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SPECIAL ARTICLE

A narrative review on invasive brain stimulation for treatment-resistant depression

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While most patients with depression respond to pharmacotherapy and psychotherapy, about one-third will present treatment resistance to these interventions. For patients with treatment-resistant depression (TRD), invasive neurostimulation therapies such as vagus nerve stimulation, deep brain stimulation, and epidural cortical stimulation may be considered. We performed a narrative review of the published literature to identify papers discussing clinical studies with invasive neurostimulation therapies for TRD. After a database search and title and abstract screening, relevant English-language articles were analyzed. Vagus nerve stimulation, approved by the U.S. Food and Drug Administration as a TRD treatment, may take several months to show therapeutic benefits, and the average response rate varies from 15.2-83%. Deep brain stimulation studies have shown encouraging results, including rapid response rates ($>$ 30%), despite conflicting findings from randomized controlled trials. Several brain regions, such as the subcallosal-cingulate gyrus, nucleus accumbens, ventral capsule/ventral striatum, anterior limb of the internal capsule, medial-forebrain bundle, lateral habenula, inferior-thalamic peduncle, and the bed-nucleus of the stria terminalis have been identified as key targets for TRD management. Epidural cortical stimulation, an invasive intervention with few reported cases, showed positive results (40-60% response), although more extensive trials are needed to confirm its potential in patients with TRD.

Keywords: Treatment-resistant depression; deep brain stimulation; vagus nerve stimulation; epidural cortical stimulation subcallosal cingulate gyrus; medial forebrain bundle

Introduction

According to the World Health Organization, depression is the leading psychiatric cause of disability worldwide, with $>$ 264 million people affected in 2017.[1,2] In addition to critical functional impairment, depression is associated with a significant economic burden and premature mortality.[3,4] While pharmacotherapy and psychotherapy are effective in reducing depressive symptoms,[5,6] a considerable number of patients (about 30%) do not achieve remission even after multiple trials.[7-9] Although there is no consensus regarding the concept of treatment-resistant depression (TRD), it is usually defined as the lack of clinical response to at least two antidepressant trials employed in adequate doses and periods.[10-15] For these patients, neurostimulation therapies (NTs) may be required to manage their symptoms.

NTs are categorized into two types according to the clinical procedure. Non-invasive methods include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation, and transcranial direct current stimulation.[16] As depicted in Figure 1, invasive techniques include vagus nerve stimulation (VNS), deep brain stimulation (DBS), and epidural cortical stimulation (ECS).[17] While the efficacy of ECT has been demonstrated since its early days, some patients still do not achieve remission and may present cognitive complaints, despite the refinement of the technique in terms of effectiveness and

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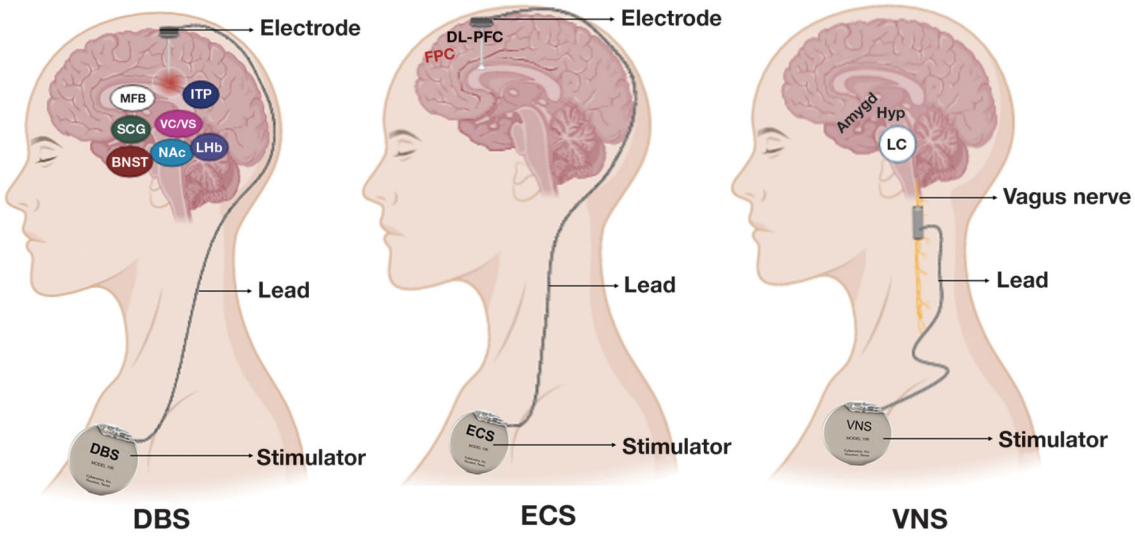


Figure 1 Schematic representation of invasive brain stimulation techniques DBS, VNS, and ECS. Amygd = amygdala; DBS = deep brain stimulation; DL-PFC = dorsolateral prefrontal cortex; ECS = epidural cortical stimulation; FPC= frontopolar cortex; Hyp = hypothalamus; ITP = inferior thalamic peduncle; LHb = lateral habenula; MFB = medial forebrain bundle; NAc = nucleus accumbens; SCG = subgenual cingulate gyrus; VC/VS = ventral capsule/ventral striatum; VNS = vagus nerve stimulation.

safety.[18-23] Repetitive transcranial magnetic stimulation is another effective non-invasive technique that has also received U.S. Food and Drug Administration (FDA) approval as a treatment for major depressive disorder.[24,25]

Invasive NTs, such as VNS and DBS, have been increasingly investigated as treatments for TRD.[17,26-30] VNS electrodes deliver a continuous low-frequency electrical signal to the left cervical vagus nerve from an implantable generator.[31] The procedure received FDA approval in 2005 for TRD. DBS electrodes are stereotactically implanted in a specific brain region and connected to a subcutaneous pulse generator that supplies power and controls stimulation.[32] The FDA approved this intervention as a treatment for essential tremor in 1997, Parkinson disease in 2002, dystonia in 2003, and obsessive-compulsive disorder (as a humanitarian device exemption) in 2009.[32,33] It is being investigated as a treatment for TRD,[34,35] addiction,[36] anorexia nervosa,[37] Alzheimer's disease,[38,39] and anxiety.[40] ECS, another brain stimulation technique that has been tested as a TRD treatment,[41] delivers electrical stimulation to the cortex without penetrating the brain tissue. ECS appears to have fewer complications than DBS,[42] and studies on this intervention have reported encouraging results.[41,43] In this review, we will briefly discuss clinical invasive NTs and data supporting their potential as a treatment for TRD.

Vagus nerve stimulation

The vagus nerve, the 10th cranial nerve, has a long path extending from the brainstem to the abdomen. It is one of the main communication pathways between the brain and peripheral organs.[44] The vagus nerve plays a pivotal role in modulating metabolic homeostasis and the neuroendocrine-immune axis through efferent and afferent pathways.[45] Glutamatergic transmission through afferent pathways sends information from the internal organs to the brain, which may influence emotion and cognition, while the efferent pathways participate in the regulation of digestive, respiratory, and circulatory systems through parasympathetic cholinergic transmission.[46] Findings that treatment with anticonvulsants[47,48] and VNS reduces seizures and is associated with mood improvement suggest that VNS has potential as a depression treatment. For instance, Harden et al.[49] investigated whether using VNS to treat epilepsy was associated with mood changes. The authors evaluated depressive symptoms before and after VNS and compared the results to those of a group of patients on stable antiepileptic drugs, such as gabapentin and lamotrigine. There was a significant decrease in depressive symptoms in the VNS group but only a trend toward significance in the antiepileptic group. In addition, patients who did and did not respond to VNS therapy for seizures did not differ in terms of depressive symptoms, suggesting that the mood improvement was not due to a decrease in seizure frequency.[49] Elger et al.[50] found similar results in 11 patients treated with VNS, whose depressive symptoms improved 3 and 6 months after implantation, independently of the therapy's effect on seizure activity. In VNS, the left cervical vagus nerve is stimulated with an implantable electrical device,[31,51] which delivers electrical signals via bipolar leads tunneled under the skin. The stimulation parameters can be programmed externally according to patient demand. VNS received FDA approval as a treatment for resistant epilepsy and depression in 1997 and 2005, respectively.[52-54] Since then, as summarized in Table 1, several clinical studies have found that chronic VNS is efficacious for TRD.[55-61]

In a multi-site, open-label pilot study of VNS in 30 TRD patients, Rush et al.[81] reported that 40% of the participants achieved at least 50% symptom reduction after

Table 1 Summary of clinical trials and case reports on epidural cortical stimulation and vagus nerve stimulation for treatment-resistant depression

Neurostimulation method/ reference	n	Clinical trial design	Follow-up	Response rates (%)	Outcomes
ECS					
Williams[43]	5	OLS	5 years	54.9	Long-term safety and efficacy of FPC and DL-PFC stimulation
Kopell[62]	12	Randomized, OLS	104 weeks	40.0	⩾ 40% improvement in six patients, ⩾ 50% improvement in five patients of depression symptoms
Nahas et al.[41]	5	OLS	7 months	60.0	54.9% improvement in HRSD score following 7 months of treatment
VNS					
McAllister-Williams[63]	156	OLS	5 years	63.0	After 5 years, VNS + TAU had a 63% response rate vs. 39% in the TAU group
Kumar[64]	599	Nonrandomized comparative study	5 years	62.5	After 5 years, VNS + TAU had a 62.5% response rate vs. 39.9% in the TAU group
Kucia[65]	6	OLS	1 year	83.0	Response rates of 40% and 83% were reported after 3 months and 1 year of VNS, respectively
Conway[60]	599	Longitudinal study	5 years	N/A	VNS + TAU improved QoL (34%) without significant effects on depressive symptoms
Jodoin[66]	14	Naturalistic longitudinal study	2 years	70.0	After 24 months of treatment, there was a 70% response rate and cognitive improvement
Trottier-Duclos[67]	10	Naturalistic study	6 years	80.0	There was significant improvement in mental and physical QoL, as well as an 80% response rate after 72 months of treatment
Aaronson[55]	795	Nonrandomized, OLS	5 years	67.6	After 5 years, there was a significantly higher response rate in the VNS + TAU group (71.3%) than the TAU group (56.9%)
Müller[68]	18	Retrospective study	104.9 months	N/A	Higher levels of depressive symptom remittance were found after longer treatment
Perini[69]	6	OLS	12 months	N/A	Increased hippocampal gray volume following VNS treatment indicated hippocampus remodeling, which also paralleled antidepressant response
Albert[70]	5	Naturalistic study	5 years	60.0	Response/remission rates were 40 and 60% after 1 and 5 years of treatment, respectively
Tisi[71]	27	OLS	5 years	47.2	VNS was successful in 20% of TRD patients
Christmas[72]	28	OLS	1 year	35.7	Corroborated the use of VNS in chronic TRD patients
Aaronson[73]	331	Multicenter double-blind	2 year	N/A	Adjunctive VNS treatment led to significant improvement in TRD patients
Cristancho[53]	15	OLS	1 year	43.0	Supported the use of VNS in TRD treatment
Bajbouj[74]	74	Randomized, OLS	2 years	53.1	After 2 years, the patients had a 53.1% response rate and a 38.9% remission rate without noticeable side effects
Burke & Husain[57]	205	Double-blind RCT	1 year	55.0	VNS + ECT was found safe and effective, and it can be given either sequentially or concurrently
Corcoran[75]	11	OLS	1 year	55.0	The depression rating was significantly reduced after 1 year of treatment
George[76]	205	Naturalistic OLS	1 year	26.8	After 12 months, the HRSD score of the VNS + TAU group was 26.8% vs. 12.5% in TAU only group
Nahas[77]	59	OLS	2 years	42.0	VNS therapy had long-term benefits, including a 42% response rate and a 22% remission rate
O'Keane[78]	11	OLS	2 years	N/A	VNS normalizes increased ACTH levels in subjects who underwent a CRH challenge
Rush[79]	235	RCT	10 weeks	15.2	After 10 weeks, the HRSD response rate in the VNS group was 15.2 vs. 10% for sham therapy, indicating no definitive evidence of short-term efficacy
Rush[61]	233	Double-blind RCT	1 year	30.0	Chronic VNS treatment was found efficacious in TRD patients
Rush[13]	59	RCT	2 years	44.0	After 2 years of VNS treatment, 44% response and 22% remission rates were found
Sackeim[80]	60	OLS	12 weeks	30.5	After VNS, the response rate was 30.5% for primary HRSD28 and 37.3% for CGI-I

ACTH = adrenocorticotropic hormone; CGI-I = Clinical Global Impressions scale-I; CRH = corticotropin-releasing-hormone; DL-PFC = dorsolateral-prefrontal cortex; ECS = epidural cortical stimulation; ECT = electroconvulsive therapy; FPC = frontopolar cortex; HRSD-28 = 28-item Hamilton Rating Scale for Depression; N/A = not applicable; OLS = open-label study; QoL = quality of life; RCT = randomized controlled trial; TAU = treatment-as-usual; TRD = treatment-resistant depression; VNS = vagus nerve stimulation.

10 weeks of treatment. Afterwards, Sackeim et al.[80] added data from 30 additional patients and reported a 30.5% response rate following 10 weeks of VNS treatment, with findings that suggested long-term therapeutic utility and good tolerability. Rush et al.[13] continued observing this sample and reported 44% response and 27% remission rates after 1 year of stimulation, and 44% response and 22% remission rates after 2 years of stimulation. In the last observation carried forward analyses, Nahas et al.[77] found the response and remission rates of 44 and 27%, respectively, after 1 year and 42 and 22%, respectively, after 2 years of adjunctive VNS. Furthermore, response rates of 43% (in 15 patients), 35.7% (in 28 patients), 20% (in 27 patients), and 55% (in 11 patients) were reported following 12-month of VNS in four other studies with TRD patients.[53,71,72,75] However, few studies have reported a poor response to VNS treatment for depression. For instance, Rush et al.[79] found a modest response to VNS in a 10-week randomized comparison of adjunctive VNS vs. sham in 222 TRD outpatients (VNS group = 112; sham group = 110). They suggested that VNS may be ineffective depending on the study sample and design and the length of treatment. The authors later reported a significant reduction in depressive symptoms, with a response rate of 27.2% after 1 year follow-up.[61] Importantly, in a non-randomized comparison study, George et al.[76] found a better response rate in patients who received concomitant pharmacotherapy + VNS than in those who received conventional treatment.

Bajbouj et al.[74] conducted a naturalistic analysis of 74 European TRD patients after 2 years of VNS, finding a significant decrease in depression symptoms at all three-time points (3, 12, and 24 months). After 2 years of treatment, there was a 38.9% (19/49) remission rate and 53.1% (29/49) response rate. In a naturalistic 5-year follow-up study of five patients, the response and remission rates were both 40% (2/5) after 1 year and 5 years.[70] The high symptom remittance levels over more extended periods ($>$ 5 years) suggest that long-term VNS treatment is beneficial.[68,82] Aaronson et al.[55] reported higher cumulative response (from 40.9 to 67.6%) and remission (from 25.7 to 43.3%) rates in a 5-year trial of 795 patients with depression. They also found a better response rate in patients treated with ECT plus VNS (71.3%) than ECT alone (56.9%), as well as decreased suicidal ideation. In open-label VNS therapy in six patients with TRD, Kucia et al.[65] reported 53 and 40% response and remission rates, respectively, after 3 months of treatment. After 1 year of stimulation, they found a significant increase in the response rate (83%). These reports indicate that longer VNS treatment enhances the response/remission rate.

In an observational study of 124 patients, Dunner et al.[83] reported remission rates of 3.6 (4/112) and 7.8% (8/103) after 12 and 24 months of treatment-as-usual (TAU), respectively. A recent study found that antidepressant TAU plus VNS over 5 years resulted in a 63% (61/97) response rate vs. 39% (23/59) in the TAU-only group,[63] in addition to lower suicidality. Kumar et al.[64] also observed similar responses in their VNS + TAU cohort. According to Montgomery Asberg Depression Rating Scale (MADRS) scores, they found a 62.5% (205/328) response rate over 5 years, compared with 39.9% (108/271) in the TAU group. A meta-analysis comparing VNS + TAU (n=1,035) vs. TAU only (n=425) revealed that participants in the combined treatment group had greater response (12, 18, 28, and 32% at 12, 24, 48, and 96 weeks, respectively) and remission rates (3, 5, 10, and 14% at 12, 24, 48, and 96 weeks, respectively). Furthermore, patients who responded to VNS + TAU by the 24th week were more likely to have a sustained response at 48 weeks (odds ratio [OR] = 1.98, 95% confidence interval [95%CI] 1.34-3.01) and 96 weeks (OR = 3.42, 95%CI 1.78-7.31).[84] Thus, adjunctive VNS could contribute to long-term response (1-5 years) in patients with TRD. VNS also resulted in clinically and statistically significant improvement in mental quality of life (QoL), physical QoL, and anxiety symptoms even if depression symptoms were not reduced.[60,67] In two TRD patients, chronic VNS stimulation after manic symptoms had been managed with standard treatments (mood stabilizers and ECT) resulted in no further mania/hypomania for up to 5 years.[85] As an adjunctive therapy for TRD patients with cognitive deficits, VNS improved learning and memory function after 2 years of treatment.[66]

VNS intensity could be associated with clinical effects. Aaronson et al.[73] tested three doses of VNS (low [0.25 mA current, 130 μs pulse width], medium [0.5-1.0 mA, 250 μs], and high [1.25-1.5 mA, 250 μs]) in 331 patients with TRD over 22 weeks plus an additional 28 weeks to assess durability of response. They found a positive association between higher electrical doses and clinical response duration. VNS modulates the functional activity of cortical and subcortical brain regions,[86,87] but few studies have addressed its mechanism of action. Few open-label trials of VNS have corroborated its utility in treatment-resistant anxiety disorders, bipolar depression, chronic refractory headaches, Alzheimer disease, or obesity.[88] Acute VNS treatment has been shown to normalize increased adrenocorticotropic hormone levels in patients who underwent a CRH challenge.[78] Increased hippocampal gray matter volume following VNS treatment indicates that hippocampal remodeling is a response marker in TRD.[69] While the precise mechanism of action of VNS is not fully known, pre-clinical and clinical studies suggest that it may act by modulating levels of crucial neurotransmitters and their metabolites such as dopamine, norepinephrine, gamma-aminobutyric acid (GABA), homovanillic acid, and 5-hydroxy indole acetic acid.[61,81,89,90] Pre-clinical and human research on VNS has corroborated the importance of norepinephrine and GABAergic neurotransmission.[91-93] VNS also stimulates the expression of c-fos, a nuclear protein that indicates excessive neuronal activation.[94] Short-term VNS treatment modulates the functional activity of cortical and subcortical brain regions, such as the orbitofrontal cortex, entorhinal cortex, inferior parietal lobule, hypothalamus, thalamus, amygdala, and cingulate gyrus.[86,87,95-98] In pre-clinical studies with models of depression, VNS treatment has also been associated with increased neuroplasticity markers, such as brain-derived neurotrophic factor (BDNF) and essential fibroblast growth factor expression, as well as mood

improvement.[99,100] Although Wu et al.[101] reported elevated levels of systemic fibroblast growth factor-2 protein and central FGFR1 RNA in major depressive disorder patients, another clinical study found unchanged plasma levels of fibroblast growth factor-2 in depressive patients.[102]

Strengths of VNS

VNS treatment plus citalopram and bupropion were found to be safe in patients with TRD, including pregnant women.[80] Long-term treatment with VNS resulted in depressive symptom remission in two-thirds of highly depressive patients.[103] The incremental benefits of adjunctive VNS therapy have also been documented,[61,63] including detectable anti-suicidal effects and remission when applied alone or in combination with other antidepressant agents.[104] VNS functioning is not affected by exposure to metal detectors, microwave ovens, mobile phones, or other electrical or electronic devices.[88] Although it is an invasive treatment, it is less invasive and risky than DBS or ECS, since the procedure can be performed on an outpatient basis. Significantly, no evidence of negative effects on cognition has been associated with VNS. Actually, improvement in some cognitive domains was observed, as well as reversal of depressive symptoms.[80]

Limitations of VNS

Since VNS may require a longer time to be effective (up to several months), it may not be an adequate option for patients in acute depressive crises, although it could be a reasonable option for patients with chronic depression.[104] Implanting a stimulation device requires a surgical procedure, which can cause infection (3-6% of patients), nausea (40%), pain (33%), and anxiety (20%). While devices implanted on the vagus nerve are related to hoarseness (73%), dyspnea (47%), voice alteration, and vocal cord paresis ($<$ 1% of patients), these potential side effects are not associated with meaningful treatment withdrawal.[53,105,106] Horner's syndrome, sore throat, shortness of breath, and coughing in $>$ 10% of patients have also been reported in VNS.[107] Moreover, 0.1% of patients had bradycardia and short-lived systole during initial stimulation and surgery.

Deep brain stimulation (DBS)

DBS is an invasive electrical stimulation technique approved by the FDA for treating essential tremors, Parkinson disease, dystonia, and obsessive-compulsive disorder.[32,33] As an experimental treatment, it is also being tested for many CNS disorders, including TRD.[34,35] In this method, DBS electrodes are implanted in a target node of the brain, such as the subgenual cingulate region (SCG), ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAc), lateral habenula (LHb), inferior thalamic peduncle (ITP), or medial forebrain bundle (MFB). Structural and functional dysfunctions involving these regions have been reported in patients with depression.[108] Thus, based on clinical studies summarized in Table 2, we can say they are potential targets for interventions.

The proposed mechanism of action of DBS is to correct connectivity dysfunctions associated with clinical impairment, including those in patients with depression.[133] DBS not only modulates the brain activity of the stimulated area, but distant regions through connected circuitry.[115,118] For instance, stimulating the SCG decreases local metabolic activity while up- and downregulating remote regions through corticolimbic networks.[134-136] Stimulating the NAc regulates depression-related hypermetabolism in the SCG and prefrontal areas, which indicates functional connectivity between these two brain structures.[117] Meng et al.[137] reported that DBS of the LHb region of rat brains increases the level of monoamines, including norepinephrine, dopamine, and 5-hydroxytryptamine (5-HT), in blood serum and brain tissues. Beyond metabolic and neurotransmitter changes, there are indications that DBS also modulates BDNF levels in the nervous system. However, the evidence is contradictory since both increased and decreased BDNF levels have been reported after DBS.[138-140]

DBS of the subcallosal cingulate gyrus

Pre-clinical studies involving DBS of the ventral medial prefrontal cortex (vmPFC) have shown antidepressant-like effects.[137,141] The rodent infralimbic cortex is assumed to be homologous to the human SCG.[142] Hamani et al.[143] reported that DBS of rat vmPFC or infralimbic cortex is associated with antidepressant-like effects. In addition, vmPFC stimulation has been shown to have antidepressant, anxiolytic and hedonic effects by modulating the dorsal raphe nucleus circuitry in a rodent depression model.[144-146] The antidepressant effect of vmPFC-DBS may be related to the modulation of prefrontal dorsal raphe nucleus projections, which are involved in serotonin synthesis and release.[147]

The first pioneering study of SCG-DBS in depression was conducted by Mayberg et al.[115] In an open-label study, they reported a dramatic antidepressant response in four out of six TRD patients after 6 months. In a subsequent open-label study, Lozano et al.[114] reported that SCG-DBS had an antidepressant effect in 40% of TRD patients 1-week post-stimulation (n=20), while 55-60% of patients reached the response threshold at 6 and 12 months. In their long-term (3-6 years) follow-up study, Kennedy et al.[113] reported depression score improvement of 62.5% in the1st year, 46.2% in the 2nd year, 75% in the 3rd year, and 64.3% in the 6th year. Crowell et al.[109] reported that a majority of the 28 participants at their single-center experienced a robust and sustained antidepressant response in over 8 years of continuous observation after SCG-DBS. Additionally, they observed that once patients responded to DBS, they tended to stay well for 8 years, which is unusual in this degree of treatment resistance.[109] In a randomized, double-blind, sham-controlled crossover study, Puigdemont et al.[112] observed improved depression scores in four out of five patients with TRD. Another double-blind, multisite, randomized, sham-controlled trial failed to find differences between active and sham stimulation after 6 months (20% response in the stimulation group vs. 17% response in the sham group).[110] These authors suggested that the

Table 2 Summary of clinical trials and case reports on DBS applied to various brain targets in TRD management

Brain target/reference	n	Clinical trial design	Follow-up	Response rates	Outcomes
SCG					
Crowell[109]	28	OLS	8 years	> 50,0	Robust and sustained antidepressant effects
Holtzheimer[110]	90	RCT	24 months	20.0	No statistically significant antidepressant effects
Merkl[111]	8	RCT	28 months	33.3	No significant antidepressant effect between sham vs. active treatment
Puigdemont[112]	5	RCT	6 months	N/A	Depression remitted in four out of five patients
Merkl[111]	6	OLS	24-36 weeks	33.3	Moderate acute and chronic antidepressant effects
Holtzheimer[110]	17	OLS	24 months	92.0	Long-term stimulation is safe; remission of depressive symptoms observed
Kennedy[113]	20	OLS	36-72 months	64.3	Long-term DBS is a safe and effective treatment for TRD
Lozano[114]	20	OLS	12 months	55.0	Mood improvement within 1 month that lasted for at least 1 year in TRD patients
Mayberg[115]	6	OLS	6 months	66.0	Reduction in local CBF and changes in downstream limbic and cortical sites; 35% improvement in CGI
NAc					
Bewernick[116]	11	OLS	12-48 months	45.5	Antidepressant effects sustained up to 4 years (five patients); improved QoL
Bewernick[117]	10	OLS	12 months	50.0	Antidepressant and antianhedonic effects in TRD patients
Schlaepfer[118]	3	OLS	1 week	N/A	Rapid and robust antidepressant effects
VC/VS or vALIC					
van der Wal[119]	21	RCT	2 years	35.3	Effective in 32% of TRD patients 2 years after surgery
Dougherty[120]	30	RCT	16 weeks	23.3 (active) 20.0 (control)	No efficacy observed in TRD patients
Malone[121]	17	OLS	14-67 months	71.0	Sustain improvement across multiple depression, anxiety, and global function scales in TRD patients
Malone[122]	15	OLS	12 months	53.3	Significant improvement in depressive symptoms
Bergfeld[123]	25	RCT	52 weeks	40.0	Significant reversal of depressive symptoms in 10 out of 25 patients
MFB					
Davidson[124]	2	Crossover design	32 weeks	N/A	No clinical response
Coenen[125]	16	RCT	1 year	100.0 and 50.0	Rapid, measurable, and long-term antidepressant response to MFB-DBS after 1 year
Fenoy[126]	6	OLS	1 year	80.0	Profound antidepressant effects observed in long-term analysis
Bewernick[127]	8	OLS	12-48 months	75.0	Long-term results suggest acute and sustained antidepressant effect
Schlaepfer[28]	7	OLS	12-33 weeks	86.0	Rapid onset of antidepressant effects, with a high response rate
BNST					
Fitzgerald[128]	5	OLS, case study	12 months	60.0	Useful for reverting the highly refractory depression
Cassimjee[129]	1	Case series	12 months	N/A	Stimulating this target reduced psychiatric disorders and improved cognitive functioning
Raymaekers[35]	7	Crossover design	3 years	N/A	Simulating the ITP and BNST may alleviate depressive symptoms in TRD patients
Blomstedt[130]	1	Case series	36 months	N/A	Dramatic improvement in depressive scores after 12 months of treatment
LHb					
Sartorius[131]	1	CR	15 months	N/A	Sustained full remission of depressive symptoms in a TRD patient
ITP					
Jiménez[132]	1	CR	3 years	85.71	HAMD scale score reduced from 42 to 6

BNST = bed nucleus of the stria terminalis; CBF = cerebral blood flow; CGI = clinical global impressions scale; CR = case report; DBS = deep brain stimulation; HAMD = Hamilton depression rating scale; ITP = inferior thalamic peduncle; LHb = lateral habenula; MFB = medial forebrain bundle; NAc = nucleus accumbens; OLS = open-label study; QoL = quality of life; RCT = randomized controlled trial; SCG = subcallosal cingulate gyrus; TRD = treatment-resistant depression; vALIC = ventral part of the anterior limb of the internal capsule; VC/VS = ventral capsule/ventral striatum.

antidepressant response to SCG-DBS may be improved by person-specific electrode implantation through brain mapping techniques such as diffusion tensor imaging tractography. Merkl et al.[111] found no significant differences in depressive symptoms in eight patients randomized to a delayed-onset SCG-DBS group (4 weeks of sham-DBS) or non-delayed group. A meta-analysis of four retrospective trials of SCG-DBS showed response and remission levels of 36.6% (95%CI 25.8-48.9) and 16.7% (95%CI 6.3-37.5), 53.9% (95%CI 38.1-69) and 24.1% (95%CI 12.9-40.5), and 39.9% (95%CI 28.4-52.8) and 26.3% (95%CI 13-45.9) at 3, 6 and 12 months of follow-up, respectively.[148] In recent years, advances in targeting through neuroimaging have resulted in even more positive antidepressant outcomes.[34] It remains to be seen whether a new clinical trial could reproduce these findings.[149-151] Despite the fact that open-label trials have consistently demonstrated that DBS has a therapeutic effect on TRD, randomized controlled trials have not found similar results, which suggests that studies with greater power, refined techniques, and better participant selection could be necessary to achieve positive clinical outcomes.

DBS of the ventral capsule/ventral striatum

The VS is anatomically and functionally connected to brain regions such as the PFC, amygdala, and hippocampus, which are involved in regulating mood disorders, including depression.[152,153] DBS of the VC/VS has been associated with symptom improvement in patients with TRD.[129,154] However, in a randomized sham-controlled trial of DBS of the VC/VS, Dougherty et al.[120] observed 20, 26.7, and 23.3% response rates at 12, 18, and 24 months, respectively, with no significant differences between the active and sham groups.

Bergfeld et al.[123] published DBS data on 25 TRD patients who were implanted in the anterior limb of the internal capsule (ALIC), which is the caudoventral part of the VC/VS. Depressive symptoms significantly decreased after the first phase of the study, a 52-week open-label trial, and 40% of the participants were classified as responders. Sixteen patients participated in a subsequent randomized crossover phase, in which the active group benefitted more than the sham group, suggesting that chronic stimulation may be necessary for DBS therapy to be effective.[123] Two years of follow-up showed that ALIC-DBS had continued antidepressant efficacy, with the symptoms remaining stable or decreasing depending on the psychometric scale used.[119]

DBS of the nucleus accumbens

Anhedonia, a core symptom of major depression, is associated with reduced NAc volume and reduced reward response.[155] It has been suggested that the therapeutic effect of NAc-DBS is achieved by modulating hot zones in the NAc rather than by modulating network circuitry.[156] Bewernick et al.[116] conducted a long-term open-label study on 11 patients with TRD, reporting that NAc-DBS produced a sustained antidepressant effect (45.5% response rate at 48 months follow-up). Millet et al.[157] conducted an open-label study of six patients, three of whom presented a clinical response with no negative impact on cognitive function. While unilateral high-frequency stimulation of the NAc shell in rats did not change the depression-like phenotype compared to non-stimulated individuals,[158] a number of preclinical studies have shown that depression remitted following NAc-DBS.[122,144,145,152] In rodent studies, although NAc-DBS had an antidepressant effect, it impacted 5-HT and dopamine levels in the brain differently.[159,160] Sesia et al.[159] reported that the effects of DBS are region-specific. They observed that stimulation of NAc increases dopamine and 5-HT levels in the NAc shell compared to its core. However, Van Dijk et al.[160] found no change in dopamine or 5-HT levels after NAc-DBS. In a subsequent follow-up study, Van Dijk et al.[161] reported that stimulating the mPFC or orbital-PFC parts of the NAc had differential effects on dopamine, 5-HT, and norepinephrine levels.

DBS of the medial forebrain bundle

DBS of the superolateral branch of the MFB has been associated with considerable improvement of depressive symptoms in patients with TRD.[125-127] Schlaepfer et al.[28] found the first clinical evidence that MFB-DBS had a rapid antidepressant effect. Their short-term study found a rapid decrease in depression severity in six out of seven patients within 2 days of bilateral MFB stimulation, and four out of seven participants had a therapeutic response 1-week post-stimulation. They continued observing all six responders for 12 to 33 weeks, and four of them recovered completely.[28] Fenoy et al.[126] reported a clinical response 7 days after MFB-DBS in four out of six participants with TRD. In their follow-up publication, the same group had a $>$ 70% decrease in MADRS scores relative to baseline at 52 weeks. In fiber tracts analysis, they observed significant common orbitofrontal connectivity to the seed region in all responders. Modulation of cortical activity following MFB-DBS, particularly in Brodmann area 10, may be critical for antidepressant effects. In another long-term MFB-DBS study by the Schlaepfer group, a stable (for 4 years) 75% decrease in depressive symptoms was found in six of eight TRD patients.[127] While the MFB-DBS results from two groups in Germany and the United States indicate that there is a rapid, robust, and impressive antidepressant effect in the majority of patients, another recent study reported that two patients had no antidepressant effects 32 weeks after stimulation.[124] The methodology used in this small sample, however, was not well described and could have contributed to the poor outcome. To date, data has been published on 22 patients who received MFB stimulation to manage depressive symptoms. Nevertheless, other clinical trials are underway (clinicaltrials.org: NCT03653858, NCT04009928, and NCT02046330),[162] and their results are awaited with interest. To summarize, single-center open-label non-randomized studies with long-term acute application of MFB-DBS have shown clinical benefits and persistent antidepressant effects.

Some pre-clinical studies have commented on the underlying mechanisms of MFB-DBS, suggesting that it effects are significant because the MFB lies at the core of the reward pathway, connecting dopaminergic inputs from the midbrain ventral tegmental region to the PFC. In this context, Dandekar et al.[163] showed that activation of dopamine receptors in the PFC underlie antidepressant phenotypes following MFB stimulation. Similarly, increased mRNA expression of dopamine receptors D1 and D2 was reported following chronic and continuous MFB-DBS.[164] MFB-DBS also triggered dopamine release in the distant NAc region in a rodent model of depression.[165] Moreover, the importance of BDNF and neuroimmune cytokines in a stress-driven chronic depression model has been described, as well as their restoration following chronic MFB-DBS treatment.[166]

Deep brain stimulation of the lateral habenula

The LHb region plays a key role in regulating mood, reward, motivation, and stress responses.[167-169] It has been observed that electrical stimulation of the LHb is associated with improvement of depressive-like behavior in rats.[170] In a preclinical study of LHb-DBS, acute 5 Hz stimulation resulted in significant depressive-like behavior, while high frequency (100 Hz) stimulation reduced despair and anxiety responses, was well as increased hedonic-like effects.[171] Sartorius et al.[131] reported persistent remission of depressive symptoms following LHb-DBS for 4 months in one TRD patient. In a pre-clinical study, Meng et al.[137] reported that LHb-DBS significantly improved norepinephrine, dopamine, and 5-HT levels in peripheral and brain regions after 28 days of therapy, which partially explains its therapeutic mechanism of action.

DBS of the inferior thalamic peduncle

The ITP is a collection of fibers that connects the non-specific thalamic system to the orbitofrontal cortex. This system induces electrocortical activation and helps suppress input from irrelevant stimuli.[172,173] The ITP is an emerging therapeutic target in the treatment of TRD and other neuropsychiatric disorders. Jiménez et al.[132] reported a decrease in Hamilton Depression Rating Scale (HAM-D) scores (from 42 to 6) in one TRD patient following ITP-DBS.

DBS of the bed nucleus of the stria terminalis

The BNST is a complex brain region spreading from the NAc to the amygdala. Some recent studies have reported using BNST-DBS to treat TRD. In an open-label case series on TRD patients, Fitzgerald et al.[128] found 20 and 60% response rates at 6 and 12 months, respectively, after treatment with BNST-DBS. Another case study found a marked reduction in psychiatric distress and improved cognition after 1 year of BNST-DBS.[129] In another case study, one patient with anorexia nervosa and depression was first treated with MFB-DBS for 2 years and was then shifted to BNST stimulation.[130] After 12 months of BNST-DBS, the patient presented marked improvement in depressive scores (MADRS = 13 from 43 and HAM-D = 6 from 22). In a double-blind crossover study, the effects of BNST and ITP-DBS were assessed in seven TRD patients.[35] The outcomes during the two crossover periods in the first 16 months after surgery suggested that the effects of BNST stimulation were better than those of ITP stimulation. Three years after implanting the DBS device, all patients were stimulated in the BNST. Five of seven patients responded, and two were in remission. The improvement after BNST-DBS was more gradual but substantial. Due to the limited number of investigations, the efficacy of DBS at the two targets was not compared. The authors concluded that both BNST and ITP stimulation may alleviate depressive symptoms in patients with TRD.

Strengths of DBS

DBS has an advantage over non-invasive techniques in that it can precisely target critical nodes of brain circuitry.[108,174] A meta-analysis found a significant reduction of depression scores in DBS studies that targeted the SCG (-3.02; 95%CI -4.28 to -1.77, $p < 0.00001$), ALIC (-1.64; 95%CI -2.80 to -0.49, $p = 0.005$), NAc (-1.30; 95% CI -2.16 to -0.44, $p = 0.003$), and MFB (-2.43; 95%CI -3.66 to -1.19, $p = 0.0001$).[175] Many clinical trials have confirmed the long-term safety and efficacy of the DBS. As with VNS, when weighing the cost and potential complications of implanting hardware, it should be pointed out that in patients who receive continuous stimulation (with either VNS or DBS) the response is maintained for years. This is particularly important in TRD patients, who have very high rates of relapse even if they respond to non-invasive treatments. Around 160,000 patients worldwide have received DBS treatment for various neurological and psychiatric disorders, including TRD. Given the heterogeneity of depression, the optimal node may vary according to the patient's clinical and neurobiological characteristics. Yu et al.[176] investigated the structural brain measures associated with clinical phenotypes in depression. A total of 213 clinical items were assessed in patients with major depression, which yielded four groups: anxious misery, positive personality traits, reported history of emotional and physical abuse/neglect and reported history of sexual abuse. These clusters were associated with particular cortical thickness/subcortical volumes. For example, the authors found that while the anxious misery cluster was negatively associated with a cortical thickness/subcortical volume in the middle cingulate gyrus and posterior cingulate gyrus, the positive trait cluster was positively correlated with a cortical thickness/subcortical volume in the same regions. Whether these findings can help determine specific neuromodulation targets for different depression phenotypes is still unknown and worth investigation.[176] A proof-of-concept study on personalized DBS to treat depression found different emotional responses depending on the target region in a severe TRD patient who was implanted multisite intracranial electrodes across corticolimbic circuits.[177]

Limitations of DBS

DBS is highly invasive and expensive, and its implantation and follow-up require a multidisciplinary team. Some potential side effects include bleeding, infection, paresthesia, muscle contraction, dysarthria, diplopia, hypomania, and anxiety.[116,178] Most studies are open-label, have small samples, and do not have a sham-control group. Of note, this technique has been tested in two clinical trials, and both failed to demonstrate its efficacy. A Dutch study on DBS of the VC/VS found that depression returned when stimulation was discontinued.[123] However, this is not the same as conducting a double-blind placebo-controlled trial, such as that of Reclaim & Broaden, which failed.[120] MFB-DBS has not yet been tested in this manner.

Epidural cortical stimulation

ECS has been employed to selectively activate the dorsolateral prefrontal cortex (DL-PFC) and frontopolar cortex regions of TRD patients.[41,43,62] In this NT modality, the stimulating electrodes are directly positioned over these cortical areas. In a open-label study of ECS, Nahas et al.[41] reported a 60% (3 of 5 patients) response rate after 7 months of follow-up (Table 1). Kopell et al.[62] recruited 12 patients for a randomized, single-blind, sham-controlled open-label trial and reported $\geqslant$ 40% improvement in 6 of 12 patients, $\geqslant$ 50% improvement in 5 of 12 patients, and $<$ 10% improvement in 4 of 12 patients 104 weeks after left dorsolateral PFC stimulation. Williams et al.[43] published 5 years of data on five TRD patients treated with frontopolar cortex ECS and DL-PFC stimulation. They reported uniform response rates (41.2-54.9) between 7 months and 5 years of ECS. These results suggest that ECS has long-term efficacy as a TRD treatment. Williams et al.[43] also reported some adverse events, such as infection in one patient and device malfunction in four patients. These data indicate that chronic bilateral ECS over the frontopolar cortex and DL-PFC could be a promising technique for TRD treatment. Taken together, evidence from 2 groups with a total of 19 patients appears to indicate that ECS may be beneficial in TRD treatment, although large trials are necessary to confirm this.

Strengths of ECS

Electrical stimulation with this method is a unique therapeutic approach, which selectively triggers the cortex without interference from the scalp and skull. This method is probably safer and is less invasive than DBS since it does not require penetration of the dura.[179]

Limitations of ECS

Device implantation may lead to infection at the wound site (3-6% of patients). Stimulating the left DL-PFC with ECS is still ambiguous due to the broad area it covers. Moreover, the precise site of electrode implantation during ECS has not been fully standardized in order to maximize the efficacy of the treatment.[180]

Conclusions

There is growing therapeutic potential for invasive neuromodulation that targets mood neurocircuitry. Given that $\sim$ 30% of depressive patients fail to fully respond to interventions, such as pharmacotherapy and psychotherapy, or to non-invasive neuromodulation approaches, such as ECT or repetitive transcranial magnetic stimulation, alternative treatment options, such as ECS, VNS, and DBS, have been considered.[41,87,114] While the clinical results of invasive NTs trials related to TRD management are still inconclusive, several clinical brain stimulation studies have documented rapid and robust antidepressant effects. Importantly, no major side effects have been reported in long-term invasive NTs trials.[181,182] Long-term VNS treatment resulted in a dramatic remission of depressive symptoms in two-thirds of depressive patients. For DBS, targets such as the SCG, NAc, VC/VS or ALIC, MFB, LHb, ITP, and BNST have been identified as critical nodes for TRD management. Although ECS is an alternative invasive treatment option, only a few cases have been reported and larger trials are needed to confirm its potential for TRD. Based on current data, invasive NTs may be considered a promising therapy for TRD. However, additional randomized and double-blind clinical trials with a greater number of patients will provide more meaningful information on the safety and efficacy of each stimulation method. It is likely that an in-depth understanding of the neurobiology of TRD may lead to precise and personalized treatments, improving the safety and efficacy of invasive NTS.

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