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MOOD DISORDERS (SM STRAKOWSKI, SECTION EDITOR)

# What Is the Role of Brain Stimulation Therapies in the Treatment of Depression?

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**Abstract** Brain stimulation therapies have demonstrated efficacy in the treatment of depression and treatment-resistant depression (TRD). Non-invasive brain stimulation in the treatment of depression has grown substantially due to their favorable adverse effect profiles. The role of transcranial direct current stimulation in TRD is unclear, but emerging data suggests that it may be an effective add-on treatment. Repetitive transcranial magnetic stimulation has demonstrated efficacy in TRD that is supported by several multicenter randomized controlled trials. Though, vagus nerve stimulation has been found to be effective in some studies, sham controlled studies were equivocal. Electroconvulsive therapy (ECT) is a well-established brain stimulation treatment for severe depression and TRD, yet stigma and cognitive adverse effects limit its wider use. Magnetic seizure therapy has a more favorable cognitive adverse effect profile; however, equivalent efficacy to ECT needs to be established. Deep brain stimulation may play a role in severe TRD and controlled trials are now underway.

**Keywords** Brain stimulation · Major depression · MDD · Treatment-resistant depression · TRD · Transcranial direct current stimulation · tDCS · Repetitive transcranial magnetic stimulation · rTMS · Magnetic seizure therapy · MST · Vagus nerve stimulation · VNS · Deep brain stimulation · DBS · Mood disorders · Psychiatry

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## Introduction

Major depressive disorder (MDD) is associated with significant morbidity and substantial impairment in functioning [1, 2]. It is estimated that by the year 2020, depression will be second only to heart disease in magnitude of disease burden as determined by disability-adjusted life years [3, 4]. Though numerous evidence-based antidepressants and psychotherapies are available, a large proportion of patients fail to respond to these treatments and develop treatment-resistant depression (TRD) [5]. TRD is defined as a failure to respond to two adequate medication trials or as a relapse during treatment [6]; it is common and leads to significant public health care costs. Only one-third of patients with MDD achieve full remission of their symptoms after a single trial of antidepressant medication. Even after multiple medication trials, 30 %–40 % of patients with MDD fail to achieve remission [5]. Results from the NIH-funded STAR*D study indicate that 60 % of patients fail to respond to two antidepressant trials of optimal dose and duration, while a further 30 % failed to respond to four medication trials [7]. Prolonged depressive symptoms and incomplete remission are negative prognostic factors for full recovery and return to normal functioning [8–10]. Thus, there is an urgent need for interventions for those who fail to respond to antidepressant medications. Electroconvulsive therapy (ECT) is the most effective treatment for TRD with remission rates between around 60 % [11–13]. Its place among the options for TRD is well established [14, 15]. However, less than 1 % of patients with TRD receive ECT in Canada or the United States [16].

The stigma and cognitive adverse effects associated with ECT have been part of the impetus to develop other brain stimulation modalities with similar efficacy, but improved adverse effect profiles. In this regard, transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), magnetic

seizure therapy (MST), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) have emerged as other brain stimulation modalities that warrant consideration in the treatment of TRD. Overall, these brain stimulation modalities have demonstrated efficacy in treating mild, moderate and severe depression. However, prolonged depressive episodes and high levels of treatment resistance also limit their efficacy [17, 18]. The negative impact of prolonged depressive episodes and higher levels of treatment resistance suggest that brain stimulation modalities should be considered earlier in the treatment of depression rather than being used as a treatment of last resort. The earlier consideration of brain stimulation treatments needs to take into account patient preference, cost, access to treatment providers, and likelihood of adhering to a rigorous and sometimes time consuming treatment regimen. Various guidelines and treatment algorithms mention some of these brain stimulation therapies, but have not included them in a systematic way [15, 19–21]. This review will summarize the recent advances in the use of brain stimulation in treating MDD and propose a role for each of these modalities in the treatment of depression.

## Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a non-invasive and non-convulsive form of brain stimulation in which a weak, direct current (2 mA) is applied using two surface scalp electrodes. Initial studies in animals suggested that such stimulation can elicit polarity-dependent alterations in cortical excitability and activity, with anodal stimulation increasing cortical excitability and cathodal stimulation causing cortical inhibition [22]. Comparable changes have been demonstrated following tDCS delivered to the human motor cortex, providing further evidence of its neuromodulatory potential [23].

Early research using tDCS as a possible treatment for depression dates back to the 1960s [24]; however, due to mixed results, methodological differences and confounding results, the use of tDCS as a treatment was not pursued. In the last 10 years there has been a renewal of interest in examining tDCS as a potential treatment for MDD. The efficacy of this treatment, as well as its optimal stimulation parameters, is still under investigation. A meta-analysis of ten studies (six of which were randomized controlled trials) reported that compared to sham tDCS, active tDCS was more effective in reducing symptoms of depression [25]. The authors cautioned that the small number of studies with limited sample sizes made generalizing from these studies difficult. The largest randomized sham-controlled trial that used anodal stimulation over the left DLPFC and cathodal stimulation over the right supraorbital region showed a significantly greater improvement in depression in subjects randomized to active tDCS than those that received sham over a 3-week controlled phase; however, categorical differences in response or remission rates were not demonstrated [26•]. After an additional 3 weeks in an open-label extension phase, those subjects who received active tDCS were significantly more likely to achieve a 50 % reduction in symptoms [26•].

The optimal placement of tDCS electrodes remains an area of investigation. Bilateral frontal stimulation with the cathode positioned over the right supraorbital region rather than over the right DLPFC has also resulted in improvement of depressive symptoms [27–29]. Fronto-extracephalic stimulation, in which anodal stimulation was directed over the right DLPFC and cathodal stimulation was directed over the right, upper arm has been used in another small positive study [30].

Many of the earlier studies demonstrated promising results in individuals experiencing mild to moderate depression without treatment-resistance [27, 28, 31]. A number of open-label studies have shown promise for left DLPFC cathodal and right DLPFC anodal tDCS configuration in more severely depressed patients [32–34]. A study that included patients with higher levels of treatment resistance, including patients that had failed ECT in the current episode, did not demonstrate benefits of left and right DLPFC stimulation over sham [35]. Similarly, in another controlled study in patients who had failed to respond to at least two previous trials of antidepressants from different classes, did not find a difference between active and sham stimulation using left DLFPC and right supra-orbital electrode placement [36]. A large recent trial—the Sertraline vs. Electrical Current Therapy (SELECT) tDCS trial—compared bilateral stimulation with a left DLPFC anodal and right DLPFC cathodal configuration, a relatively low dose of sertraline (50 mg/day), or their combination in subjects who were typically treatment naïve with a mean episode duration of 3 months [37••]. In this study, tDCS and low dose sertraline had comparable response rates, but combining sertraline and tDCS had an additive effect suggesting that this is a potentially viable approach to improving response rates to a first-line antidepressant.

*Recommendation* Overall the data for tDCS in TRD have been conflicting. At this time, there is insufficient evidence to support its use in moderate to severe depression with more than one treatment failure [38]. However, tDCS may enhance outcomes in patients with mild to moderate non-treatment resistant depression. Though further replication is required, it is reasonable to consider combining tDCS with an antidepressant in mild to moderate non-treatment resistant depression. Another important question for future

research is whether tDCS can exert a similar additive effect to evidence-based psychotherapy in a mild to moderate depression, due to its ability to enhance plasticity.

## Repetitive Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS) is another noninvasive and nonconvulsive form of brain stimulation. Administration of rTMS requires a stimulator and coil; various coil configurations exist with different abilities to stimulate specific regions of the cortex [39, 40]. The stimulator generates an electrical current that is then converted, according to Faraday's law, into a magnetic pulse within the coil. Unlike direct electrical current stimulation, magnetic pulses pass through cranial tissue largely without impedance or attenuation, maintaining the intensity and fidelity of the pulse delivered. The delivered pulses then induce eddy currents depolarizing cortical neurons, in particular those oriented perpendicularly to the coil thus modulating circuits involving the prefrontal and limbic regions [41•].

The last several years have seen the emergence of rTMS as an evidence-based treatment for TRD. Several multicenter trials have shown a favorable adverse effect profile and demonstrated efficacy. Both a large industry-sponsored and an NIMH-funded study of rTMS using a figure-of-eight coil demonstrated efficacy over placebo in subjects with early stages of TRD [42••, 43]. Both of these studies administered rTMS using high frequency (10 Hz) stimulation to the left DLPFC with 3000 pulses. The results of the industry-sponsored study in the patients with greater than one treatment failure were not better than placebo, leading the FDA to limit the indication to only one treatment failure.

Very few adverse effects were reported in these studies: approximately 5 % of patients were unable to tolerate the treatment due to pain or headache, however the rate of headache was similar in the active and sham groups [42••, 43]; there were no seizures, or treatment induced hypomanic or manic episodes; and the rate of treatment-emergent suicidal events was lower in the active ($n=1$) than sham ($n=10$) group during the treatment phase in one of the studies [43]. The main safety concern associated with rTMS is the possibility to induce a generalized seizure. The risk of seizure induction is dependent both on patient selection and stimulation parameters. In trials that have included many thousands of patients rTMS has unequivocally induced a seizure in only 16 individuals [39].

Another industry-sponsored study using a coil that can stimulate deeper regions of the cortex [44] has recently been completed (NCT00927173) and the FDA has approved this new device, although the findings have not yet been published. Smaller studies, using standard figure-of-eight coils, have demonstrated efficacy in patients with higher levels of treatment resistance; but most studies have not included patients who have failed a course of ECT [45]. Meta-analyses of the studies that have used low frequency right-sided stimulation have confirmed the efficacy and tolerability of this stimulation approach [46, 47]. The combination of low frequency right-sided stimulation followed by left sided stimulation have been shown to be more efficacious than sham stimulation [48]. However, this efficacy of bilateral stimulation compared to high frequency left-sided treatment alone is uncertain since studies have yielded conflicting findings [49–51]. The use of imaging data in several clinical trials has led to a change in the practice of approximating the most optimal spot for stimulation [41•]. A more anterior and lateral placement of the coil has been associated with better outcomes [52]. Furthermore, analysis of one of the clinical trials has shown that adjusting treatment intensity in relation to scalp to cortex distance does not improve outcomes and that stimulation at 120 % of motor threshold is acceptable [53].

Other methods to improve the speed with which rTMS can lead to symptomatic improvement are currently being studied. These methods involve multiple treatment sessions per day [54] and use of a different stimulation pattern called theta burst stimulation [55, 56]. While these methods have shown promise there is insufficient evidence to recommend their incorporation into clinical practice.

As rTMS (high frequency left-sided stimulation of the DLPFC in particular) is increasingly used in clinical practice [57•], the issue of how to prevent relapse will become more salient. Few studies have examined post-acute rTMS treatment outcomes in depressed patients. In one study, only 13 % of patients who were initially treated with rTMS monotherapy and subsequently transitioned to maintenance antidepressant monotherapy relapsed over a 24-week follow-up period [58]. Of those who initially responded to rTMS monotherapy, approximately 75 % maintained full response over the follow-up period. Of the 38/99 (38.4 %) who worsened clinically but did not relapse during the follow-up period, 32/38 (84.2 %) benefitted from re-introduction of rTMS. A number of economic analyses of rTMS have been conducted [59, 60]. These analyses occurred before more optimal forms of treatment have been introduced and a reappraisal of the cost-effectiveness of rTMS is warranted. Although rTMS devices can be expensive, the cost of hospitalization for only a handful of patients with TRD can far exceed the cost of a device. Therefore the ability of rTMS to be delivered on an outpatient basis to potentially reduce hospitalization in patients who might otherwise require admission must be part of these economic analyses.

*Recommendations* Based on the evidence currently available, rTMS using high frequency left sided stimulation at 120 % motor threshold for 3000 pulses per session can be recommended as treatment after failure of a first line antidepressant. Firm recommendations regarding the use of deep rTMS have to await the publication of the completed multicenter clinical trial. There are also data suggesting that rTMS may be effective after failure of more than one antidepressant, although lower remission rates are expected in these circumstances. Future research on how to prevent relapse after acute treatment with rTMS is needed. We expect that the efficacy and efficiency of rTMS will continue to evolve with newer approaches such as accelerated treatment and theta burst stimulation.

## Magnetic Seizure Therapy

Magnetic seizure therapy (MST) was developed as a potential alternative to ECT. It involves applying a train of high frequency magnetic stimuli to produce electrical current indirectly in the brain via electromagnetic induction to induce a seizure. With ECT, 80–95 % of the electrical activity is shunted by the skull and conducted by the CSF, resulting in widespread stimulation of cortical and subcortical regions [61]. Only a small proportion of the electric current delivered is focused toward the frontal cortex, with the remaining current resulting in non-focal brain activation [62]. Compelling evidence suggests that it is the focal component of ECT that leads to its therapeutic effect while the non-focal component leads to adverse cognitive effects [63–66]. By contrast, with MST, magnetic fields are not impeded nor shunted by the skull and CSF. Therefore, the fields produced do not result in diffuse brain activation [67]. Also, MST limits the seizure spread as the induced magnetic field can be focally targeted based on the geometry of the stimulating magnetic coil [68].

MST was initially developed in non-human primates. This was achieved through the development of modified rTMS devices that were capable of producing the intensities and frequencies necessary to generate seizure activity. These initial studies demonstrated that MST produced no identifiable histological lesions in primate brains [69]. Primate evidence also suggested fewer adverse cognitive effects with MST as compared to ECT [70].

Seizures were first induced with MST in humans in 1998 [71]. Early studies suggested that MST applied at 40–50 Hz is safe, well tolerated and effective in alleviating depressive symptoms [71, 72]. One of the first studies comparing MST to ECT in 10 TRD patients suggested that MST was better tolerated than ECT and was as efficacious [73]. In a second trial using a case-control design, 20 patients underwent a course of 10–12 MST sessions or ECT applied as bifrontal stimulation using standard pulse width parameters. Patients showed a more rapid post-stimulus reorientation with MST than with ECT [74]. The magnitude of mood improvement with MST was less than that achieved through ECT, which the authors attributed to lower MST intensities compared to ECT. Potentially greater efficacy could have been achieved by stimulating at higher intensities, consistent with the high intensities needed for RUL ECT to be effective [75]. MST devices available at that time were not capable of delivering these high intensities.

Since these initial studies, MST devices have advanced considerably. Two companies (Magstim in the UK and MagVenture A/S in Denmark) have developed MST devices with maximal stimulation intensities (i.e., 100 % of stimulator output) at 100 Hz for up to 10 seconds. In primates, these parameters consistently produce seizures with fewer adverse cognitive effects than with ECT [76]. These stimulation parameters have also been tested in humans: 11 patients were stimulated with 100 Hz MST in a single session while receiving a concomitant course of ECT [77]. These patients experienced a mean post-ictal recovery that was 15 minutes shorter with MST than with ECT and they also reported less confusion. One of the largest MST studies to date ($N$=20) [78•] reported comparable remission rates with MST and standard pulse width RUL ECT with no significant cognitive impairments (e.g., reorientation, memory) reported in either group. Some pilot data from an MST open trial has shown regional brain changes in the depression circuit [79, 80].

*Recommendations* MST has still only been studied in small open studies and a couple of randomized studies. In order to establish MST as a viable alternative to ECT, it must be studied in a randomized non-inferiority trial that is adequately powered. Until such a study demonstrates that MST is as effective as ECT and has less adverse cognitive effects, it will not be incorporated into clinical practice. However, if such a study is successfully completed, MST could become a first line convulsive therapy for patients with TRD.

## Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is a minimally invasive treatment that involves the implantation of an electrode around the vagus nerve. After improvement in mood was seen in patients treated with VNS for epilepsy, VNS was investigated for the treatment of TRD [81–84]. The FDA has approved VNS for the treatment of depression that has not responded to multiple antidepressants; however most US insurers do not cover this

treatment. One of the largest acute efficacy studies failed to demonstrate a difference from placebo [82]. Other open label studies have reported response and remission rates around 30 % and 15 % [82, 84–87]. A recent meta-analysis has shown better response and remission rates with VNS than with treatment as usual. However, the remission rates were still quite low [88].

*Recommendations* Open label studies and some controlled studies support the use of VNS in patients with TRD who have had multiple medication failures. However, the lack of difference from placebo in controlled studies led to limited adoption of VNS. At this time, VNS can be considered as a possible therapeutic option after multiple treatment failures. However, this consideration needs to be weighed against a lack of robust efficacy data and the surgical nature of the procedure.

## Electroconvulsive Therapy

Electroconvulsive Therapy (ECT) is the most well established brain stimulation modality for the treatment of TRD. The evidence base for ECT has accumulated over the last 70 years [14]. Despite its robust efficacy (remission rates around 60 % range in TRD), cognitive adverse effects and stigma remain major deterrents to the acceptability of the treatment [11]. In the last decade, progress has been made on the selection of the stimulus pulse width and electrode placement to optimize outcomes while reducing cognitive adverse effects [89–91]. Several large trials have also clarified issues related to the use of concomitant psychotropic medications and electrode placement. The efficacy of ECT has been shown to be enhanced with concomitant use of nortriptyline or venlafaxine [13]. In this study, high dosage right unilateral ECT was also shown to be equally as effective as moderate dosage bitemporal ECT with reduced cognitive adverse effects. In the 6-month continuation phase of this study, a 50 % relapse rate was observed despite continuation pharmacotherapy with both antidepressant and lithium. In two previous studies of post-ECT continuation pharmacotherapy, the use of antidepressant combined with lithium was associated with somewhat lower relapse rates of 39 % [92] and 41 % [93]. These high relapse rates after remission with an acute ECT course remains another major problem for the field. Another large multicenter study reported a higher remission rate and more rapid resolution of symptoms with bitemporal ECT than with high dose right unilateral ECT [12]. However, this study did not demonstrate differences in the efficacy or cognitive effects of high dose right unilateral or bifrontal electrode placement [12]. This study clarified that bitemporal ECT is the treatment of choice for urgent clinical situations and that there is no significant advantage to bifrontal electrode placement. Further refinements to ECT using focal electrically administered seizure therapy are under investigation in clinical trials [94, 95].

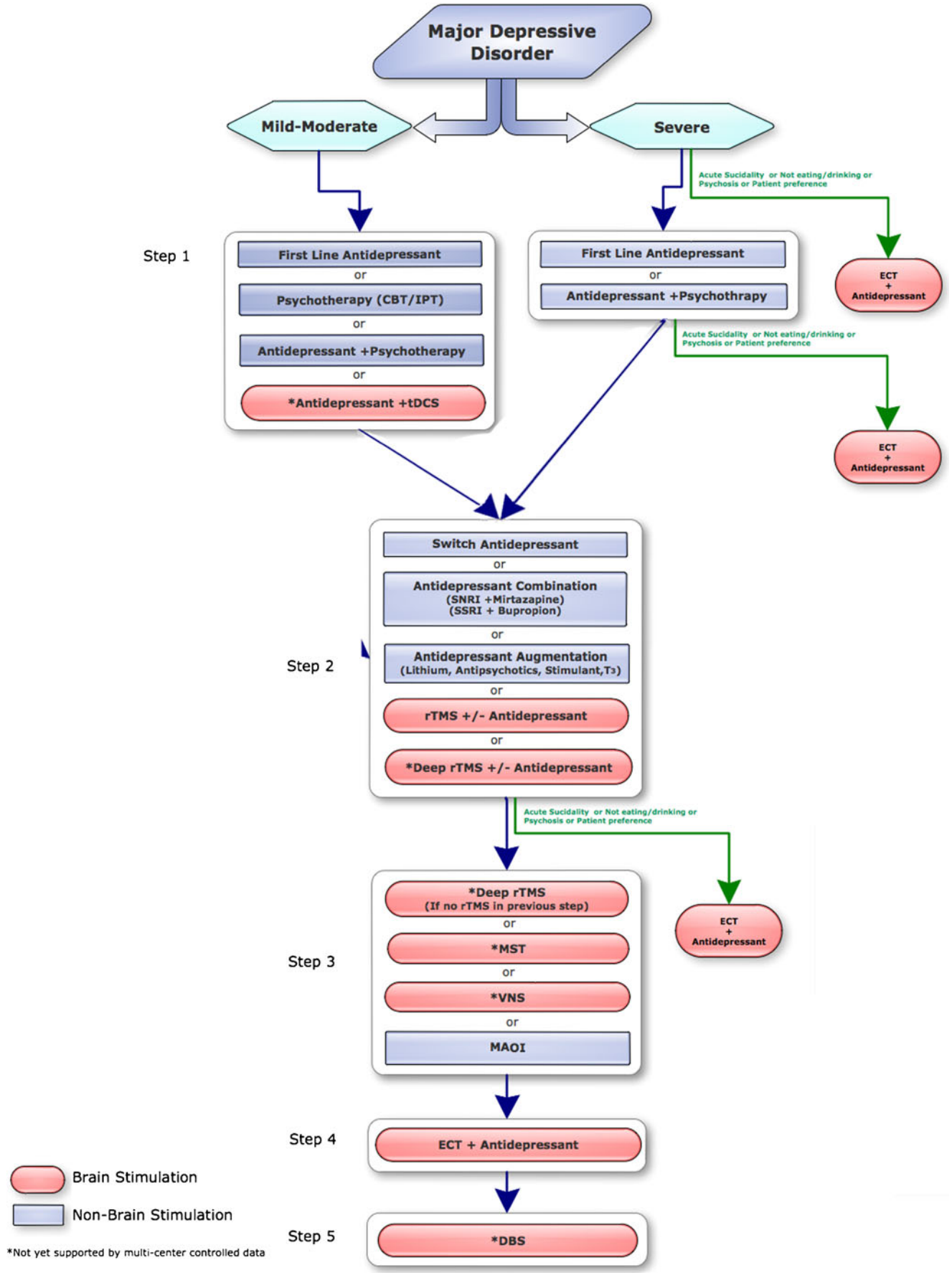
*Recommendations* The efficacy of ECT for TRD has been clearly demonstrated. Bitemporal ECT should be considered first line treatment in cases of depression requiring urgent treatment due to acute suicidality, risk of dehydration due to poor oral intake, or psychotic features. In less severe cases the use of high dose right unilateral ultra-brief pulse width should be considered first due to its more favorable cognitive adverse effect profile.

## Deep Brain Stimulation

Deep brain stimulation (DBS) involves the neurosurgical implantation of electrodes within the brain, using a stereotactic approach. The impetus for DBS studies in depressed patients came from the success of DBS in refractory movement disorders and from imaging data localizing brain dysfunction in TRD to Brodmann area 25 and the subgenual cingulate [96]. To be eligible for participation in these DBS clinical trials, patients were required to have failed to respond to at least four adequate trials. In most studies, deep stimulation of the subgenual cingulate resulted in remission rates ranging from 18 % to 60 % depending on the duration of stimulation. No cognitive adverse effects have been observed with long-term DBS [97, 98]. One DBS study has shown a placebo effect with a 4-week lead in phase, however, ethical concerns have limited early DBS studies from comparing active to placebo stimulation [97]. Several placebo-controlled studies are now underway (NCT01801319, NCT01778790). Results from these studies should help to determine the role of DBS in the treatment of depression.

*Recommendation* DBS has demonstrated promise in relieving depression in patients with high levels of treatment resistance. However, the small number of patients treated and the lack of double-blind controlled data limit the broader applicability of this treatment at this time. If DBS shows efficacy over placebo ("sham") stimulation in pivotal

**Fig. 1** Current and future roles for brain stimulation therapies in the treatment of depression CBT: Cognitive Behavioral Therapy DBS: Deep Brain Stimulation ECT: Electroconvulsive Therapy IPT: Interpersonal Psychotherapy MAOI: Monoamine Oxidase Inhibitor MST: Magnetic Seizure Therapy rTMS: Repetitive Transcranial Magnetic Stimulation tDCS: Transcranial Direct Current Stimulation VNS: Vagus Nerve Stimulation * Not yet supported by published multicenter clinical trial data


Major Depressive Disorder
Mild-Moderate
Severe
Acute Sucidality or Not eating/drinking or Psychosis or Patient preference
Step 1
First Line Antidepressant
or
Psychotherapy (CBT/IPT)
or
Antidepressant +Psychotherapy
or
*Antidepressant +tDCS
First Line Antidepressant
or
Antidepressant +Psychothrapy
ECT + Antidepressant
Acute Sucidality or Not eating/drinking or Psychosis or Patient preference
ECT + Antidepressant
Step 2
Switch Antidepressant
or
Antidepressant Combination (SNRI +Mirtazapine) (SSRI + Bupropion)
or
Antidepressant Augmentation (Lithium, Antipsychotics, Stimulant,T3)
or
rTMS +/- Antidepressant
or
*Deep rTMS +/- Antidepressant
Acute Sucidality or Not eating/drinking or Psychosis or Patient preference
ECT + Antidepressant
Step 3
*Deep rTMS (If no rTMS in previous step)
or
*MST
or
*VNS
or
MAOI
Step 4
ECT + Antidepressant
Step 5
*DBS
Brain Stimulation
Non-Brain Stimulation
*Not yet supported by multi-center controlled data

trials then its role as a treatment after multiple antidepressant failures and even failure of ECT would be established.

## Conclusion

The field of brain stimulation is expanding rapidly. Figure 1 depicts where the reviewed brain stimulation therapies currently fall in the stepwise treatment of depression and where they may be situated once early findings are confirmed and replicated. Noninvasive treatments such as tDCS have begun to show promise in mild to moderate depression and as an add-on to antidepressant treatment. Its role in the treatment of depression is likely as an early step to optimize outcomes to early treatment interventions with pharmacotherapy or psychotherapy. rTMS has demonstrated efficacy after one treatment failure and deep rTMS may be effective after more than one treatment failure. The results of blinded VNS studies have failed to demonstrate efficacy over placebo, and thus its role in the treatment of depression must be considered with this in mind. MST has shown promise as a potential alternative to ECT. However, larger randomized trials comparing its efficacy and cognitive adverse effects to ECT are required. DBS has also shown promise as an effective treatment for severe TRD; however, pivotal trials demonstrating efficacy under controlled design are still underway. At this time, ECT remains the most effective available treatment for severe TRD. Advances in the stimulus parameters used in ECT have mitigated some of the cognitive adverse effects of ECT. However, early relapse after remission is still an area that requires further attention.

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- • Of importance
- •• Of major importance

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