

Hospital Staging Model suggested a quantitative scale to help characterize the degree of treatment resistance in which a higher score corresponds to a higher level of resistance.[3] For every failed 6-week trial with adequate dose of an antidepressant, the patient is given a score of 1. The patient receives an extra .5 point for failure to respond to optimization of the dosage and augmentation with another medication. The patient also is given 3 points for failure to respond to ECT. Souery et al[4,5] proposed a model in which they defined TRD as a failure to respond after ≥1 adequate antidepressant trials of ≥12 weeks.

Treatment resistance often is the result of inadequate treatment of depressive symptoms. Inadequate treatment includes an inadequate dose of antidepressants and/or an inadequate duration of treatment. Treatment of depression also is often complicated by medical (cardiovascular, neurologic, endocrine disorders) and psychiatric (substance abuse disorders, personality disorders) comorbidities (***Table 2, page 28***). Patients with such comorbidities are at increased risk of mortality, and have lower response rates and increased morbidity.[6]

Electroconvulsive therapy

ECT involves the application of electric current to induce a self-limiting seizure. It affects multiple brain functions to produce its antidepressant effects. Patients with depression have a reduced concentration of γ-aminobutyric acid (GABA) in their plasma, CSF, and cortex. ECT increases GABAergic transmission in cortical circuits as demonstrated by increased levels of GABA in the occipital cortex, which may be responsible for ECT's antidepressant effects.[7] Sensitization of the 5-HT1A receptors and increased dopamine receptor binding in the striatum also have been associated with the antidepressant action of ECT.[8] The antidepressant effects of ECT also can be attributed to increased neuroplasticity, as evidenced by increased neurotrophic factors and cell proliferation in animal models.[9] Dysfunction of the HPA axis has long been associated with depressive disorders; ECT improves this dysfunction, as evidenced by normalization of the dexamethasone suppression test in patients who receive ECT.[7]

The results of neuroimaging studies exploring the effects of ECT vary widely based on the specific neuroimaging method, population, and statistical methods used to assess the changes. Some of the most consistent findings include reduced glucose metabolism in the frontal brain regions; reduced glucose metabolism in the hippocampus and medial temporal lobes; and reduction in functional connectivity in the

Clinical Point

The remission rate among patients receiving ECT whose depression did not respond to pharmacotherapy is approximately 48%

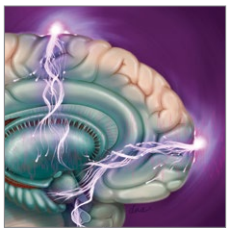

Table 2

Factors that can complicate treatment of depression

Medical conditions	Psychiatric conditions
HIV/AIDS	Inappropriate dosages of antidepressants
Cardiovascular disease	Noncompliance
Stroke	Comorbid personality disorder
Cancer	Comorbid substance use disorders
Epilepsy	

anterior cingulate, parietal, medical frontal, and dorsolateral prefrontal cortex (DLPFC).[10]

Randomized control trials (RCTs) have established the superiority of ECT over pharmacotherapy and sham ECT. Compared with other neuromodulatory treatments, ECT has higher remission rates. On average, the remission rate among patients receiving ECT whose depression did not respond to pharmacotherapy is approximately 48%; this increases to 64.9% among patients who previously had responded to a medication.[11]

Some earlier trials found bilateral ECT to be more effective than unilateral ECT.[12] Recent studies suggest that high-dose unilateral ECT (6 times the seizure threshold) is as effective as bilateral ECT.[13] Studies have shown no significant differences in efficacy or treatment outcomes between twice- and thrice-weekly ECT regimens. Some studies suggest that twice-weekly ECT may be associated with a lower risk of short-term cognitive impairment compared with thrice-weekly ECT.[14]

In highly refractory cases, the effects of ECT can be augmented by using pretreatment strategies such as hyperventilation, which may increase the duration of the seizure, and remifentanil, which helps reduce the anticonvulsant effect of agents used for anesthesia.[15] Advanced age, psychotic features, resistance to pharmacotherapy, and comorbid personality disorders predict poor response to ECT.[16]

Adverse effects. Concerns about cognitive deficits secondary to ECT may curtail its use. Retrograde and anterograde amnesia are the most common deficits observed acutely after ECT.[12] Other commonly affected cognitive functions include processing speed, attention/working memory, verbal and visual episodic memory, spatial problem solving, and executive functioning. The specific patterns of these deficits (in terms of duration and severity) vary between studies. In general, high-dose, thrice-weekly ECT and bilateral ECT are associated with greater cognitive deficits, whereas twice-weekly ECT and unilateral ECT are associated with a lower risk of cognitive adverse effects.[12] A recent meta-analysis by Semkovska and McLoughlin[17] found that most cognitive deficits seen after ECT are limited to the first 3 days after treatment. The authors of this meta-analysis concluded that these impairments improve over time and approach baseline 2 weeks after treatment. In fact, some of these impairments (processing speed, working memory, anterograde memory, and some aspects of executive function) improved beyond baseline after 15 days of treatment.[17] The need for anesthesia and associated potential adverse effects also are a cause of concern with ECT.

Combining ECT with medication. Several patient-specific factors, including medication regimen and comorbid medical conditions, need to be considered before using ECT in combination with pharmacotherapy. Although most antipsychotics are safe to use with ECT, concomitant use of agents with higher antihistaminic properties may increase the risk of delirium. The risk of delirium also is increased with the use of anticonvulsants and mood stabilizers (eg, lithium) because these agents increase the seizure threshold. The potential for drug interactions may affect the choice of the anesthetic agents. Also, SSRIs and serotonin-norepinephrine reuptake

Clinical Point

A meta-analysis found that most cognitive deficits seen after ECT are limited to the first 3 days after treatment

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inhibitors can increase the duration of induced seizures.[18]

Vagus nerve stimulation

VNS, in which an implanted device stimulates the vagus nerve with electrical impulses, initially was used to reduce the frequency of seizures in patients with epilepsy and treatment-resistant partial onset seizures.[19] VNS was FDA-approved for TRD in July 2005.[20] One VNS system, the NCP System, consists of an implantable, multi-programmable generator, known as a pulse generator, that is subcutaneously placed in the anterior chest wall during an outpatient surgical procedure. Separate bipolar nerve-stimulating electrodes are surgically wrapped around the left cervical vagus nerve, and then connected to the generator via a tunneling procedure. A telemetric wand is subsequently linked to a portable computer and used to adjust stimulation parameters.[21,22]

Support for using VNS for TRD came from a multitude of investigations and observations. Harden et al[23] and Elger et al[24] prospectively evaluated epileptic patients with standard depression symptom severity rating scales. They found that VNS was associated with statistically significant improvements in mood that were not related to reductions in seizures.[23,24]

The mechanism of action of VNS is not clear. Earlier researchers had found evidence that VNS affected brain regions associated with norepinephrine[25] and serotonin systems[26]; both of these neurotransmitters have been implicated in the pathophysiology of depression. Positron emission tomography studies conducted during VNS treatment of epilepsy showed metabolic changes in cortical and subcortical areas of the brain, including the amygdala, hippocampus, and cingulate gyrus, all structures implicated in the pathophysiology of mood disorders.[27]

Most studies conducted to evaluate the efficacy of VNS have been observational, looking at depression ratings before and after treatment with VNS. The short-term studies measured the difference in depression rating scales at baseline and after 10 weeks of treatment. In most of these studies, treatment with VNS resulted in a statistically significant drop in depression rating scales scores, such as on the Hamilton Depression Rating Scale (HAM-D). Based on the study design and number of study participants, response rates have varied from 13%[28] to 40%,[29] whereas remission rates have varied from 15.3%[30] to 28%.[31] More than one-half of the reduction in symptoms occurred after 6 weeks of treatment.[30] In longer-term follow-up studies, the antidepressant effect generally was sustained over time. Response rates remained essentially unchanged, but the remission rates increased to approximately 29%.[29] Only 1 RCT has compared patients with controls; it found no significant differences in the response or remission rates between active VNS and sham VNS.[32] In this study, all patients had VNS implanted, but in the control group, the VNS was never turned on.[32] In a meta-analysis conducted by Martin and Martín-Sánchez,[33] 31.8% (95% confidence interval [CI], 23.2% to 41.8%; $P < .001$) of patients treated with VNS had a significant reduction in HAM-D scores. The response rate in patients with TRD ranged from 27% to 37% and the remission rate was approximately 13%. In studies that followed patients over longer periods, both the remission and response rates increased over time.[34]

Recent evidence suggests that the effectiveness of VNS may depend on the stimulation level. A multi-center double-blind study randomized patients to receive either a low (0.25 mA current, 130-millisecond pulse width), medium (0.5e1.0 mA, 250 millisecond), or high (1.25e1.5 mA, 250 millisecond) dose of VNS.[35] Although all dose levels were associated with improvement in symptoms, a statistically significant durability in response was associated with the medium- and high-dose treatments.

Adverse effects. VNS has no major adverse effects on cognitive functioning, and some studies have found improvement in executive functioning that corresponded to improvement in depressive symptoms.[30] VNS also may result in improved sleep patterns as evidenced by EEG changes.[31] The most commonly reported adverse effects

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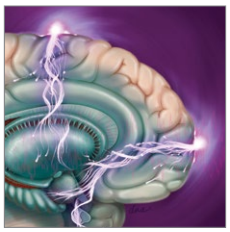
In longer-term studies of VNS, the antidepressant effect generally was sustained over time



include pain in the incision site, hoarseness of voice, throat pain, and neck pain.[36]

Repetitive transcranial magnetic stimulation

rTMS is a noninvasive technique that uses high-intensity magnetic impulses to stimulate cortical neurons. A magnetic field is produced when current passes through a coil, which in turn causes electrical stimulation in the cortical neurons that results in transient changes in the excitability of the cortical neurons.[37] Although many stimulation parameters exist for TMS, high-frequency stimulation to the left prefrontal cortex (HFL-rTMS) and low-frequency stimulation to the right prefrontal cortex (LFR-rTMS) have been shown most efficacious for treating depression.[38] High-frequency (5 Hz to 20 Hz) stimulation using rTMS increases cortical neuron excitability, whereas low-frequency (approximately 1 Hz) is associated with reduced cortical neuron excitability.[39] The choice of targeting the DLPFC stems from a large body of functional neuroimaging studies that have shown reduction in activity/blood flow in the left DLPFC and abnormal activity/blood flow in the right DLPFC.[40]

Clinical Point

Low-frequency rTMS applied to the right DLPFC was associated with a remission rate of approximately 34.6%

There is no dearth of RCTs evaluating the efficacy of rTMS vs sham rTMS (where no magnetic stimulation was provided). In a meta-analysis of 8 RCTs, low-frequency rTMS applied to the right DLPFC was associated with a remission rate of approximately 34.6%, compared with a 9.7% remission rate with sham rTMS.[41] A response rate of approximately 38.2% was observed with HFL-rTMS, compared with a response rate of 15.1% for sham rTMS.[41]

Gaynes et al[42] conducted a meta-analysis to determine the efficacy of rTMS in TRD. They found that for patients with TRD, rTMs produced a response rate of 29% and a remission rate of 30%. In long-term, naturalistic, observational studies, the response rates and remission rates were much higher (58% and 37.1%, respectively).[43] Over a 1-year follow-up, almost two-thirds of patients continued to meet criteria for response to treatment.[44] Trials comparing HFL-rTMS and LFR-rTMS have found no significant differences in efficacy.[45]

Advanced age, psychotic symptoms, and a longer duration of the current depressive episode predict poor response to rTMS. Also, imaging studies have shown that a lower metabolism in cerebellar, temporal, anterior cingulate, and occipital parts of the brain correlate with better response to HFL-rTMS.[46,47]

Adverse effects. The major adverse effect associated with rTMS is the risk of inducing seizures, which is more commonly associated with high-frequency rTMS. Other common adverse effects include headache, facial muscle twitching, and tinnitus.[37]

Deep brain stimulation

DBS is an invasive stereotactic surgical procedure. It involves unilateral or bilateral placement of electrodes at neuroanatomical locations to deliver continuous stimulation from a subcutaneously implanted pulse generator.[48] In the past, destructive surgical procedures were used to treat intractable depression. Surgeries such as anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy have been shown to effectively reduce depressive symptoms.[49] The advantages of DBS over destructive procedures include the fact that DBS is reversible and that the stimulation levels can easily be adjusted, and the treatment can easily be stopped or restarted.

There is no consensus on the optimal anatomic locations for the electrode implantation in DBS. Electrodes have been implanted in the subcallosal cingulate gyrus, inferior thalamic peduncle, ventral capsule/ventral striatum, superolateral branch of the medial forebrain bundle (MFB), and nucleus accumbens.

The choice of anatomic locations stems from the large body of neuroimaging literature characterizing functional changes associated with acute depression and response to treatment. The electrode placement targets "nodes" that form an integral part of the affected neural circuits that are responsible for regulating depressive symptoms.[50] Increased metabolic activity and blood flow to the subgenual cingulate gyrus and reduction in the blood flow to the DLPFC

and the striatum have been associated with active depressed states. Response to antidepressant treatment has been associated with reversal of these findings.[51] Functional magnetic resonance imaging studies have consistently shown increased activity in the amygdala in response to negative stimuli among patients with depression.

Regardless of the site of electrode placement, studies have reported symptomatic improvement among patients with depression who are treated with DBS. In 2 case reports, the electrode was implanted in the inferior thalamic peduncle.[52,53] Each study had 1 participant, and each patient remitted.[52,53]

Placement of the electrodes in the nucleus accumbens resulted in a response rate of 45% in 1 study,[54] whereas in a different study, all patients reported improvement in anhedonia.[55] A response rate of 71% and a remission rate of 35% were observed in a study in which the electrode was implanted in the ventral capsule/ventral striatum area.[56]

Berlim et al[57] published a systematic review and exploratory meta-analysis of studies in which the electrode had been implanted in the subgenual cingulate cortex. At 12 months, the response rate was 39.9% (95% CI, 28.4% to 52.8%), and 26.3% (95% CI, 13% to 45.9%) of patients achieved remission. The most significant drop in depression scores was observed 3 to 6 months after the surgery. No significant change in scores was observed between 6 to 12 months after surgery.[57]

The MFB, specifically the superolateral branch, is emerging as an exciting new target for electrode placement in DBS. Schlaepfer et al[58] studied the effects of electrodes implanted bilaterally in the superolateral branch of the MFB. They observed an almost 50% reduction in symptoms by Day 7, and at the last follow-up visit (12 to 33 weeks) 4 of the 6 patients had achieved remission.[58] In a recent systematic review, Gálvez et al[59] found most studies had high response/remission rates without any significant adverse effects. In a recent study of DBS targeting the MFB, 3 of 4 patients had a >50% reduction in Montgomery-Åsberg Depression Rating Scale scores at the end of first week. Although 1 patient withdrew, 2 of the other 3 patients continued to report a >80% reduction in depressive symptoms, even at Week 26.[60]

Accurate localization of target areas (white matter tracts) and subsequent electrode placement might be an important factor governing treatment response. Riva-Posse et al[61] found that clinical response was seen when the electrodes stimulated 3 specific white matter bundles. Interestingly, nonresponders were converted to responders simply by changing the position of the electrodes to include these white matter tracts.[61]

Adverse effects. The most common adverse effects noted during studies of DBS include pain at the site of implantation and wound infection. Other adverse effects include lead fracture, transient dysphagia, and other hardware-related problems.[49]

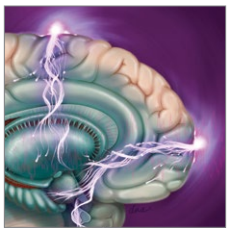
Sorting out the evidence

In the absence of head-to-head trials, it is difficult to establish a hierarchal algorithm for use of the 4 neuromodulatory treatments discussed in the article. If we were to base our decision solely on the current literature, ECT by far has the most evidence and highest remission rates.[11] We can reduce the risk of cognitive deficits by using twice-weekly instead of thrice-weekly ECT, or by using unilateral instead of bilateral ECT.[12] Another strategy for reducing adverse effects associated with long-term maintenance ECT is by using it in combination with VNS. ECT and VNS can be used safely concomitantly; ECT can be used to treat acutely worsening depression, and VNS for maintaining the antidepressant effect.[62]

Aside from ECT, rTMS is the only other treatment that has evidence from RCTs. Although the remission rates are not as high as ECT, its preferable adverse effects profile, noninvasive nature, and comparative low cost (compared with surgical procedures) make it a favorable choice. The Canadian Network for Mood and Anxiety Treatment guidelines suggest rTMS as the first-line treatment for patients who do not respond to pharmacologic treatments.[63] ECT can be

Clinical Point

There is no consensus on the optimal anatomic locations for the electrode implantation in DBS



Neuromodulatory treatments

considered second-line treatment unless the patient has acute suicidal ideation, catatonia, psychotic features, greater treatment resistance, or physical deterioration, in which case ECT should be tried before TMS.[63]

Among the invasive options, VNS has more evidence and is FDA-approved for TRD. However, DBS has shown great promise in early studies, with remission rates as high as 35%.[56] DBS has the advantage of being reversible, and the amount of stimulation can be adjusted easily. Despite early promise, more research is needed before DBS can be widely used in clinical settings.

Clinical Point

ECT can be used to treat acutely worsening depression, and VNS for maintaining the antidepressant effect

Related Resource

- Bewernick B, Schlaepfer TE. Update on neuromodulation for treatment-resistant depression. 2015;4. doi: 10.12688/f1000research.6633.1.

Drug Brand Names

Lithium • Eskalith, Lithobid
Remifentanil • Ultiva

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Bottom Line

When considering neuromodulatory treatments for patients with TRD, current evidence suggests electroconvulsive therapy and repetitive transcranial magnetic stimulation are preferable options. Vagus nerve stimulation and deep brain stimulation have also shown promise.

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Clinical Point

Among the invasive options, VNS has more evidence and is FDA-approved for TRD