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REVIEW ARTICLE

Can Deep Brain Stimulation Be a Promising Treatment for Treatment-Resistant Depression?

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Abstract

Background: In recent decades, despite remarkable advances in antidepressant medication, psychotherapy, and electrical stimulation, between 20%-30% of patients suffering from major depressive disorder remain untreated or are at a high risk of relapse. Deep brain stimulation (DBS) is a recently invented modality that has been under investigation since 2005, however, the US Food and Drug Administration (FDA) has not yet approved it as a final line in treating severe depression.

Methods: In this study the author tried by reviewing the evidence-based articles on applying DBS for treating human depression, to reach a conclusion whether DBS has the potential to be the ultimate treatment for depressive disorder. Data were derived from evidence-based studies published on PubMed/Medline, the Cochrane Central Register of Controlled Trials, ScienceDirect, EMBASE, and APA PsycINFO. The emphasis was on applying DBS for human depression, consequently after refining inclusion and exclusion criteria, 42 articles that contain the results of 446 tested patients were reviewed.

Conclusion: Data reanalysis demonstrated, DBS has the capability for treating severe measure depressive disorder (MDD) or refractory depression as an adjunctive treatment if its weaknesses including, the lack of consensus on DBS protocol and its stimulation parameters, duration of treatment, the effect of placebo, and considering the individualized pattern of depression become resolved through doing further highly controlled studies that compare the short-term and long-term effects.

Keywords

Depression, Major depressive disorder, Treatment resistant depression, Deep brain stimulation, DBS

Introduction

Depression is a mood state characterized by sadness and/or despair, feelings of worthlessness and/or emptiness, and an inability to experience pleasure [1]. The World Health Organization [2] state, the prevalence rate of depressive disorder is more than 300 million people worldwide and in the United States, it affects more than 17 million people that causes them to live their life years with disability [3]. Remarkably, up to 10% of people suffering from major depressive disorder (MDD) will attempt suicide [4]. A major depressive disorder is a recurrent episodic illness, with each episode increases the risk of future episodes by about 20% per year, however, when the duration of recovery increases, the risk of recurrence decreases [5,6]. Although some depressed people improve significantly that they no longer meet the criteria for the diagnosis of MDD, they continue to experience subclinical depression for years.

Approximately 20-30% of patients with major depressive disorders (MDD) do not respond to any antidepressant modality including medication, psychotherapy, or physical treatment and stimulation [3]. The term treatment-resistant depression (TRD) is used when patients with MDD do not respond to at least two adequate trials of antidepressant medication from different drug classes with or without psychotherapy or physical stimulation [7]. Treatment-resistant depression not only jeopardizes patients' physical and mental health but also influences their social life and provides them with significant personal and societal costs. They undergo more medication trials and hospitalization,

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have higher rates of unemployment, and have higher rates of suicide [8,9].

Although in recent decades there are salient advances in depression treatments, an estimated one-third of patients with major depressive disorder have treatment-resistant depression (TRD) [10]. Pharmacotherapy in conjunction with psychotherapy, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and Vagus nerve stimulation (VNS) are all effective modalities and treatments in altering depression symptomatology, however, these methods are not successful for all patients [3,11], and between 20%-30% of people suffering from MDD remain depressed or are at a high risk of relapse [3]. Deep brain stimulation (DBS) is a newly invented treatment that is considered to treat patients suffering from major depressive disorder resistant to treatment. This procedure initially developed for the treatment of movement disorders such as Parkinson's disease and then extended to neurological conditions including essential tremor, dystonia, epilepsy, chronic pain, and even mental disorders such as obsessive-compulsive disorders (OCD) [3]. So far, the US Food and Drug Administration (FDA) has approved utilizing DBS for treatment of all illnesses and disorders listed above, however, for depression, this procedure is still under investigation. This study aims by reviewing all evidence-based studies on applying DBS for treating human depression, investigate DBS superiority compare to other depression treatments and look over its capability for being a final line treatment.

Methods

Data for this review study were collected from the evidence-based articles published between 2005-2020 in PubMed/Medline as the primary search engine, the Cochrane Central Register of Controlled Trials, EMBASE, and PsycINFO. All the empirical studies in the form of randomized clinical trials (RCTs), cohort study, open-label study, case-control study, case-report and series, meta-analysis, and systematic review articles that evaluate safety and efficacy of DBS for human depression were included. At the preliminary searching in the proposed search engines, 397 articles were found. Since the aim of this study was to evaluate the effect of DBS on human depression, using the phrase "deep brain stimulation for treatment-resistant depression", studies that concentrate on the molecular, cellular, or physiological mechanisms of DBS or using animal samples, were excluded and the number of articles decreased to 42 articles that include the results of evaluation and analysis of 446 patients.

Overview on Pharmacotherapy, ECT, TMS, VNS, and DBS for Treating Depression

Pharmacotherapy

Prior to the advent of antidepressant medications in the late 20 century, surgical ablation was the only option for treating patients who suffered from severe depression in the US and Europe [12]. The history of neurosurgical treatment in humans dates back to 1936 when Moniz and colleagues performed the first "Leucotomy" surgery that disrupted afferent/efferent pathways of the frontal lobe. Although this procedure produced partial efficacy in treating psychotic illness (i.e., most of the time it affected patients' cognition), with the discovery of pharmacotherapy in 1950, and their extensive application, interest in surgery decreased rapidly [13]. However, pharmacotherapy was not shown enough promising in treating severe major depressive disorder and led to the emergence of treatment-resistant depression [14]. Improvement in neuroimaging technology, pet scan, fMRI, and stereotactic methodology allowed to identify pathophysiology of depression precisely along with defining new targets for psychosurgery with minimal lesions and side effects [13]. For example, functional imaging (fMRI) has revealed, MDD is associated with increased activity in the subcallosal cingulate cortex (SCC), a brain area involved in mood regulation, and self-generated sadness.

One reason for a change in mood and behavior is a chemical imbalance, such as an imbalance in serotonin, dopamine, and norepinephrine in depressive disorders. Antidepressant drugs through altering chemical balances of neurotransmitters in the brain alleviate depression symptomatology. However, these medications enter the blood flow and impact other parts of the brain and even the whole body. One class of antidepressant medications is selective serotonin reuptake inhibitor (SSRI), which influences the brain serotonin level. Therefore, they may recover the signs of depression but exert some side-effects. SSRI antidepressants generate side effects that include anxiety, sleep disturbances, sexual dysfunction (decreased libido and reduction in arousal), and gastrointestinal disturbances. Bupropion from another antidepressant medication class induces overstimulation, agitation, insomnia, and nausea. Moreover, studies have shown that pharmacotherapy is effective in mild to moderate depression, and in severe depressive condition has not shown to be successful [15].

Electroconvulsive therapy (ECT)

Electroconvulsive therapy is the first type of electrical stimulation therapy in TRD and has been shown to have a 50%-60% rate of efficacy. It is very effective in depression, with remission rates of 60%-90% reported in clinical trials, but relapse rates are high (almost 10%-50% relapse), and long courses of ECT have cumulative cognitive side effects that many times become intolerable for patients [16]. Electroconvulsive therapy is mainly considered for the treatment of severe depression, in the context of unipolar or bipolar disorders. Apart

from depression, ECT is used in schizophrenia, bipolar manic (and mixed) states, schizoaffective disorder, schizophreniform disorder, and catatonia [17]. In the United States, ECT largely used as a secondary treatment for depression, when one or more psychotropic medications have failed [17], however, it is indicated as a primary treatment in some urgent conditions, such as suicide risk, malnutrition, dehydration from loss of appetite due to depression, and agitated psychosis, which rapid symptomatic improvement needed. The mechanism of action in ECT is based on four theoretical perspectives. The neuroendocrine theory suggests, ECT through influencing the release of hypothalamic or pituitary hormones, including prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, and endorphins, produces antidepressant effects. The second theory is an anticonvulsant theory, which posits that ECT's efficacy results from its anticonvulsant nature. It means that ECT by generating seizure in some parts of the brain ameliorate depressive symptoms. The neurotrophic theory proposes that ECT induces neurogenesis and increases neurotrophic signals in the brain. In animal models, increased neurotrophic factors after ECT, have been observed [18].

The main concern regarding ECT is its effects on cognition and inducing cognitive impairment [17]. Other disadvantages include acute rapid relapse, greater acute efficacy compared with long-term relief, acute and chronic cognitive side effects (memory disturbance), and lack of appeal to patients [19]. In the United States, ECT is usually done 3 times a week and in some countries two times a week, however, studies have shown that three times weekly may produce the results more quickly but cause more cognitive impairments [20].

Repetitive transcranial magnetic stimulation (rTMS)

Janicak, et al. [21] believed the dorsolateral prefrontal cortex (DLPFC) is the part of the brain that is dysregulated in patients with major depression, resulting in symptoms consistent with this kind of depression. In repetitive transcranial stimulation (rTMS) a high-frequency electromagnetic stimulation induced over the left DLPFC to effectively treat the behavioral dysregulation in patients with major depression [22]. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines recommend rTMS as a first-line intervention after the failure of one adequate antidepressant trial [23]. Usually in rTMS protocols for MDD, patients being treated with 10 Hz stimulation of the left dorsolateral prefrontal cortex (DLPFC) at an intensity of 120% of the resting motor threshold (RMT) over 4-6 weeks in once-daily stimulation sessions [24]. However, some studies recommend five daily treatment sessions over three to six weeks, that is, 20 to 30 sessions during treatment [22].

The mechanism of action in rTMS is still under investigation and somehow unknown, albeit, some study proposed that TMS induces increased blood flow in the cortical region, and some studies suggested that TMS increases the functional connectivity of the left DLPFC with the limbic system [22,25]. Although in some studies rTMS significantly improved all symptoms of depression [26], it has been shown to have a comparable effect to ECT and antidepressant medication [27], and statistically significant antidepressant effects [28], response rates (i.e., at least 50% reduction in depression severity) are relatively low, 15%-20% after 3-4 weeks of treatment and 24% after 6 weeks of treatment. Remission rates are even lower, 7%-14% with at least 3 weeks of treatment and less than 18% after 6 weeks of treatment, therefore, in patients with more resistant depression rTMS does not have adequate efficacy [29]. Reddy & Vijay [30] in their literature review reported the response rates to rTMS range between 50% and 55%, and the remission rates range between 30% and 35% in patients with major depression. Kedzior, et al. [31] state rTMS response rates in patients who have failed ECT are remarkably low; McClintock, et al. [32] recommend rTMS is better to be considered prior to ECT or as an add-on strategy and that patients who have not responded to ECT are unlikely to respond to rTMS treatment sessions alone.

The common adverse effects of rTMS are transitory and/or recurrent headaches, a tingling sensation on the scalp and face, and ipsilateral lacrimation [33]. Seizure activity is rare, and Durmaz, et al. [34] reported trigeminal autonomic cephalalgia in one patient after the administration of rTMS for refractory depression. Even if, the side effects of rTMS are mild and of short duration and some studies [24] suggest rTMS as a therapy for common depression treatment and demonstrate that it is beneficial when combined with other standard treatments, such as pharmacotherapy and/or psychotherapy and other neurostimulation options, Rizvi & Khan [22] believe, patients compliance can be affected, as it needs frequent visits to the clinic, and Burt, et al. [35] described it as a burdensome treatment (daily 40-minute sessions for up to 6 weeks) and presumed patients with high levels of treatment resistance are less likely to respond.

Vagus nerve stimulation (VNS)

The third type of electrical stimulation for depression is Vagus nerve stimulation (VNS). In 2005, FDA approved VNS as a treatment for patients above 18-years-old suffering from TRD. In VNS therapy, low-frequency, chronic, intermittent-pulsed electrical signals delivered to the left cervical Vagus nerve. Studies have described a slow but sustained clinical response [36] and have demonstrated the need for assessing outcome in a longitudinal and of sufficient duration (usually improved clinical response was observed 6-24 months following

implantation) with the mean time-to-first response of 12 months. The proposed mechanism of action for VNS based on the brain images and cerebrospinal fluid studies is VNS may induce changes in the prefrontal, cingulate, and insular cortex, as well as the brain stem [37-39] besides, dopamine may play a key role in the antidepressant effects of VNS [38,40]. Since most of the current antidepressants do not powerfully influence the dopaminergic brain pathways, the involvement of the dopaminergic system in VNS may be critical [41].

The advantages suggested for VNS in these clinical studies are: 1) The risks of VNS surgery are relatively low, and long-term treatment is generally well tolerated [42]; 2) VNS may decrease the overall mortality and suicidality and severity of symptoms for either ECT responders or ECT non-responders [36,43]; 3) It enhances the quality of life in patients with unipolar or bipolar disorder, even when the response is lower than 50% reduction from baseline score [41]; 4) VNS therapy improves cognitive and clinical measures in TRD patients [44]; 5) It is associated with localized changes in the brain as evidenced by fMRI techniques [41]; and 6) Patients who failed ECT or whom psychiatric care offers limited therapeutic options may benefit from VNS therapy [36]. Ayres Ribas, et al. [45] compared SCC-DBS with VNS and concluded these two procedures have a similar efficacy (in VNS response rate was 42%, in DBS it was 37%; the remission rate for VNS was 22.3% in DBS it was 26.2%).

The main disadvantages of VNS therapy can be as: i) Antidepressant effects of VNS in short-term (10-12 weeks) sham study demonstrated to be statistically nonsignificant, albeit, open-label long-term response and remission rates were high (27% response rate and 16% remission rate after 12 months of stimulation) and statistically significant [46], the average response time in VNS is 9 months after stimulation onset [47]; ii) In the longer-term study, 21%-50% of responders to VNS failed to maintain at least a 40% reduction in baseline depression severity over 1-2 years [39]; iii) VNS has no acute efficacy in the treatment of TRD but has shown to be effective in the treatment of chronic depression [48,49]; iv) Its high cost, lack of Medicare or Commercial coverage, and inadequacy in treating acute depression caused the number of patients benefitting from this treatment modality is low despite 15 years of commercial availability [16]; v) Although most of the VNS side effects are generally reversible, the most frequent acute complications include temporary salivation, coughing, paralysis of the vocal cords, lower facial weakness, rarely bradycardia, and, very rarely, asystole.

Deep brain stimulation (DBS)

Deep brain stimulation is a surgical procedure in which a pulse generator device is being implanted subcutaneously in the upper chest, near the clavicle and some electrodes are stereotactically implanted in certain brain regions. The electrodes are powered via leads by a pulse generator [50,51] that sends electric impulses via 1 or 2 leads tunneled under the scalp to the anchoring points in the skull. DBS induces an electrical field in the brain tissue that attenuates exponentially with the distance from the electrode. Deep brain stimulation is thought to inhibit or functionally override hyperactivity in limbic-cortical connections, which is implicated in the pathophysiology of major depression [52]. These inhibitory effects of DBS are mediated by depolarization blockade, synaptic inhibition, and synaptic depression. Contemplating on advantages and disadvantages of ECT, rTMS, and VNS leads us to realize why in recent years, researchers made an effort to find a different method for helping patients suffering from TRD and ameliorate their stubborn depressive symptoms.

Advantages of DBS include: 1) In contrast to pharmacotherapy, ECT, and rTMS, which affect even those areas of the brain that are not associated with depression, and induce side effects to various degrees, DBS is extremely focused and directly influences a very small part of the brain tissue [11], it provides an adjustable and reversible precise method of focally altering the activity of dysfunctional brain circuit with electrical stimulation; 2) DBS offering persistent antidepressant effects over many years, at the chronic stimulation condition, its antidepressant effects were consistent for 2-4 years [53]; 3) DBS has the potential to become a therapeutic alternative for the long-term management of sever and chronic TRD [13,54,55]; 4) "Successful DBS is supposed to modulate dysfunctional limbic circuits while sparing activation of networks supporting other brain functions" [56]; 5) Studies on DBS proved that unlike to ECT, DBS generates no cognitive side effects [54,55]; 6) One of the critical advantages of DBS is that most of its side effects are reversible and can be controlled by adjusting stimulation parameters (e.g. reducing the amplitude of the delivered current) [57]; 7) DBS not only works by altering function with neural circuits, but also by structurally altering circuits at the cellular level [58], Timmerman, et al. [59] proposed long-term DBS probably causes neuroplasticity and CNS remodeling effects that are necessary for the treatment response; 8) The higher rates of response and remission, in contrast to ECT, rTMS, and VNS that represented inadequacy in treating acute depression, severe MDD, and TRD situation [3], in some clinical studies that electrodes were implanted based on the patient's specific white matter trajectories, the average response and remission rates for DBS were more than 75% and 50% respectively [52,60-66]; 9) Moreover, the results of open-label studies on patients with TRD, shown that approximately 40% of patients lose at least half of their symptoms following DBS [60].

Disadvantages of DBS include: 1) Responding time in DBS studies comparing to the TAU studies

including pharmacotherapy, psychotherapy, or ECT is longer. In TAU, the antidepressant effects can be seen after a month of starting treatment, however, the establishment of sustained amelioration and adapting to the stimulation in DBS needs up to 6 months and causes emerging its efficacy in a longer time [53]; 2) The antidepressant effects of DBS required chronic and continuous stimulation, cessation of the stimulation intentionally [67] or accidentally leads to relapse or clinical worsening [68]; 3) In terms of safety and side effects, VNS was superior to DBS. The severity of adverse effects was higher in DBS [45]; 4) The cost of DBS implantation (100,000$) is significantly higher than VNS surgery (25000$), VNS is less invasive and the surgery time is shorter (2 hours), therefore, cost-benefit analyses will help to assess the true value of VNS and DBS.

Side effects and complications of deep brain stimulation (DBS): The side effects and complications of DBS are either related to the surgery for implanting the device under the chest skin and into some areas of the brain or possible complications after surgery. Although these side effects are rare in some clinical trials, a few of them have been developed. For example, in studies that investigated SCC-DBS, some of the participants represented infection, intraoperative cortical hemorrhage, pain and discomfort around the pulse generator, agitation, increased depression and anxiety, and postoperative seizure [3,60]. When DBS induced to the MFB, hyperkinesia, vision disorder at high amplitude, dizziness, restlessness, sweating, intraocular pressure, dyskinesia, slurred speech, anxiety, and motor rigidity were observed in a very small percentage of patients, however, the cognitive performance was stable in all patients [52,69,70]. In the studies on VC/VS-DBS, swollen eyes, infection of the wounds and dysphagia, seizure, hemorrhage, and postoperative delirium were observed [60]. Although uncontrolled case series reported cognitive function improvement, in one clinical controlled study, it caused a faster decline in recent autobiographical memories compared to healthy controls, albeit smaller than following a course of ECT [9].

Complications of surgery may include: misplacement of leads, bleeding in the brain, stroke, infection, breathing problems, nausea, heart problems, and seizure. Other drawbacks related to DBS include the need for repeated surgeries over time (e.g., from 6 months to 5 years) to replace pulse generator and the need for avoiding the situations or conditions which may damage the device or heat its components and cause injury to the patients, such as metal detectors, strong magnetic fields, and diathermy [42]. However, one of the main advantages of DBS is most of its side effects are reversible and can be managed by adjusting stimulation parameters such as decreasing the amplitude of the delivered current [57].

DBS targets with the most effectiveness for treating TRD

The three common regions in the brain that have been used for inducing DBS are subcallosal cingulate cortex (SCC or SCG), medial forebrain bundle (MFB), and VC/VS (including nucleus accumbens, NAs). Almost all of the targets in the human brain that have been utilized for investigating the safety and efficacy of DBS have functional/or structural connections together. Although so far there is no evidence-based study that compared the effectiveness of these targets, in some clinical study the response and remission rates for specific targets have been shown to be remarkable. For instance, when DBS applied to the medial forebrain (MFB), the immediate antidepressant was observed 1 week after stimulation onset, and > 70% of patients were responders and > 50% were considered as remitters [52,60,62,70,71] in their meta-analysis underscore the relatively high response rated with MFB-DBS compared to the other targets in the brain. Studies have shown that SCG plays an important role in the mood regulation circuitry, therefore, DBS to this region of the brain may help to treat unipolar and bipolar depression without producing manic episodes [13,72] other RCTs confirmed this SCG-DBS effects [68]. The SCC had been the most studied target for inducing DBS in almost all types of clinical studies, and the result was similar to the MFB and demonstrated > 70% and > 50% response and remission rates respectively [3,14,58,73-75].

Schlaepfer, et al. [11] in their study concluded DBS to the ventral striatum and in particular, the nucleus accumbens, is effective in the TRD treatment as; 1) The ventral striatum is strongly implicated in both normal and abnormal reward processes; 2) The NAs acts as a motivation gathering between limbic systems involved in both emotion and motor control. Anatomically, NAs is connected to both limbic and prefrontal regions (Cg25) and operates as a gateway to convey, and enhance or degrade information from the emotional centers of the brain to the motor regions; 3) The ventral striatum is uniquely located to modulate activity in the other brain regions, which means the NAs receives projections from midbrain areas that produce dopamine (such as the ventral tegmental area), from areas involved in emotion (such as the amygdala, orbitofrontal cortex, and medial prefrontal cortex), from motor regions (such as the dorsal caudate and Globus pallidus), and from regions involved in memory (such as the hippocampus) [76]. The NAs in turn indirectly projects to cortical regions including Cg25 and medial prefrontal cortex, the ventral pallidum, the thalamus, amygdala, and hypothalamus [77-79]. Since these connections can be GABA-ergic (inhibitory) or glutamatergic (excitatory), stimulating the NAs can modulate neural activity in other emotion and motivation centers of the brain.

Applying DBS to NAc and slMFB also demonstrated

promising effects on TRD patients [61], in Eitan, et al. [80] study, slMFB-DBS showed the fast time to response (1 week), the high proportion of respondents (100% of patients), the stability of response (60.4% of months staying remitted) as well as the significant reduction severity, all of these proposed the slMFB as a proper candidate for being used in DBS. Deep brain stimulation of ITP and LH has been a case report and still needs to evaluate their effectiveness in a big sample size to conclude their effectiveness. Eitan, et al. [80] state the plausible reason for observing the failure of the therapy in some patients can be utilizing improper brain targets or the mode of stimulation might not have therapeutic relevance for all patients and need to be tailored to each individual's specific characteristics. For example, when Guinjoan, et al. induced stimulation to the left side Cg25, not only there was no improvement compared to the bilateral situation, but also caused the deterioration of anxiety, mood, and energy, whereas, stimulating the right side Cg25 brought about full symptom remission within 4 weeks that continues to over 12 months later. This observation proved the asymmetrical response of this patient to Cg25-DBS and suggests the differential contribution of the left and right Prosencephalic structures in mood regulation. Consequently, although in some clinical studies or case-report studies, some DBS targets demonstrated the better outcome, the differences in study method, patient's specific characteristics, and depression heterogeneity restrict the comparison of targets' capability.

Can deep brain stimulation be a promising treatment for TRD patients?

There are many factors that may influence depression, including the existence of hypermetabolism in some areas of the brain (Subgenual Cingulate Cortex in depressed *vs.* remitted patients), hyperactivity (such as the response of the amygdala to the negative stimuli), and the areas with hypometabolism (the dorsolateral prefrontal cortex and striatum) [81,82]. Furthermore, many factors can impact the outcome of treatment, such as the heterogeneity of depression, individual neuroanatomical variability, variable time courses of the therapeutic effects of stimulation, psychosocial support, personality, temperament, variability in treatment protocol, and stimulation parameters. For instance, Schlaepfer, et al. [11,52] proposed, a combination of functional neuroimaging with specific biomarkers could be helpful in identifying biologically distinct phenotypes within the TRD spectrum. According to what Dougherty, et al. concluded from their study, the important factors for DBS to be successful in treating depression will depend on the integration of advances in neuroimaging, neurophysiology, and clinical expertise to devise new multicenter trials that will replicate, on a larger scale, the observations of different research groups, and thus ensuring a safe and long-lasting treatment option for the TRD population.

The case-series studies and open-label studies demonstrated promising results for DBS, however, the outcome of RCTs and double-blind studies showed some inconsistencies and warned for considering the role of placebo and insertion in an acute reduction in depressive symptomatology. In Eitan, et al. [80] study, the highlighted improvement in depression systems was detected immediately after surgery, in this study, one patient represented significant improvement and decreases in depression severity 2-4 weeks after implantation surgery that strengthens the possibility of insertion effect or the influence of mild edema as the electrode reaches the target [83]. Eitan, et al. suggested, this insertion effect might be a predictor for future clinical improvement. In addition to the effect of placebo on DBS, still, there is no consensus on DBS treatment protocol and treatment parameters. For instance, Bewernick, et al. [61] indicated the efficacy of DBS antidepressant for > 4 years, whilst, if stimulation discontinued, its effects vanished and increases the likelihood of relapse and reoccurrence of symptoms. Given that patients with TRD are highly vulnerable to recurrent depressive episodes, considering the ability of DBS to support long-term maintenance of antidepressant effects and prevention of relapse in severe and intractable depression would be an important treatment advance [3] and required the persistent DBS stimulation which the tolerability of this continuous stimulation by TRD patients is of paramount importance and needs special attention.

Another remarkable factor in DBS efficiency is selecting the proper target for implantation. Although most of the targets which have been used for implantation represented adequate safety and efficacy, one or two of these targets displayed superiority compared to others, such as the medial forebrain (MFB) and subcallosal cingulate cortex (SCC), however, because there are significant differences between the research methodology and treatment protocols (i.e., double-blind or open-label, short-term or long-term follow-up, stimulation parameters, and effective size) there is no possibility for comparing the effectiveness of each target and make it difficult to draw a conclusion. Moreover, sometimes inducing DBS to one specific target for all patients is not applicable, as the study by Islam, et al. [84] on a patient with refractory OCD showed, in this patient, DBS-NAs did not demonstrate any improvement in OCD symptoms, but applying stimulation to the VC/VS provided a statistically significant reduction in OCD severity. Smart and Veerakumar, et al. [85,86] state, identifying clinical, imaging, or physiological characteristics of patients that may respond to DBS can help to increase the chance of DBS success.

Besides, as Bergfeld & Figee [60] state, the focus of earlier studies was on gray matter nuclei (such as SCC), however, the newer studies shifted to the white matter bundles implicated in depression and

produced improved results for DBS. The reason for this mind-change for selecting DBS targets, rooted in the electrophysiological evidence shown that DBS exerts most of its effects in axons. Consequently, as Kisely, et al. concluded from their study, although DBS renders promises for treatment-resistant depression, it remains an experimental treatment until further data are available and its ambiguous points became resolved. In the following, some of the DBS disputable issues are discussed in more detail.

Deep brain stimulation limitation and complication

The limitations and complications of DBS therapy can be categorized into: (i) device complications; (ii) DBS protocol; (iii) DBS studies limitations.

Device complication: Studies [75] have shown that delivering longer pulse width (270 µs - 450 µs) may enhance stimulus optimization for the SCC-DBS, whilst this considerable amount of electrical current can deplete the battery and need to recharge or replace the pulse generator which is unpleasant for patients [13]. Although it was rare, in some studies, contact malfunction and infection around the IPG and the breaking of extension or lead were among the device complications [52,69,70].

DBS protocol: Still, there is no consensus for deep brain stimulation procedures. Some clinical trials used high frequency (130 Hz) and some other low frequency (20 Hz), which demonstrated different results. Eiten, et al. [80] in their study tested the effect of high *vs.* low frequency DBS to SCC, their result represented the better antidepressant effect in high frequency (130 Hz). There is no evidence-based data to support a protocol for optimization of stimulation in TRD or MDD patients and adjustment of optimal stimulation parameters is guided by the clinician's knowledge and experience. Stimulation using longer pulse width (270-450 µs) was related to short-term clinical improvement and positive mood response in 3 of 4 patients. Shorter pulse width with higher amplitude stimulation (up to 9V) and longer pulse width with lower amplitude stimulation may produce comparable benefit [75]. Although the mechanism underlying these diversities in effectiveness in different stimulation is unknown, one possibility is the spread of current to other pathways projecting to or from ventromedial and orbitofrontal cortical areas that are modulated by SCC-DBS in responders [68]. Longer pulse duration could influence pathways farther from the electrodes [75]. However, longer pulse width is not tolerable for all patients, in some patients it produces insomnia, confusion, and drowsiness [75]. It decreases the battery life and increase the need for battery replacement. So, the better way is compounding longer pulse with lower battery voltage. Moreover, Puigdemont, et al. [67] suggested for preventing relapse after remission, continuous electrical stimulation after more than 3 months of stable remission is required to maintain therapeutic effects.

DBS studies limitation: A double-blind study design for DBS is of paramount importance. Tave [87] states, the operation, and electrodes implantation have a high placebo rate and in studies that use sham surgeries, placebo showed a dramatic effect on the results. Brunoni, et al. [88] indicated that the placebo response in depression is large in both pharmacological and nonpharmacological interventions. In Eitan and Fenoy, et al. [64] the acute effects of DBS within 1-4 weeks before the onset of stimulation, proved the effect of micro-lesioning and placebo effects. In studies on Parkinson's disease, amelioration of symptoms before the onset of stimulation was alleged as the micro-lesioning effect. Bewernick, et al. [61] believed, the acute amelioration of symptoms either in TRD or in using DBS surgery in movement disorders suggests the micro-lesioning effects and can predict the future stimulation efficacy. In studies with limited time of stimulation, there was no significant difference between active and sham stimulation [89], however, studies with longer duration (more than one year) for stimulation, demonstrated a statistically significant difference between sham and active stimulation and confirmed the effectiveness of DBS for decreasing depression symptoms [58]. Consequently, the newer techniques that define the electrode targets based on the patient's specified white matter trajectories report a response rate of around 75%; although this approach has yet to be corroborated in placebo-controlled studies [60]. One major problem of most DBS clinical trials is that follow-up periods are relatively short in consideration of the long duration of patients' depressive episodes [3].

Conclusion

Pondering on the results of the open-label studies, case-series and cross-sectional studies, and even the RCTs are promising and demonstrated DBS superiority compared to other electrical stimulation procedures. So far, all the researchers who have worked from 2005-2020 on the safety and efficacy of DBS, acknowledged its capability for treating severe MDD or refractory depression as an adjunctive treatment, and with no exception, all of them have emphasized doing a well-controlled study on an effective number of TRD patients, the need for doing a highly controlled study on an effective number of patients with TRD, and comparing the long-term with the short-term results optimizing the stimulation parameters, and considering the individualized pattern of depression.

The privilege of DBS compared to other depression treatment modalities probably grounded in first, the mechanism of action in DBS is different from pharmacotherapy, ECT, and rTMS, against to these methods, DBS influences those brain regions implicated

in depression focally and does not impact other brain areas. In each DBS target, DBS works not only by altering function within the neural circuit but also by structurally altering circuits at the cellular level second, DBS has no adverse cognitive impacts and almost all its side-effects are reversible. However, DBS treatment needs to be refined, and achieving a consensus on its protocol makes it closer to becoming a promising treatment for depression. Determining the ultimate stimulus parameters and the proper target for implantation play a very important role in enhancing DBS antidepressant effects. Moreover, almost in all of the clinical studies and case reports, DBS was investigated as an adjunctive treatment while the TRD patients were on at least two different classes of antidepressant medications, the need for assessing the confounding or reinforcing effects of medications on deep brain stimulation is apparent.

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Conflict of interest

Nazanin Amirani declares that she has no conflict of interest concerning the publication of this article. This article was extracted from Nazanin Amirani's master's project. She used no financial support for doing her master's project. Dr. Ijeuma Nwachuku is affiliated with California Southern University and as a master's project advisor received the advising fee from this university. California Southern University has no restriction for learners to publish their thesis, articles, or doctoral project.

Data availability statement

This study was a re-analysis of the existing data and drew on the evidence -based published articles and/or their supplementary materials that are openly available at locations cited in the reference section. Datasets analyzed during the current study are available in the following public domain resources: https://pubmed.ncbi.nlm.nih.gov, https://www.sciencedirect.com, https://www.cochranelibrary.com/search, https://www.elsevier.com/solutions/embase, and https://www.apa.org/pubs/databases/psycinfo.

Ethical statement

The authors declared that this review article is not currently considered for publishing elsewhere. Since this paper is based on the results derived from previously published empirical studies, all the sources and articles that have been used are properly disclosed and correctly cited. There is no conflict of interest or financial support that influenced the outcome of this review study.

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