Clinical Application of Neurostimulation in Depression

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20.1 Introduction

There is a growing interest in biological non-pharmacological treatments for depressive disorders, and this is probably due to the limitations of psychotherapies and psychopharmacological treatments. Many patients do not adhere to psychotherapies, and even for those who adhere, it frequently takes a long time for the improvements to occur. A significant portion of patients does not respond or has a weak response to antidepressants and other pharmacological agents. The side effects of these drugs are very common; some patients do not tolerate them and abandon the treatment. Psychopharmacological agents are also contraindicated for special populations, such as pregnant women, patients with liver failure, and other clinical conditions.

The terms neuromodulation and neurostimulation have been used to describe procedures that use magnetic or electrical stimulation on the brain to treat psychiatric or neurological disorders through cortical activity modulation. The term neurostimulation is more adequate for those treatments, since neuromodulation is also applied to neurobiological changes from chemicals and drugs. Neurostimulation methods may be noninvasive, like transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and magnetic seizure therapy (MST), or invasive, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS) (Table 1.1).

As discussed in Chap. 15, the use of electrical charges in the brain has been studied since the classical antiquity, but the major turning point was the invention of ECT in the 1930s. For many decades, ECT was the most important treatment for depressive disorders, but the discovery and development of psychopharmacological agents, along with cultural and political influences, produced a decrease in the use of ECT. However, ECT is still considered an invaluable treatment option for depressive disorders, especially for severe or treatment-resistant major depressive disorder (MDD). On the one hand, there is abundant evidence demonstrating the efficacy of ECT, both as short-term and long-term treatment for MDD. On the other hand, studies also show that the risks, side effects, and costs of ECT may become a problem in some cases.

The TMS has been extensively studied since its discovery in the 1980s. Clinical trials indicate that magnetic stimulation is effective in the treatment of depressive disorders, even in treatment-resistant disorders. Most of the studies with TMS are short-term studies, but there are also a few long-term studies. TMS is associated with less

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Table 1.1 Neurostimulation methods

Modality	Pretreatment	Target region	Mode of action	Recommendation
ECT	Anesthesia and muscle relaxant	Cerebral cortex	Electrical current produces seizure	+++
MST	Anesthesia and muscle relaxant	Cerebral cortex	High-intensity magnetic pulses produce seizure	+
TMS	–	Cerebral cortex	Low-intensity magnetic pulses produce low electrical currents in the brain	+++
tDCS	–	Cerebral cortex	Low-intensity continuous electrical current	++
VNS	Implantation of pulse generator and electrode	Vagus nerve	Electrical pulses are transmitted to the brain through the vagus nerve	++
DBS	Implantation of pulse generator and electrode	Nucleus accumbens, ventral striatum, inferior thalamic nucleus, peduncle, lateral habenula, subgenual cingulate	Electrical pulses are delivered to deep brain structures by electrodes	+

ECT electroconvulsive therapy, *TMS* repeated transcranial magnetic stimulation, *MST* magnetic seizure therapy, *tDCS* transcranial direct current stimulation, *VNS* vagus nerve stimulation, *DBS* deep brain stimulation (Milev et al. 2016; Akhtar et al. 2016)

risks and side effects than ECT. Nevertheless, magnetic stimulation seems to be less effective than electroconvulsive stimulation, especially in the treatment of severe depressive disorders. Both ECT and TMS are approved by the US Food and Drug Agency (FDA) and are widely used throughout the globe.

MST, tDCS, DBS, and VNS are mainly experimental treatments for depressive disorders, and the clinical trials with these techniques are scarce. The FDA approved VNS vagus nerve stimulation (VNS) only for adult patients with severe or recurrent treatment-resistant depression; the other treatment modalities are not FDA approved.

20.2 Electroconvulsive Therapy

ECT is the oldest somatic treatment among those currently used in psychiatric practice, and it is also the most controversial. ECT was a popular treatment for mental disorders between the 1940s and 1960s. After the 1960s, the use of ECT met resistance, and it was no longer a treatment option for many psychiatrists and psychiatry services. It was seen as a psychiatric asylum practice, and there was an erroneous association with punishment and torture. The prejudice against this technique was probably due to ECT applications without the patient's consent and its indiscriminate use. Rudimentary ECT devices, lack of anesthesia, and lack of muscle relaxants were associated with higher risks and side effects, reinforcing the negative public perception of ECT. In the 1990s, a new interest on ECT emerged with a great increase of clinical trials and publications. The efficacy of ECT has been confirmed by several studies in the last two decades. In addition, modern devices and advanced anesthesia methods made ECT an extremely safe method that does not produce any discomfort for the patients. Despite all that, ECT is frequently considered as the last therapeutic resource, reserved for very severe and refractory cases, demonstrating that the stigma about this method still exists (Mochcovitch et al. 2016).

Recent studies indicate that methods used in ECT applications, such as the position of the electrodes, current intensity, wavelength, frequency, session duration, time between applications, and number of sessions, may influence both positive

and negative outcomes of this therapy. In order to produce effective seizures, unilateral ECT requires higher electrical current doses, bifrontal ECT requires lower doses, and the lowest doses are those applied in bitemporal ECT. This electrode placement is associated with more cognitive side effects, especially memory deficits, compared to unilateral and bifrontal positions. However, it is still under debate if bifrontal and right unilateral ECT are as effective as bitemporal ECT. In right unilateral ECT, the application of brief pulses (1.5 ms) was demonstrated to be more effective than ultrabrief pulses (0.3 ms), although the former is associated with more cognitive side effects than the latter. Ultrabrief pulses are not effective in bitemporal ECT. Prolonged convulsions and poor ventilation were also correlated to cognitive deficits (Mochcovitch et al. 2016; Sackeim et al. 2008; Tor et al. 2015). The Canadian Network for Mood and Anxiety Treatments (CANMAT) classified right unilateral ECT and bifrontal ECT as a first-line treatment and bitemporal ECT as a second-line treatment, due to its cognitive side effects (Milev et al. 2016).

20.2.1 Short-Term Treatment

The American Psychiatric Association (APA) and the CANMAT consider ECT the most recommended treatment when there is a need for rapid improvement, severe depression symptoms, high risks related to drugs, lack of response to pharmacological agents, patient preference, pregnancy, or lactation. APA also points out that ECT should also be considered when the psychopharmacological treatment is only partially effective or produces intolerable side effects. The World Psychiatric Association (WPA) also recommends ECT as an early acute treatment for severe MDD, especially in depression with psychotic symptoms or at high risk of suicide. ECT is highly effective in unipolar and bipolar depression, with remission rates of 55, 61, and 64% for right unilateral, bifrontal, and bitemporal ECT, respectively. It is also effective in the treatment of antidepressant-resistant depression, rapid improvement of catatonia symptoms, or prolonged severe manic disorder. Both unipolar and bipolar depressive disorders are the main indications for ECT, accounting for 80–90% of them. This is probably due to the superior efficacy of ECT in relation to pharmacotherapy. ECT is effective for patients with or without psychotic symptoms, but the latter respond more rapidly to this treatment. It may be administered to pregnant or lactating women, children, elderly people, or patients with severe clinical comorbidities, neuroleptic malignant syndrome, or Parkinson's disease. Recent studies indicate that maintenance ECT is also effective, and its efficacy is equivalent to the efficacy of continuation pharmacological treatment (Kellner et al. 2006; Milev et al. 2016; Mochcovitch et al. 2016; Pastore et al. 2008).

Patients should receive ECT until there is remission of symptoms or the response reaches a plateau. The clinical response should dictate how many sessions a patient should receive, usually ranging from 6 to 15 sessions. Cognitive side effects are cumulative, and if they are too severe, the treatment should be abbreviated. On the one hand, low charges are not effective; on the other hand, high charges produce more cognitive side effects. For this reason it is important to determine the adequate dose for each patient. The best method to find the correct dose is to administer repeated stimuli with increasing loads until there is a generalized seizure, consequently establishing the seizure threshold. Typically, for bitemporal or bifrontal ECT, the charge should be about 1.5 to 2 times the seizure threshold, whereas for unilateral ECT, the load should equal 6 times the seizure threshold (Milev et al. 2016; Mochcovitch et al. 2016).

In the past, the occurrence of generalized seizures was considered necessary and sufficient to produce the therapeutic effect of ECT. However, it is now clear that seizures can be ineffective, and this depends on the anatomical position of the electrodes, the dose of the electrical stimulus, and the patient's seizure threshold. The minimum duration of the observed seizure should be 20 s or 25 s if measured with the electroencephalogram. Studies have shown that the efficacy of ECT is correlated with a high ictal amplitude, especially in slow waves, and with great postictal suppres-

sion. Modern ECT devices allow quantitative analysis of the ictal and postictal EEG, so that mathematical parameters (such as ictal power and coherence) can be calculated, helping to determine if a seizure was effective or not. If the ictal power is low or there is no postictal suppression, the stimulus dose should be augmented. Increased blood pressure and heart rate just after the seizure are also associated with a greater efficacy of ECT (Mochcovitch et al. 2016).

20.2.2 Long-Term Treatment

Maintenance ECT may be administered after the remission of depressive symptoms for an indefinite period of time. The applications of maintenance ECT usually occur two to four times per month (Mochcovitch et al. 2016).

A study with MDD patients (Kellner et al. 2006) compared maintenance ECT with the combination of nortriptyline and lithium for 6 months. Differences regarding efficacy and tolerability between the two treatments were not observed. In a clinical trial with elderly patients with psychotic depression (Navarro et al. 2008), nortriptyline was compared to nortriptyline plus ECT for 2 years. In patients who received the combined treatment (nortriptyline + ECT), the relapse rate was significantly lower than in the nortriptyline group.

20.2.3 Adverse Events

The most frequent immediate side effects of ECT are headache, muscle soreness, nausea, and emesis, which vary depending on the anesthetic used. More than 45% of patients report headache, which can be treated symptomatically with the use of analgesics. Patients suffering from migraine attacks are more predisposed to headache after ECT. Mild and transient cardiac arrhythmias may occur during ECT application, especially in patients with prior heart disease. Arrhythmias result from brief postictal bradycardia and therefore can often be prevented by increasing the dosage of anticholinergic medication. Other arrhythmias are secondary to the tachycardia observed during the seizure and may occur while the patient returns to consciousness. The short-term neurological side effects normally associated with ECT are mental confusion and delirium, shortly after the seizure and anesthesia recovery. Significant confusion may occur in up to 10% of patients within the first hour after the seizure. Delirium is usually more prominent after the first applications and in patients who received bilateral ECT or who have coexisting neurological disorders. Delirium typically disappears within days or a few weeks at most. The severity, type, and duration of cognitive dysfunctions seem to be associated with the methodology of ECT administration, including electrode positioning, wave type, and frequency of procedure. Impairment of anterograde memory is one of the most commonly observed short-term side effects, but it lasts only for a few days. These side effects can be attenuated with the use of ultrabrief pulses, unilateral electrode position, and a larger interval between sessions (Milev et al. 2016; Mochcovitch et al. 2016).

Cognitive effects may be persistent, and its intensity and duration are closely related to the ECT parameters. Anterograde amnesia remits faster than retrograde amnesia, which may be persistent in some patients. Apparently, cognitive impairments before ECT and postictal disorientation predict amnesia. Usually cognitive side effects improve after the end of the treatment, and 6 months after the last treatment, there are no memory deficits anymore (Cohen et al. 2000; Ghaziuddin et al. 2000; Mochcovitch et al. 2016).

The mortality rate related to ECT is 2 in 10 per 100,000 patients, which is comparable to the risk of death from anesthesia in general procedures. There is an increased risk of complications in patients with arrhythmias, severe arterial hypertension, congestive heart failure, large aneurysms, insulin-dependent diabetes, brain tumors, traumatic brain injury, cerebrovascular accident, epilepsy, cerebrovascular malformations, and narrow-angle glaucoma, but these are not absolute contraindications for ECT (Milev et al. 2016; Mochcovitch et al. 2016).

20.3 Repetitive Transcranial Magnetic Stimulation

In TMS, repetitive magnetic pulses are delivered over cortical areas through a coil positioned on the scalp. The magnetic field produces electrical currents in the brain, stimulating or inhibiting brain structures. There are two types of TMS, one is more superficial and the other is deeper. In conventional TMS treatment, the electromagnetic waves have a reach of 3 cm from que coil surface to the cortex, while in deep TMS the reach is approximately 5 cm. Several types of coils are used in TMS, and they vary in size, format, focality, and reach. Theta burst (TBS) is a new form of TMS, which consists of three bursts of pulses at 50 Hz every 200 ms. This form of TMS is as effective as TMS with 10 Hz, but the duration of the session decreases about 5 times, which allows services to treat a larger number of patients (Milev et al. 2016).

All kinds of TMS can be inhibitory or excitatory. These treatments can be an add-on treatment or monotherapy for depression. Commonly, psychotropic medications are maintained while performing neurostimulation treatment. The patient sits in an upright position and is conscious during the whole procedure, and there is no need for anesthesia.

Usually the sites of stimulation are the left and right dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex. Regarding DLPFC, excitatory stimuli are applied on the left hemisphere, while inhibitory stimuli are applied on the right hemisphere. Some researchers had attempted to combine both excitatory stimulation on the left DLPFC and inhibitory stimulation on the right DLPFC, but it did not show additional benefits, compared to unilateral stimulation (Janicak and Dokucu 2015).

Stimulus intensity ranges from 1.5 to 3.0 tesla, but intensity is based on resting motor threshold (RMT), which is the minimum intensity to contract a patient's thumb. Patients have their own RMT, and the stimulus intensity is calculated as a percentage of this RMT. The stimulus intensity applied to patients is predetermined, generally 110–120% of RMT in TMS and 70–80% for TBS. Less intense stimuli are not effective (Janicak and Dokucu 2015).

Standard protocols for MDD consist of 20–30 daily sessions, over a course of 4–6 weeks. Clinical observations have shown that patients must demonstrate some improvement within 20 sessions. If not, they will probably not benefit from additional sessions. On the other hand, improvement before 20 sessions predicts response and remission in a 30-session treatment (Loo and Mitchell 2005; Milev et al. 2016). TMS treatments with three sessions per week (in different days) have been reported, but the total number of sessions remains the same. In accelerated protocols, the number of sessions is about the same as in conventional protocols too. Multiple TMS sessions (2–10) are administered in 1 day, producing quick results and decreasing the duration of the treatment (Loo and Mitchell 2005; Milev et al. 2016).

Frequencies of 1 Hz or less are considered inhibitory and are applied to right DLPFC. Excitatory frequencies, which are applied to the left DLPFC, range from 1 to 20 Hz. A 50 Hz excitatory frequency is used in TBS. The number of stimuli per session ranges from 120 to 3000, and better results were obtained with more than 1000 stimuli per session (Lefaucheur et al. 2014).

TMS is already considered a first-line treatment for patients with treatment-resistant depressive disorder, who have not had a significant improvement to at least one antidepressant (Milev et al. 2016). Several regulatory agencies approved TMS for the treatment of MDD in patients that have not responded to one antidepressant. Young patients, patients without psychiatric comorbidities, and those with few failures in previous treatment attempts tend to respond better to TMS, compared to those who do not have these features (Lee et al. 2012).

Due to its safety and efficacy in short-term treatment, especially in patients with treatment-resistant depression, TMS was considered by the CANMAT a first-line treatment for MDD patients who failed to respond to at least one trial with an antidepressant (Milev et al. 2016).

20.3.1 Short-Term Treatment

Several studies and meta-analyses showed similar efficacy of the right and left DLPFC TMS for MDD. Based on these evidences, it was hypothesized that bilateral stimulation, which is the combination of inhibitory and excitatory TMS over the right and left DLPFC, respectively, could have a better outcome, compared to unilateral stimulation. However, the results did not show a significant statistical difference (Milev et al. 2016). In a meta-analyses with 34 TMS studies, patients who received TMS (n = 751) had more significant improvements compared to those who received sham stimulation (n = 632), and the mean effect size weighted to sample sizes was 0.55. The effect size of unilateral TMS in the left DLPFC was similar to the one of bilateral TMS. Unilateral TMS at the right DLPFC yielded a somewhat higher effect size (0.82) (Slotema et al. 2010).

The most widely used and studied magnetic stimulation technique is conventional TMS, but experience with TBS is increasing rapidly. TBS protocols over DLPFC have demonstrated positive results for the left intermittent TBS, which is excitatory, but not for the right continuous TBS, which is inhibitory. Bilateral TBS stimulation studies have shown mixed results (Milev et al. 2016). One study demonstrated that TBS in dorsomedial prefrontal cortex was as effective as TMS in the left DLPFC. The advantage of TBS was the reduced session duration (6 min) compared to TMS (30 min). Some health-care systems are interested in treating larger numbers of patients, which is easier with TBS, compared to conventional TMS (Bakker et al. 2015). When a fast symptom improvement is needed, accelerated protocols using TBS could also be a good alternative to conventional TMS, in which the sessions are much longer (Loo and Mitchell 2005; Milev et al. 2016).

Other TMS optimization strategies are accelerated protocols and extended number of pulses per session. Indeed, additional studies are necessary to evaluate the efficacy of these methods and to observe the occurrence of adverse events, especially seizure (Lee et al. 2012).

The meta-analyses of 81 randomized controlled trials (n = 4233) concluded that the efficacy and tolerability of low-frequency unilateral TMS and bilateral TMS had better results than other TMS modalities, especially new TMS methods for treatment-resistant depression, such as accelerated protocols and deep TMS (Brunoni et al. 2017).

ECT is the gold standard treatment for treatment-resistant MDD but requires anesthesia and frequently causes cognitive side effects, while in the treatment with TMS, there is no need of anesthesia, and cognitive side effects are not common. Six randomized trials compared ECT (n = 102) and TMS (n = 113) and demonstrated the superiority of ECT over TMS, with a mean weighted effect size of −0.47 (Slotema et al. 2010).

20.3.2 Long-Term Treatment

It is well established that depression relapse and recurrence are common after short-term pharmacological treatment. There is also a high risk of relapse from 2 to 12 months after acute treatment with TMS. However, evidence also indicates that, in patients with treatment-resistant MDD who achieved remission after acute treatment with TMS, maintenance treatment with the same neurostimulation method could prevent recurrence. Nevertheless, there is no consensus on the maintenance treatment protocols, and some maintenance studies had positive results, but further clinical trials are needed (Loo and Mitchell 2005; Milev et al. 2016).

In some studies, patients were followed after acute treatment with TMS, and in those who presented a new depressive episode, TMS was resumed. These studies showed that 50–85% of patients had benefited from additional TMS sessions (Demirtas-Tatlidede et al. 2008; Fitzgerald et al. 2013). However, it is still important to ascertain if a maintenance treatment could reduce relapse rates.

20.3.3 Adverse Events

The most common adverse events are mild, and the patient can take symptomatic medications

to relieve them. Those adverse events usually decrease in intensity or disappear during the treatment. Common adverse events are scalp discomfort or pain, headache, facial twitching, and local erythema. Drowsiness and tearfulness have also been reported (Slotema et al. 2010).

The most severe adverse events that can occur are vasovagal syncope and seizure, but both are rare. Until now, fewer than 30 cases of seizure have been reported worldwide despite the large number of treatments that have been performed. In the current available literature, no cognitive impairment has been reported (Loo and Mitchell 2005; Milev et al. 2016). In order to avoid or minimize risks and adverse events related to TMS, safety guidelines must be followed (Rossi et al. 2009).

20.4 Other Neurostimulation Methods

20.4.1 Magnetic Seizure Therapy

MST is a noninvasive convulsive technique that generates tonic-clonic seizures through a strong electromagnetic field. A coil positioned on the skull produces this electromagnetic field in the same way as in other magnetic neurostimulation techniques (Milev et al. 2016). As in ECT, anesthesia and muscle relaxants are needed in MST. Due to the loud clicking of the device, earplugs are also recommended (Engel and Kayser 2016). MST stimulates the superficial cortex producing seizures, but there is no direct electrical stimulation of the temporal cortex, which explains the absence of cognitive side effects in this treatment. Recent studies demonstrated that MST is effective for treatment-resistant MDD, but it is not as effective as ECT (Cretaz et al. 2015).

Still there is no consensus on the optimal delivery parameters for MST, but most studies have used a coil placement at the vertex with a frequency of stimulation of 100 Hz, pulse width of 0.2–0.4 ms, and stimulation duration of 10 s. The schedule for MST is similar to the one for ECT, with a total of 12 sessions spread over a period of 4–6 weeks (Milev et al. 2016). The "figure of 8" coil is not considered effective to produce seizures, but the nonfocal round coil and the double-cone coil are considered reliable to induce seizures. In MST, the stimulus intensity is always above the seizure threshold (Cretaz et al. 2015).

Currently, there are a few studies with small samples sizes evaluating the effectiveness of MST in treatment-resistant depression. In one of the MST studies with a large sample (n = 13), three patients responded and two achieved remission (Fitzgerald et al. 2013). In the largest MST study (Kayser et al. 2015), 26 patients with treatment-resistant depression were enrolled in an open-label clinical trial. The response rate was 69%, and the remission rate was 46%. This study showed that MST was effective in the treatment of treatment-resistant depression and anxiety (Kayser et al. 2015). Both studies found that MST is a safe and well-tolerated treatment. Overall, studies show response and remission rates similar to ECT (Milev et al. 2016). A systematic review of eight studies of MST treatment in patients with treatment-resistant MDD showed remission rates from 30 to 40% and less cognitive impairment, compared to ECT (Cretaz et al. 2015). There are no maintenance treatment studies following MDD patients after MST short-term treatment.

One randomized within-patient study (Lisanby et al. 2003) compared MST to ECT in what regards adverse events and seizure characteristics. Ten inpatients in a major depressive episode were directed to ECT. Then, they were randomized to receive two MST sessions in the first four ECT sessions. Side effects and cognition were evaluated before and after sessions. MST seizures were shorter, with smaller ictal amplitude, and patients showed faster poststimulus reorientation.

The adverse events associated with MST are headache, muscle aches, disorientation after the procedure, and anterograde and retrograde amnesia (Milev et al. 2016). Cognitive side effects are usually mild or absent (Cretaz et al. 2015).

Due to the low level of evidence on MST, especially on maintenance treatment, the

CANMAT rated this neurostimulation technique as investigational (Milev et al. 2016).

20.4.2 Transcranial Direct Current Stimulation

tDCS is an electrical neurostimulation method with constant low-amplitude current focalized in specific cortical areas through electrodes placed on the scalp. This neurostimulation method increases cortical excitability in cortical areas under the anodal electrode, while it decreases cortical excitability where the cathodal electrode is placed. This effect is produced by the neuronal depolarization and hyperpolarization, respectively. There are basically two options of electrode placing: (1) anodal electrode over the left DLPFC and cathodal electrode grounded in a noncortical area or (2) anodal electrode over the left DLPFC and the cathodal over the right DLPFC. The stimulus intensity ranges from 1 to 2 mA, and the sessions last for 30 min or more. Daily sessions for at least 2 weeks are needed to obtain an antidepressant effect. Six-week treatments were more effective than shorter treatments, and tDCS combined with antidepressants was more effective than tDCS alone (Milev et al. 2016).

Studies using tDCS to treat treatment-resistant MDD have shown mixed outcomes, with small to moderate effect sizes of active treatment, when compared to sham (placebo). Two meta-analyses (Kalu et al. 2012; Shiozawa et al. 2014), which included, respectively, six and seven randomized controlled trials (n = 259), concluded that active tDCS was more effective than sham (Kalu et al. 2012; Shiozawa et al. 2014). On the other hand, the meta-analysis from Berlim et al. (Berlim et al. 2013), which also included six randomized controlled trials, did not find any significant difference between both groups, even when analyzing only studies with at least 10 sessions and 2 mA.

In some studies, patients were followed for 1 month after the end of treatment to evaluate the sustained improvement of depression. In three of four studies, it was confirmed that patients who received active tDCS maintained their levels of improvement (Kalu et al. 2012). tDCS has also been evaluated as a cognitive improvement tool. In a double-blind, randomized, controlled study (Fregni et al. 2006) with 18 outpatients with unipolar depression, patients showed working memory improvement after five tDCS sessions, even without depression enhancement. In the CANMAT guidelines, tDCS is considered a third-line treatment for MDD, although it is not recommended for relapse prevention because there are no controlled studies on maintenance treatment (Milev et al. 2016).

The most common adverse events of tDCS are discomfort, itching, tingling, burning sensation, and headache. Hypomania has also been reported (Kalu et al. 2012).

20.4.3 Deep Brain Stimulation

DBS consists of neurosurgical implantation of electrodes under magnetic resonance imaging (MRI) guidance in selected brain areas connected by a wire to a neurostimulator (NS) or an implantable pulse generator (IPG). The NS/IPG, usually placed into the right chest below the clavicle, sends electrical pulses to brain electrodes in order to modulate an adjacent neural network. DBS parameters can be monitored and programmed remotely with a handheld device in a similar way to pacemakers and VNS. There is also a patient controller to turn it on and off, check battery status, and self-adjust parameters provided by the DBS programmer (Milev et al. 2016).

DBS is mainly used to improve motor symptoms of Parkinson's disease, but it is also been studied in treatment-resistant depression, dystonia, essential tremor, epilepsy, Alzheimer's disease, and obsessive-compulsive disorder (OCD). Studies using DBS to treat treatment-resistant depression are increasing; but this technique still needs to find more appropriate brain areas related to this disorder for the implantation of electrodes to have more consistent results. The psychopharmacological and psychotherapeutic treatments are usually performed in tandem with each other (Milev et al. 2016).

The main anatomical target for DBS in most studies is the subcallosal cingulate (SCC) white

matter, but also the ventral capsule/ventral striatum (VC/VS), nucleus accumbens and medial forebrain bundle (MFB), inferior thalamic peduncle, lateral habenular complex, and rostral cingulate gyrus (Delaloye and Holtzheimer 2014; Milev et al. 2016).

Currently there is no consensus on what the optimal stimulation parameters are. However, trials in animals concluded that some parameters are more effective for the ventromedial prefrontal cortex/SCC such as high frequency (130 Hz) and current intensity (100–300 mA). These studies also identified that prelimbic stimulation was more effective than infralimbic stimulation and that left unilateral and bilateral stimulation had similar results (Milev et al. 2016).

DBS is indicated only when it is determined that other pharmacological and neurostimulation treatments, like ECT, do not produce a clinical response. Therefore, the patients submitted to DBS have ultra-resistant depression. Additionally, it is difficult to evaluate DBS effectiveness since the published literature is limited, and most studies are noncontrolled, nonrandomized, and consist of small sample sizes. Research shows that response rates range from 30 to 60% and the remission rates range from 20 to 40% after 3–6 months of treatment with DBS. Only a small open-label study with DBS over MFB, with 7 patients, showed higher response (85.7%) and remission (57.1%) rates (Milev et al. 2016).

Most studies followed up patients for 6–12 months, but one study (Malone et al. 2009) was able to follow up patients up to 51 months. In this study, response and remission rates were, respectively, 40% and 20% at 6 months and 53% and 40% in the last follow-up. In addition, DBS showed good tolerability.

In another study (Kennedy et al. 2011), MDD patients were followed for 3–6 years after DBS implantation to the subcallosal cingulate gyrus. This study had the following response rates over the years: 62.5% after 1 year, 46.2% after 2 years, 75.0% after 3 years, and 64.3% at last follow-up visit. It started with 20 patients, and at the end of the first year, 16 patients were still in the study and at the end of 3 years 14 patients, and at the end of the fourth year, nine patients completed the follow-up. Eight of the eleven patients that responded were already responders at the first year. Remission rates were 18.8% after 1 year, 15.4% after 2 years, 50% after 3 years, and 42.9% at the last follow-up visit. DBS was also well tolerated in this study; however, two patients committed suicide because of depressive relapse.

It is possible that some adverse events, such as intracranial hemorrhaging or infection, could result from the neurosurgery itself. Regarding adverse psychiatric events, psychosis and hypomania were reported after changes in stimulation parameters. Blurred vision and strabismus were also reported in patients after having increased the amplitude of the parameters. However, these events were reversible after an adjustment to the stimulation parameters (Milev et al. 2016). No cognitive side effects were reported. Approximately 11% of the patients abandoned the treatment before the end. Patients had no cognitive impairment in long-term treatment (Delaloye and Holtzheimer 2014).

The CANMAT considers DBS as an experimental treatment because there are too few studies documenting its safety and efficacy (Milev et al. 2016).

20.4.4 Vagal Nerve Stimulation

In VNS, an IPG is implanted subcutaneously in the left chest, and the electrodes from the IPG deliver low-frequency, intermittent pulses to the left vagus nerve (Daban et al. 2008). VNS vagus nerve stimulation (VNS)demonstrated to be safe in pregnant women. VNS can be used concomitantly with psychotropic drugs and electroconvulsive therapy (ECT) (Howland 2014).

The electrical stimulation through the vagus nerve provides stimulation to the nucleus tractus solitarius that modulates several subcortical and cortical regions of the brain through the neural networks (Milev et al. 2016). Treatment parameters are similar to other devices which include the intensity of the electrical stimulus (mA), pulse width (microseconds), frequency (Hz), duration of the stimulus, and interval between them (seconds or minutes) (Howland 2014). There is still no consensus on what the optimal stimulation

parameters for MDD would be. Most studies used the output current beginning at 0.25 mA, 500-μs pulse width, and 20- or 30-Hz frequency for 30 s of stimulation and a non-stimulation interval of 5 min. In one long-term study, the electric current was increased to 1 mA (Daban et al. 2008). There seems to be better response rates and decreased suicide attempts in VNS with higher electrical charges, compared to low charges (Milev et al. 2016).

Currently, there is only one randomized, controlled study with VNS to treat TRD (Rush et al. 2005). This 10-week study evaluated 235 patients, of whom 210 are with nonpsychotic treatment-resistant depression and 25 with bipolar depression. There were no statistically significant difference between VNS and sham in short term. A meta-analysis of uncontrolled studies of VNS in the treatment of TRD (Martin and Martin-Sanchez 2012) showed a significant improvement based on scale scores and response rates (31.8%, $p < 0.0001$).

Studies have shown that MDD patients improve with VNS over a long time. The average time necessary to show improvement was approximately 3 months, but patients may need to wait for another 6 months to have a significant improvement. The response and remission rates vary significantly across studies. A meta-analysis of six multicenter studies (Berry et al. 2013), with a total sample size of 1035 patients with treatment-resistant depression treated with VNS and 425 patients treated as usual, indicated a response rate of 32% for VNS and 14% for treatment as usual after 96 weeks of treatment. The response rates for VNS and treatment as usual after 48 weeks of treatment were similar.

The stronger predictor of bad response to VNS in patients with treatment-resistant depression (failure in at least two trials with antidepressants of different classes) is probably ultra-treatment-resistant depression. In the study from Sackeim et al. (Sackeim et al. 2001), patients who failed to respond to more than seven antidepressant trials or who have already been treated with ECT were unlikely to benefit from VNS.

Voice changes, hoarseness, coughing, and dyspnea with physical exertion are adverse events usually associated with the current intensity and usually improve with the reduction of current intensity. Other possible adverse events are headache, dysphagia, paresthesia, and pain (Howland 2014; Sackeim et al. 2001). Complications are expected in about 1% of surgeries and may include wound infection and hoarseness. Hoarseness may be the result of limited or long-lasting vocal cord paralysis (Howland 2014).

Considering these factors, only ultra-treatment-resistant depression patients are eligible for this treatment. VNS is considered a third-line treatment for MDD in CANMAT and merits further study (Milev et al. 2016).

Conclusion

All neurostimulation techniques discussed in this chapter were beneficial to patients with MDD. In these treatments, the stimulation is targeted to brain areas related to MDD, avoiding stimulation of peripheral areas, due to its potential side effects. Depending on the method, neurostimulation can have a very fast antidepressant effect, or it could take many months for it to take effect. These non-pharmacological treatments may provide improvement for a group of patients that have already tried several psychopharmacological treatments and psychotherapy and did not achieve remission.

Above all, benefits and risks should be weighed before indicating a neurostimulation treatment. Patients should receive information about the treatment and consent to it. Patients and family members should know beforehand that these treatments have risks of adverse events and their efficacy is limited.

Neurostimulation is a field of psychiatry that is in continuous development. Currently, ECT and TMS are the most extensively studied neurostimulation methods, while MST, tDCS, VNS, and DBS have to be studied thoroughly so that their efficacy and safety are evaluated. There is a substantial amount of evidence supporting ECT and TMS as routine treatments for MDD; still technical refinements are needed to improve the efficacy and reduce adverse events.

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