The Application of Vagus Nerve Stimulation and Deep Brain Stimulation in Depression

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Abstract
Despite the progress in the pharmacotherapy of depression, there is a substantial proportion of treatment-resistant patients. Recently, reversible invasive stimulation methods, i.e. vagus nerve stimulation (VNS) and deep brain stimulation (DBS), have been introduced into the management of treatment-resistant depression (TRD). VNS has already received regulatory approval for TRD. This paper reviews the available clinical evidence and neurobiology of VNS and DBS in TRD.

The principle of VNS is a stimulation of the left cervical vagus nerve with a programmable neurostimulator. VNS was examined in 4 clinical trials with 355 patients. VNS demonstrated steadily increasing improvement with full benefit after 6–12 months, sustained up to 2 years. Patients who responded best had a low-to-moderate antidepressant resistance. However, the primary results of the only controlled trial were negative. DBS involves stereotactical implantation of electrodes powered by a pulse generator into the specific brain regions. For depression, the targeted areas are the subthalamic nucleus, internal globus pallidus, ventral internal capsule/ventral striatum, the subgenual cingulated region, and the nucleus accumbens. Antidepressant effects of DBS were examined in case series with a total number of 50 TRD patients. Stimulation of different brain regions resulted in a reduction of depressive symptoms. The clinical data on the use of VNS and DBS in TRD are encouraging. The major contribution of the methods is a novel approach that allows for precise targeting of the specific brain areas, nuclei and circuits implicated in the etiopathogenesis of neuropsychiatric disorders. For clinical practice, it is necessary to identify patients who may best benefit from VNS or DBS.

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Introduction
Depression with its serious medical, social and economic consequences represents a major burden to the patients, their families and the society. One-year prevalence of major depressive disorder (MDD) found in the US population sample was 6.6% and the lifetime prevalence was 16.2% [1]. In a large European epidemiological project, the 12-month prevalence of depression was 3.9% (2.6% for males and 5.0% for females) and the observed lifetime prevalence was 12.8% (8.9% males, 16.5% females) [2]. Depression is among the leading causes of disability; the WHO ranks it as a number one cause indexed by the
years lost due to disability’ across the world, in both low- and middle-income countries [3]. The WHO projects that, according to the measure ‘disability-adjusted life year’, depression will rise from number 3 among the 10 leading causes of burden of diseases in 2004 to the global top position in 2030. The financial costs of depression in 2000 were USD 83.1 billion per year in the US [4] and over GBP 9 billion in the UK [5].

Despite the progress in the pharmacotherapy of depression, there is still a substantial and growing proportion of patients who are not responding to available antidepressants, do not tolerate drug therapy, are partial responders, display residual symptoms, or are labeled as treatment resistant. Treatment-resistant depression (TRD) affects from 15% up to one third of depressive patients [6, 7]. TRD is defined as an episode of depression that does not respond to 1 or typically 2 or more adequate treatment trials. TRD is not a nosological entity, and most likely does not share a common etiology and pathological mechanisms [8]. Treatment-refractory patients are quite a heterogeneous group not responding or not tolerating treatment due to different reasons. In addition to the recommended pharmacological strategies how to overcome treatment resistance (e.g. switch to a different class of antidepressant, augmentation, or combination) [6], other therapeutic options, nonpharmacological interventions, are tested [8].

Modern stimulatory methods were introduced into psychiatry in the 20th century: ‘shock therapy’, insulin-induced coma, Metrazol-induced convulsion, electroconvulsive therapy (ECT), and nonspecific and targeted psychosurgery [9, 10]. The renewed interest in stimulatory methods came along with the safer interventions allowing for precise targeting of key structures and with a better understanding of underlying neurobiological mechanisms of psychiatric disorders. In addition to the traditional ECT, repetitive transcranial magnetic therapy, magnetic seizure therapy, vagus nerve stimulation (VNS), and deep brain stimulation (DBS) have become alternative nonpharmacological treatment options for many psychiatric patients. Other experimental procedures, such as epidural prefrontal cortical stimulation, are under investigation [11].

VNS and DBS were adopted from neurology. The rationale behind the first use of VNS and DBS in affective disorders was originally based on anecdotal observations and case reports of neurological patients who improved independently of seizure reduction. Additional lines of reasoning stem from the administration of anticonvulsants and induced seizures (ECT) in the therapy of mood disorders. In this paper, we review the current state of the clinical evidence, the neurobiological basis, and evaluate the potential for clinical application of VNS and DBS in depression.

Vagus Nerve Stimulation

VNS has been available for treatment-resistant epilepsy since the 1990s; for depression, it was first registered in Europe and in Canada in 2001, and in the US in 2005. VNS is approved for patients with chronic or recurrent depression who failed to respond to at least 4 antidepressant interventions, but patients are not required to have failed to respond to ECT [12].

Principles of VNS

The term ‘vagus nerve stimulation’ generally refers to several different techniques used to stimulate the vagus nerve [13]. In animal studies, the vagus may be accessed via the abdomen and diaphragm. VNS in humans specifies stimulation of the ascending fibers of the left cervical vagus nerve using a programmable neurostimulator, pacemaker-like device, implanted in the left chest wall. The battery-powered stimulator delivers electrical impulses through a subcutaneous bipolar lead. The electrode is wrapped around the left vagus nerve in the neck, near the carotid artery. Implantation is usually an outpatient procedure under local anesthesia requiring two small incisions and is typically performed by a neurosurgeon. The neurostimulator programming wand with software and a portable computer provide telemetric communication with the pulse generator that enables device programming and data retrieval. Stimulator settings are programmed to deliver intermittent stimulation with a current of 0.25–3.0 mA, a frequency of 20–50 Hz, and a pulse width of 500 ns for 30–90 s every 5–10 min. Each patient is given a magnet that, when held over the pulse generator, turns stimulation off. When the magnet is removed, stimulation resumes [13].

The device is turned on after the recovery postimplantation period, in most cases after 2 weeks. In the reviewed studies, stimulation parameters were adjusted gradually over the course of the next 2 weeks with increasing intensity (increments of 0.25 mA output current) to the maximal level that could be comfortably tolerated by the patient. Additional adjustments (increase or decrease) during long-term follow-up can be made according to ef-
ficacy and safety. The frequency of visits is initially once a week, biweekly during the acute phase and monthly in the chronic phase. In the course of VNS therapy, concomitant treatment with antidepressants, mood stabilizers, or other psychotropic drugs is permitted. Patients with VNS can be administrated ECT when the stimulator is turned off. The duration of therapy depends on the battery life (several years, depending on the settings); the stimulator is replaceable.

**Neurobiology of VNS**

The exact mechanism of antidepressant action of VNS is not fully understood. Hypotheses are based on the neurobiology of the vagus nerve and its effects on brain functions implicated in mood control [14, 15]. The vagus nerve is a mixed nerve composed of about 80% afferent fibers. Antidepressant effects are attributed partially to the projection of afferent fibers to the nucleus tractus solitarius that relays incoming sensory information to the brain through an automatic feedback loop, direct projections to the reticular formation in the medulla, and ascending projections to the forebrain via the parabrachial nucleus and the locus coeruleus. The locus coeruleus is the site of many norepinephrine-containing neurons that have important connections to the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions responsible for mood and anxiety regulation [14–16].

Both human and animal studies indicate that VNS evokes changes in neurotransmitters implicated in the pathophysiology of depression, i.e. serotonin, norepinephrine, GABA, and glutamate [17–21]. Neuroimaging studies with SPECT, PET, and functional MRI demonstrate that VNS induces changes in regional cerebral blood flow (rCBF) similar to those seen with antidepressants [22–24]; either in the amygdala or in the hippocampus or parahippocampus [14].

Hypothesized antidepressant action is further supported by the findings from animal studies. Acute VNS in rats increased the expression of brain-derived neurotrophic factor and fibroblast growth factor in the hippocampus and cerebral cortex, decreased the abundance of nerve growth factor mRNA in the hippocampus, and increased the norepinephrine concentration in the prefrontal cortex [25]. Similarly, chronic VNS increased neuronal plasticity and brain-derived neurotrophic factor activity in rats’ hippocampus [26]. However, no changes in brain-derived neurotrophic factor concentrations following VNS were found in patients [27].

**Clinical Trials of VNS in Depression**

In a study sample of 20 adult epilepsy patients who underwent VNS implantation and 20 patients with no intervention, mood was assessed at baseline and after 3 months [28]. In addition to the reduction of seizure frequency, the VNS group showed a significant improvement in depression rating scales across time. However, no change was detected in anxiety measure and the groups did not differ significantly in mood improvement. Similar results, i.e. mood improvement independent of seizure control, were observed in 11 patients receiving VNS for epilepsy [29]. In the Czech case series of 3 TRD patients, VNS was found to be well tolerated, with a gradual onset of action and fluctuating course of depression over the long-term follow-up of 4–6 years [30]. Besides anecdotal and case reports, efficacy of VNS in treatment of depression was investigated in a total of 4 study samples (table 1). All the trials, referred to under code labeling from a device manufacturer (D01–D04), were add-on and included treatment-resistant patients.

The first open trial examined 30 patients who failed to respond to ≥2 antidepressant medication treatments from different classes during the current episode [31]. VNS efficacy was evaluated during a 10-week active stimulation with a follow-up of 10 months. As a concomitant therapy, antidepressants and/or mood stabilizers at a stable dosage from baseline throughout a 12-week active period were allowed. Study results demonstrated that a baseline 28-item Hamilton Rating Scale for Depression (HRSD28) score of 38.0 ± 5.5 significantly decreased at the acute study exit (23.0 ± 10.8). Similar improvement over time was reported for the Montgomery-Asberg Depression Rating Scale (MADRS) scores (33.8 ± 5.6 and 20.1 ± 12.2, respectively). Response rates, defined as ≥50% reduction in baseline scores, were 40% for both HRSD and the Clinical Global Impressions-Improvement and 50% for the MADRS. No patient discontinued due to adverse events. The most frequently reported events were hoarseness, throat pain, headache, shortness of breath, general pain, neck pain, and abnormal wound healing.

Investigators continued with subject enrollment over time and the original study sample doubled in size; 60 patients had implanted VNS. Reassessments of the total study group were performed at 10 weeks [32] and 24 months [33]. Data from the 10-week evaluation of 59 patients showed a 30.5% response rate for HRSD28, 34.0% for MADRS, and 37.3% for Clinical Global Impressions. Voice alteration or hoarseness was the most common side
effect. The 2-year outcome analysis demonstrated increasing improvement reaching the maximum at 1 year, which was maintained for the rest of the follow-up [32]. Analysis of the primary treatment outcome detected that the HRSD$_{28}$ response rate at 3 months was 31%, after 1 year 44%, and at the endpoint of 2 years 42%. Remission rates were 15, 27, and 22%, respectively. Side effects diminished over time, with a low dropout rate; at the endpoint, 90% of patients had their device still implanted and 81% activated.

The European D03 study [34, 35] was an open-label add-on trial with 74 TRD patients, using a design identical to that in the US D01 trial. European patients were more frequently diagnosed with recurrent unipolar depression, had more lifetime episodes of depression, less treatment trials and a marginally lower score in HRSD$_{28}$.

### Table 1. Add-on studies of VNS in TRD

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Number</th>
<th>Duration of active treatment</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>D01 (open, pilot)</td>
<td>Rush et al. [31], 2000</td>
<td>30</td>
<td>10 weeks</td>
<td>Response rates HRSD: 40% MADRS: 50%</td>
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<tr>
<td></td>
<td>Sackeim et al. [32], 2001</td>
<td>59</td>
<td>10 weeks</td>
<td>Response rates HRSD: 31% MADRS: 34%</td>
</tr>
<tr>
<td></td>
<td>Nahas et al. [33], 2005</td>
<td>59</td>
<td>24 months</td>
<td>Response rate HRSD: 42% Remission rate HRSD: 22%</td>
</tr>
<tr>
<td>D02 (double-blind acute phase plus open-label follow-up)</td>
<td>Rush et al. [36], 2005</td>
<td>222 (112 active, 110 sham)</td>
<td>10 weeks</td>
<td>Response rates (HRSD) Active: 15% Sham: 10% (n.s.) Response rates (IDS-SR) Active: 17% Sham: 7% (p &lt; 0.03)</td>
</tr>
<tr>
<td></td>
<td>Rush et al. [37], 2005</td>
<td>205</td>
<td>12 months</td>
<td>Response rates HRSD: 27% MADRS: 28% Remission rate HRSD: 16%</td>
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<tr>
<td>D03 (open-label)</td>
<td>Schlaepfer et al. [34], 2008</td>
<td>74</td>
<td>12 months</td>
<td>Response rate HRSD: 53% Remission rate HRSD: 33%</td>
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<tr>
<td></td>
<td>Bajbouj et al. [35], 2010</td>
<td>49</td>
<td>24 months</td>
<td>Response rate HRSD: 53% Remission rate HRSD: 39%</td>
</tr>
<tr>
<td>D04 (open, comparative)</td>
<td>George et al. [38], 2005</td>
<td>205 (VNS + TAU)$^a$</td>
<td>12 months</td>
<td>Improvement (IDS-SR) VNS+TAU &gt; TAU Response rate (HRSD) VNS+TAU: 27% TAU: 13% (p &lt; 0.01)</td>
</tr>
</tbody>
</table>

IDS-SR = Inventory of Depressive Symptomatology – Self-Report; n.s. = not significant.

$^a$ Study sample from D02.
but not in MADRS. Response rates (HRSD28) increased from 37% after 3 months to 53%, which is the rate that was sustained up to 2 years (53.1%). Remission rates were 17, 33, and 38.9%, respectively. The most common side effects were voice alteration, coughing, and pain. Of the total sample of 74 patients who had VNS implanted, 60 patients (81.1%) were evaluated at the end of the 12-month period and 49 (66.2%) at the 2-year endpoint. Of the 24 patients who terminated prematurely, 8 (33.3%) met response criteria, and 2 patients committed suicide.

A double-blind trial compared active stimulation versus sham in 235 subjects with a DSM-IV diagnosis of MDD (unipolar or bipolar) who had been in the current episode of depression for a minimum of 2 years or who had at least 4 lifetime depressive episodes [36]. All participants were implanted with a VNS device and randomized 1:1 to active or inactive (sham) stimulation. After a 2-week recovery period following the surgical procedure, patients with an HRSD23 score ≥18 entered the acute phase. The active group had stimulation parameters adjusted over the first 2 weeks and subsequently fixed for the remaining 8 weeks of the study. The primary outcome measure was response, i.e., a ≥50% reduction of the total HRSD24 score. However, study results failed to detect a significant difference between the response rate to active and sham stimulation (15 vs. 10%, respectively; p = 0.251). Of the secondary measures, only subjective self-report of depression (Inventory of Depressive Symptomatology) yielded statistical difference favoring active intervention (response rates: 17 vs. 7.3%, respectively; p = 0.032). Two patients from the active group did not complete the study because of adverse events; one due to infection related to implantation and the second committed suicide. The most frequently reported side effects were voice alterations, cough, dyspnea, dysphagia, neck pain, paresthesia, vomiting, laryngismus, and dyspepsia.

Following the acute phase of the original study, all patients could enter a 12-month open extension trial [37]. The subjects who previously received sham treatment were eligible if their HRSD24 score was ≥18. The analysis demonstrated a significant reduction of depressive symptoms in the primary outcome measure: the mean rate of improvement in the HRSD24 score was 0.45 points (SE = 0.05) per month (p = 0.001). The response rate at the endpoint was 27.2% and the remission rate (HRSD24 ≤9) was 15.8%. Similar results were shown for secondary measures, i.e., MADRS and Clinical Global Impressions: response rates were 28.2 and 34%, respectively. The most common side effects included voice alteration, dyspnea, and neck pain.

The study sample (n = 205) from the extension trial [37] was used for a retrospective, nonrandomized comparison of combined VNS plus ‘treatment as usual’ (TAU) intervention versus TAU alone (n = 124) after 12 months of stimulation [38]. Combined intervention was found to be more effective on both primary (Inventory of Depressive Symptomatology-Self-Report; p < 0.001) and secondary measures: HRSD24 response rates were 27% for VNS + TAU versus 13% for TAU (p < 0.01).

Evaluation of the VNS Data

Slower onset of antidepressant action suggests that VNS is not suitable for acute treatment of TRD [39]. Given the fact that full benefit is observed after 6–12 months of stimulation with sustained efficacy up to 2 years, VNS may be indicated for long-term control of symptoms of depression. VNS proved to be effective in reducing severe, persistent symptoms and in reducing exacerbations of depression. Patients who respond best to VNS are those with a low-to-moderate, but not extreme antidepressant resistance and patients with a lower number of unsuccessful drug trials during the current mood episode. For example, in the study D01, patients who never received ECT were found to be 4 times more likely to respond to VNS; none of the 13 patients who had failed to respond to more than 7 adequate antidepressant trials in the current episode responded, compared to 39% of the rest of the patients [32].

The number of female subjects in the VNS trials (63–68%) approximately represents the clinical population. Although no additional analysis of efficacy or tolerability according to gender was performed, examination of predictors of outcome in the D01 study found that gender was not a prognostic factor of response [32]. No further information was provided on the efficacy and safety in elderly patients. The median age of stimulated subjects was 47–48 years, and inclusion criteria set the upper age limit to 70 years in the US studies and 80 years in the European trial. The oldest patient was 78 at the time of implantation; no specific age-related complications were reported [35]. Whereas VNS in epilepsy is labeled for use in children from 12 years of age, its use for treatment of mood disorders in children and adolescents has not been studied.

Post hoc analysis of the controlled D02 trial examining a small subpopulation (n = 25) of patients with bipolar I and II disorder [40] suggested that VNS may also be effective in bipolar disorder. Index episodes of bipolar depression were as severe as unipolar depression but of shorter duration; nevertheless, acute and long-term (12-
and 24-month outcomes were similar. Rapid-cycling bipolar patients were unvaryingly excluded from the reviewed studies; the first data on the application of VNS in this difficult-to-treat population was reported by Marangell et al. [41]. The results from 9 outpatients with treatment-resistant rapid-cycling bipolar disorder showed that VNS can over the course of 1 year produce significant improvement in the global measure of illness, as well as in specific symptom domains. The pilot data need further replication. The rate of stimulation-induced switch to mania or hypomania in the VNS trials was low (2–3 per study), mostly in patients with bipolar disorder or a history of drug-induced switch. From the clinical point of view, the switch can be considered as an indirect evidence of antidepressant activity. The manic symptoms usually subsided with adjustment of stimulation parameters. The number of suicide attempts (3–5% per study) was higher than expected in a population of treatment-resistant patients [35]; nonetheless, it should be noted that more than 50% of patients who attempted suicide had a prior history of at least one suicide attempt.

Overall, VNS is safe and well tolerated. VNS had no deleterious cognitive effects [42], improved sleep architecture [43] and in one case report was found to be safe in pregnancy [44].

Negative results of the only controlled trial with VNS in primary outcome measure are intriguing and require closer scrutiny. Since the open trials have shown additional improvement in symptoms beyond 12 weeks, the double-blind study may not have been of adequate duration. Moreover, the patients may have been undosed (varying dosages of concomitant medication), or the study was not sufficiently powered to detect a smaller amount of benefit. Finally, the comparable rate of objectively measured improvement between active and sham stimulation may indicate a strong placebo effect of the procedure.

Deep Brain Stimulation

The main clinical use of DBS is in neurological conditions, essential tremor, motor symptoms in Parkinson’s disease, dystonia, epilepsy, and chronic pain [45, 46]. In psychiatry, DBS has been examined first in the treatment of refractory obsessive-compulsive disorder (OCD) and Tourette syndrome, and more recently in major depression [47]. In 2009, DBS was approved for treatment of otherwise intractable OCD in Europe and the US FDA approved the administration of DBS under the Humanitarian Device Exemption program for chronic and severe OCD [48].

Principles of DBS

DBS is a surgical procedure that involves stereotactic implantation of electrodes into the targeted brain regions. The electrodes are powered via leads by a subcutaneously placed pulse generator. During a surgical procedure, a pulse generator is being implanted subcutaneously in the chest, near the clavicle [45, 46, 49]. The generator sends electric impulses via 1 or 2 leads tunneled under the scalp to the anchoring points in the skull. The anchoring points are attached to the electrodes stereotactically implanted into the brain. The paired electrodes include up to 5 platinum/iridium contact areas that usually spread sequentially to cover additional parts of the targeted anatomical site. Stereotactical techniques using neuroimaging methods, a surgical navigation computer, together with stereotactic brain atlases enable to aim any intracranial structure within millimeter precision [45].

Programmable contact sites on the leads allow for the adjustment of stimulation in different anatomical regions. Stimulation parameters are set and modulated by the portable device that programs the pulse generator. Self-programming devices also allow patients to activate and deactivate the stimulation. The settings may vary greatly, with a pulse width between 60 and 450 μs, voltage between 0 and 10.5 V, and pulse frequency from 2 to 250 Hz. Stimulation can be either continuous or intermittent.

Currently, there is no standardized procedure for active stimulation onset, setting adjustment, or frequency of visits for depressive patients. The postoperative recovery phase with stimulation turned off can thus last from 1 up to 4 weeks. Adjustment of stimulation parameters in the acute phase is typically gradual, at least once a week, with increasing intensity while observing for immediate response. Chronic stimulation parameters are set on the basis of positive mood effects and absence of adverse effects. The frequency of visits during the chronic phase is once a month or less, depending on the protocol. As in the VNS, duration of stimulation is limited by the battery life.

Neurobiology of DBS

Similarly to VNS, the precise mechanism of action remains largely unknown [45]. DBS induces an electrical field in the brain tissue that attenuates exponentially with the distance from the electrode. Originally, inhibitory effects of DBS mediated by depolarization blockade,
synaptic inhibition, and synaptic depression were assumed. However, an excitatory response to high-frequency DBS has also been found [50]. The most likely explanation is a stimulation-induced modulation of impaired network activity. DBS is not producing a lesion; it may rather alter complex firing patterns of the neurons in the region and thus modify activity in the neuronal circuits. Gray matter and neurons have different responsiveness, as well as myelinated and unmyelinated fibers. Moreover, effects on glia may also play an important role and the therapeutic effects of DBS differ across the target points [51].

The targeted brain structures for Parkinson’s disease are subthalamic nuclei, for dystonia the globus pallidus internus, for cluster headache the ipsilateral ventroposterior hypothalamus, for OCD the anterior limb of the capsula interna, and for depression the subthalamic nucleus, internal globus pallidus, ventral internal capsule/ventral striatum, subgenual cingulate region, nucleus accumbens (NA), inferior thalamic peduncle, and the lateral habenula [47, 52]. There are several physiological methods for verification of the anatomical target, including micro-electrode and semi-microelectrode recording of the spontaneous and evoked electrical activity, or macro-

### Table 2. Case series of DBS in TRD

<table>
<thead>
<tr>
<th>Target area</th>
<th>Reference</th>
<th>Number</th>
<th>Duration of follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgenual cingulate gyrus</td>
<td>Mayberg et al. [62], 2005</td>
<td>6</td>
<td>6 months</td>
<td>Response rate</td>
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<tr>
<td></td>
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<td></td>
<td>HRSD: 67%</td>
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<td>Remission rate</td>
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<td></td>
<td>HRSD: 50%</td>
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<td>Lozano et al. [63], 2008</td>
<td>20</td>
<td>12 months</td>
<td>Response rate</td>
<td>HRSD: 55%</td>
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<td>Remission rate</td>
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<td></td>
<td></td>
<td>HRSD: 35%</td>
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<tr>
<td>Kennedy et al. [80], 2011</td>
<td>20</td>
<td>36–72 months</td>
<td>Response rates (HRSD)</td>
<td>Year 3: 75%</td>
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<td>Last follow-up: 64%</td>
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<td>Remission rates (HRSD)</td>
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<td></td>
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<td>Year 3: 50%</td>
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<td>Last follow-up: 43%</td>
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<tr>
<td>Ventral capsule/ventral striatum</td>
<td>Malone et al. [64], 2009</td>
<td>15</td>
<td>6–51 months (mean 23.5 months)</td>
<td>Response rates</td>
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<td></td>
<td>HRSD: 53%</td>
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<td>MADRS: 53%</td>
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<td></td>
<td>Remission rate</td>
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<td>HRSD: 40%</td>
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<td></td>
<td></td>
<td>MADRS: 30%</td>
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<tr>
<td></td>
<td>Malone [65], 2010</td>
<td>17</td>
<td>14–67 months (mean 37.4 months)</td>
<td>Response rate</td>
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<td>MADRS: 71%</td>
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<td>Remission rate</td>
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<td></td>
<td>MADRS: 35%</td>
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<tr>
<td>Anterior limb of capsula interna</td>
<td>Gabriëls et al. [69], 2007</td>
<td>3</td>
<td>6 months</td>
<td>Response rate</td>
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<td></td>
<td>MADRS: 100%</td>
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<td></td>
<td>Remission rate</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MADRS: 66.6%</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>Schlaepfer et al. [70], 2008</td>
<td>3</td>
<td>‘several months’ (on/off)</td>
<td>Improvement</td>
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<td></td>
<td></td>
<td>HRSD (p &lt; 0.01)</td>
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<td>MADRS (p = 0.03)</td>
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<tr>
<td></td>
<td>Bewernick et al. [71], 2010</td>
<td>10</td>
<td>12 months</td>
<td>Response rate</td>
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<td></td>
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<td>HRSD: 50%</td>
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stimulation. Alternatively, preoperative diffusion tensor imaging for connectivity-based cortical mapping was suggested for more precise targeting of the key structures within the anterior cingulate cortex [53].

**Clinical Trials of DBS in Depression**

Introduction of DBS into psychiatry was based on the first anecdotal cases reporting stimulation-provoked mood changes, depression and mania in patients without psychiatric history. Antidepressant effects following the stimulation of the globus pallidus internus and subthalamic nuclei in several subjects with movement disorders were documented with the depression rating scales [54, 55]. In a case series of 27 patients with Parkinson’s disease, a significant improvement of mood at 5 weeks and 3 months after surgery and stimulation of the bilateral subthalamic nucleus was demonstrated [56]. However, the antidepressant effect was lost at 6, 12, and 18 months, and the HRSD score was similar to the control group. In a case report of a female patient with comorbid MDD and borderline personality disorder and bulimia, who underwent DBS in the inferior thalamic penduncle under a double-blind protocol (alternating on and off stimulation), depressive symptoms significantly diminished and neurocognitive performance improved during active stimulation [57, 58]. Reduction of depression symptoms in a patient with comorbid OCD and MDD was found after implantation of electrodes into the ventral caudate nucleus, when the tip of the electrode stimulated the NA [59, 60]. Interestingly, a similar case report of OCD-depression comorbidity, where the electrode did not reach the NA, described worsening of depression symptoms after active stimulation and the patient required reintroduction of antidepressant medication [60]. A complete remission of severe TRD was reported in a 64-year-old female patient after bilateral stimulation of the lateral habenula, the site of interaction of the serotonergic, noradrenergic, and dopaminergic systems [61].

Pilot data from nondepressed patients and individual case vignettes were subsequently examined in several case series of patients with TRD; the total number of subjects in published reports on case series is now 50 (table 2).

In an open study of 6 TRD patients, Mayberg et al. [62] implanted DBS bilaterally in the white matter fibers connecting to the Brodmann area 25 in the subgenual cingulate gyrus and used chronic high-frequency stimulation. All 6 patients reported acute improvement following stimulation. After 2 months, 2 subjects demonstrated a more than 50% decrease in the HRSD score. At 6 months of DBS, 4 subjects out of 6 achieved response and 3 remission of MDD (HRSD score \(\leq 8\)). At 1 month of DBS, rCBF was decreased in the stimulated area and adjacent orbital frontal cortex. Responders had an additional reduction in rCBF of the medial cortex, and an increase in CBF to dorsal prefrontal anterior cingulate and parietal cortices, unlike nonresponders.

The original study sample was expanded to include a total of 20 patients followed up for up to 3–6 years [63, 80]. The results indicate progressive improvement from week 1 (40% of patients responded, 1 in remission) to 6 months when a plateau was reached (60% responders, 35% remitters). Long-term follow-up indicates a fluctuating course that is difficult to interpret. Response rates between year 1 and 2 decreased from 62.5% to 46.2% and increased up to 75% at year 3 and 64.3% at the last follow-up visit (observed cases). Similarly, remission rates after 1, 2, and 3 years were 18.8, 15.4, and 50%, respectively [80]. PET scans (using \(^{18}\)FDG) confirmed metabolic changes in the specific cortical and limbic regions implicated in the pathogenesis of depression [62]. DBS was well tolerated; however, 2 patients died by suicide during depressive relapses, 2 other patients made suicide attempts and one died from causes unrelated to depression [80]. Most frequently reported adverse events were perioperative headache and wound infections (both \(n = 4\)); 3 patients had their hardware removed with 1 subsequent re-implantation. One patient experienced a generalized seizure at the evening of surgery.

A different stimulation area for TRD, i.e. ventral capsule/ventral striatum, was targeted in a multicenter study reported by Malone and colleagues [64, 65]. The ventral capsule/ventral striatum region is traditionally stimulated in OCD; in addition, it also has a pathophysiological role in depression [66, 67]. Moreover, stimulation of the ventral capsule/ventral striatum resulted in a PET-measured reduction of subgenual cingulate activity, otherwise hyperactive in depression [68]. Fifteen or 17 [65] chronic refractory patients were followed for a minimum of 6 months up to 4 years. Both continuous and categorical primary efficacy measures (HRSD, MADRS, Global Assessment of Functioning) demonstrated statistically significant improvement. In the total study sample of 17 patients, the response rate for the MADRS (\(\geq 50\%\) reduction) was 53% at 3 months, 47% at 6 months, 53% at 12 months, and 71% at the last follow-up (range from 14 to 67 months; mean 37.4 months). Remission rates according to the MADRS were: 35, 29, 41, and 35%, respectively.
There were a total of 25 serious adverse events reported in 6 patients. Four of them were DBS-related: 1 case of occipital pain, 1 case of a lead fracture, and 2 incidents of hypomania.

A case series of 3 subjects with TRD reported clinically significant improvement after 6 months of bilateral DBS in the ventral part of the anterior limb of the internal capsule [69]. All 3 patients, who previously failed to respond to years of pharmacotherapy, psychotherapy, and ECT, yielded ≥50% reduction in severity of depression on the MADRS and 2 of them achieved remission. Quality of life improved as well.

Schlaepfer with collaborators [70, 71] selected to target the reward system, presumably impaired in depression [72–74]. In an account of 3 severely depressed patients who failed to respond to psychotherapy, pharmacotherapy, and ECT trials, DBS stimulated the NA in a double-blind manner, alternating voltage from 0 to 4 V. Immediately after switching the stimulation on, 2 out of 3 patients reported spontaneously increased exploratory motivation, consistent with the role of NA in the reward-seeking behavior. Clinical assessments in all 3 subjects (using HRSD and MADRS) demonstrated significant improvement when the stimulator was on and immediate worsening during periods when it was turned off. A negative correlation between stimulation and depression rating scores was found (increased stimulation resulted in score reduction). No side effects were reported. PET imaging using 18FDG showed significant metabolic activation in the bilateral ventral striatum (including NA), the bilateral dorsolateral and dorsomedial prefrontal cortex, the cingulate cortex, and the bilateral amygdala. Decreased metabolism after stimulation was detected in the ventromedial and ventrolateral prefrontal cortex, dorsal caudate nucleus, and thalamus.

Long-term stimulation of the NA over the course of at least 12 months in an extended sample yielded positive response (defined as 50% reduction in the HRSD score) in 5 out of 10 refractory patients [71]. Moreover, secondary analyses demonstrated reduction of anxiety symptoms in responders and an increased level of positive ("hedonic") activities in the total sample. Functional imaging assessment of 7 patients with PET revealed decreased metabolic activity in the prefrontal subregions (orbital prefrontal cortex, subgenual and posterior cingulate cortices, thalamus, and caudate nucleus) and an increase in the precentral gyrus. In contrast to the previous report [70], long-term DBS did not induce an increase in NA metabolism, suggesting thus different effects of acute and chronic stimulation. It may be of interest that the originally planned sham-controlled design had to be changed by the authors to open-label. The reason was rapid and massive worsening of depressive symptoms during off phases or accidental discontinuation of stimulation.

**Evaluation of the DBS Data**

Data from a small set of patients suggest an antidepressant effect of DBS in different brain regions. Numerous stimulation targets producing similar effects plus a small number of subjects make it difficult to draw any definite conclusions. Initial mood improvement, observed immediately after implantation without electrical stimulation, suggests a possible placebo effect. However, in a controlled paradigm (on/off comparison), active stimulation was clearly separated from inactive intervention.

A small number of depressed patients treated with DBS does not allow for any detailed analysis of efficacy and safety according to gender or to examine effects in elderly patients. The proportion of females in study samples varied from 40 to 73%, the mean age from 46 to 49 years. The oldest patient with provided age was 66 years at the time of implantation [70]. Almost all subjects were diagnosed with unipolar major depression, reports identified 1 patient with bipolar I [64] and 1 patient with bipolar II [62, 63] disorder. A stimulation-induced switch to hypomania that resolved after parameter modification was registered in a patient with bipolar I disorder [64] and in 2 patients from a German case series [71].

Previously, there have been reports on series of suicides in patients successfully treated with DBS of the subthalamic nucleus for movement disorders [75–77]. An international multicenter retrospective survey of 5,311 Parkinson’s disease patients treated with DBS found a rate of completed suicides of 0.45% and a rate of suicide attempts of 0.90% [76]. The authors identified postoperative depression, a history of impulse control disorder, and some demographic factors (being single, younger age at onset, history of suicide attempt) as risk factors associated with suicide risk. A second retrospective analysis of a sample of 200 patients confirmed postoperative depression and impaired impulse control, but not other demographic or clinical characteristics as predictors of suicide attempt [77]. In addition, in an animal study high-frequency stimulation of the subthalamic nucleus resulted in a decrease in the neighboring serotonin neurons and subsequent depressive-like behavior in rats [78]. This effect was reversible with antidepressant modulating serotonin.
neurotransmission. It should be noted that suicide behavior in depressed patients with DBS was observed with the stimulation of different brain regions: 2 patients with increased suicidality (13.3% of the study sample) after stimulation of the ventral capsule/ striatum [64], 1 completed and 1 attempted suicide (20% of the sample) after stimulation of the NA [71], two deaths by suicide and two suicidal attempts (40% of the sample) following stimulation of the subgenual cingulum [80]. Although no general conclusions can be drawn at this point, a relatively high rate of suicidal behavior in a small set of patients warrants caution.

Neuropsychological assessment of 6 patients from the Mayberg sample found improvement in several cognitive measures from baseline, not attributable to the antidepressant effect [62, 79]. Likewise, no deleterious effects on cognition were reported in a subset of patients from the Malone study [64].

**Conclusions**

The data on the use of VNS and DBS in the treatment of depression are encouraging. Whereas VNS has been approved for TRD, DBS still remains an experimental intervention. The major contribution of the methods is a novel approach, an alternative to the current antidepressant modalities, with assured compliance. Invasive stimulatory procedures allow for precise targeting of the specific brain areas, nuclei and circuits implicated in the etiopathogenesis of neuropsychiatric disorders and may thus replace traditional psychosurgery.

Nevertheless, several issues need to be clarified prior to the general embracement and implementation of the methods into therapeutic algorithms. First, in order to unequivocally assess pros and cons, more controlled data with higher statistical power are needed. The review evidences that, despite the apparent methodological difficulties, such research is feasible. For obvious reasons, invasive therapeutic methods will not become a first-line choice. Thus, it is essential to identify potential responders, patients who may best profit from VNS or DBS. Another key aspect is economics, the cost of the devices that is considerable. Cost-benefit analyses will be necessary to assess the true value of VNS and DBS.

Finally, new therapeutic approaches also present new ethical challenges and dilemmas. In addition to the historically negative perception of psychosurgery, considerations concerning availability, or alternatively fear of indiscriminating use of invasive stimulation methods in psychiatry may be of concern. Moreover, new philosophical questions regarding personality 'integrity', 'manipulation' or 'control' of mental functions may arise.

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