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The Effectiveness of Deep Brain Stimulation in the Treatment of Bipolar Disorder

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Abstract
Background: *Bipolar disorder (BD) is a chronic debilitating illness associated with socioeconomic burdens on patients and their caregivers. Presenting a challenge to diagnose, the management of bipolar disorder with existing first-line pharmacologic and psychological therapies has not yielded much significant results. As a result, there is the need to explore other more efficacious modalities of treatment of the condition. This systematic review analyzes the efficacy of deep brain stimulation (DBS), a novel neuropsychosurgical intervention, in managing bipolar disorder, with specific focus on neuroanatomical and neurophysiological circuitries involved in the pathophysiology of bipolar disorder.*
Methods: *A search of online databases was conducted using the following keywords: deep brain stimulation, bipolar disorder, mania, depression, and treatment. Articles selected for use included those which have been peer-reviewed, and contained either case reports, case series, open-label, single-blind, and randomized double-blind sham-controlled studies.*
Results: *Significant evidence supports the increased use of DBS in bipolar depression, with a reduced risk of triggering mania in bipolar depressed patients. Low-quality evidence also suggests increased positive response in manic patients with bipolar disorder. There is minimal information in medical literature relating to acute adverse effects associated with the use of DBS in bipolar disorder. However, there is a dearth of evidence concerning what happens to patients in terms of relapse, response, or remission, years after cessation of stimulation.*
Conclusion: *The use of DBS in patients with BD requires a lot more exploration. However, present evidence shows that it is effective for patients with bipolar depression. Its use in manic individuals has not been well elucidated. Further research should explore its efficacy in manic individuals; and especially how to further refine the approach in order to increase efficacy and reduce the risk of adverse events in patients with bipolar disorder.*
Keywords: *Bipolar disorder, deep brain stimulation, mania, depression, unipolar depression.*

Introduction

Commonly referred to as manic-depressive illness, bipolar disorder (BD) is one of the chronic mood affective disorders with severe debilitating symptoms that have significant effects on both the patients involved and their caregivers [1]. In most cases, BD commences typically from adolescence or may start in early adulthood, with life-long negative consequences on the patient's mental and physical health, interpersonal relationships, educational and occupational functioning [2]. The disease has been estimated to have a lifetime prevalence of 3.9% in the United States regardless of gender, race or ethnicity [3,4].The treatment of the BD is still has low efficacies with patients having persistent and/or repeat symptoms for about 31.9% of the time over almost 13 years [5]. This leads to long-term suboptimal outcomes with enormous economic burdens that exceed 120 billion US dollars in a year in the United States [6]. This huge economic burden points at the need for more research and to improve the management of BD in affected patients.

Often misdiagnosed and under-recognized, BD is a complex disorder that is a challenge to diagnose [7].Patients with BD experience recurrent and alternating episodes of mania or depression – both are pathologic mood states, with intervening periods of euthymic states [8]. The diagnosis of BD is in line with criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), which notably defines the depressive aspects of BD with the same criteria needed to diagnose Major Depressive Disorder (MDD) [9]. Distinguishing MDD from BD requires a history of symptoms suggestive of mania or hypomania [7].

A number of treatment options are currently available for the management of BD. For the past few decades, pharmacotherapy and psychosocial therapies has been the first line treatment modalities for the disease [10]. However, the use of mood stabilizers, antipsychotics, and other adjuvant medication has had relatively low success rates in patients with BD [11]. This has led to the use of electroconvulsive therapy (ECT) in patients who are unresponsive to the first-line treatments, and in whom it has been reported to be comparatively more successful with rapid results [12-14]. One major challenge of treating BD is to differentiate and categorize the BD patients into: bipolar type I, bipolar type II, mixed BP, sub-mixed or cycling BP. This makes it difficult to select appropriate doses of medications [15]. In order to effectively treat these cases, professionals are turning towards alternative treatments such as ECT, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VMS), and deep brain stimulation (DBS) [11,12,16,17].

DBS is a form of neurostimulation in which a surgically implanted electrode is placed bilaterally in the brain guided by stereotactic magnetic resonance imaging (MRI), with the aim of providing focal electric modulation of neural circuits [16,18]. Recently developed, it is beginning to gain grounds in the treatment of psychiatric disorders, and has been proven to be effective in the treatment of hyperkinetic movement disorders like Parkinson's disease (PD), dystonia, treatment-resistant depression (TRD), and different forms of obsessive-compulsive disorder (OCD) [16,18-20]. However, there are still associated surgical risks and other challenges that are yet to be addressed. More so, the use of DBS in the treatment of BD is yet to be well defined, well-argued, and well-executed, hence the main focus of this systematic review is to provide unbiased information as regards to the efficacy of DBS in the management of BD.

Method

We conducted a search on online databases using the keywords: bipolar disorder, unipolar depression, deep brain stimulation (DBS), mania, depression, and psychosurgery. We included case reports, case series, open-label, single-blind, and randomized double-blind sham-controlled studies. The data sources were PubMed from MEDLINE, PsycINFO, COCHRANE, and EMBASE.

Eligibility Criteria

Studies that reported results arising from the use of DBS in depression, treatment-resistant depression, unipolar depression, mania, bipolar disorder, or affective disorders were included in this study. There were no limitations as regards the size of the subject populations, specific outcomes of the researches, and the selected study designs. Only research papers in English language were selected. Lists of references of several systematic reviews were also used for scanning further references.

Bias was eliminated by two independent reviewers who screened the titles and abstracts of the final selections. Articles and papers that did not meet the eligibility criteria were excluded. Final decisions on the papers that were later included were made by the authors and reviewers.

Exclusion Criteria

All the resulting studies from the selected sources were reduced by the elimination of studies that were not directly related to the study of the use of DBS in depression, treatment-resistant depression, unipolar depression, bipolar depression, mania, and/or bipolar disorder. Studies that discussed the use of DBS in Tourette's syndrome, Parkinson's disease, Alzheimer's disease, or addiction were eliminated.

Results

In the treatment of the depressive aspect of BD with DBS, there are four main targets areas of the brain, which are the subcallosal cingulate brain area 25 (SCC-BA25), the Nucleus Accumbens (NAcc), the medial forebrain bundle (MFB), and the ventral capsule/ventral striatum (VC/VS) [21-23]. In addition to these, the lateral habenula (LHb), and the inferior thalamic peduncle (ITP) have also been shown to be excellent targets for DBS [21,22]. The earlier four main targets have been shown to be efficacious for DBS using small scale studies. However, there exists no standard randomized controlled trial to evaluate their comparative efficacies. In evaluating the treatment of depression, response is measured using the Hamilton Depression Rating Scale (HDRS) and/or the Montgomery-Asberg Depression Rating Scale (MADRS). A 'response' refers to a reduction of greater than or equal to 50% in either the HDRS and/or MADRS or both, while 'remission' refers to a score of "nondepressed" on either of the two scoring systems [18].

Efficacy of DBS at the Subcallosal Cingulate (SCC-BA25)

The significance of the SCC (BA25) as an important target for DBS was first pointed out by converging datasets which showed the modulation of this area will result in an antidepressant response and symptomatic improvement in patients with both unipolar and bipolar depression [24,25]. It has the advantage of not tilting patients with bipolar depression towards mania, a common side effect of medications used to treat BD. Using the SCC DBS, response rates between 41% and 66% have been recorded within 24-26 weeks, which later increased to 64% to 92% after two to six years [26]. In this same study on patients with unipolar depression, the remission rate was between 42% and 58%. These results are unprecedented for any form of therapy for bipolar depression. The ability of SCC DBS to influence interest, mood, psychic anxiety, suicidality, and middle insomnia at the same time is a major contributor to the marked improvement in the HDRS score.

Considering the effect of DBS on bipolar depression, however, 17 participants were entered into a study in which they were initially treated with single-blinded stimulation for 4 weeks, and continuous active stimulation for another 6 months [27]. Monitoring continued for 2 years after the start of active stimulation. There was a significant antidepressant response of 42% and 65% after 6 and 24 months, respectively; in addition to an improvement in function. The remission rates were 18% and 58% within the same time intervals [27]. None of the patients experienced spontaneous relapse, and there were no symptoms suggestive of hypomania, mania or hypermania. This result has also been replicated in

another study, indicating the ability of DBS to effectively treat bipolar disorder [28].

Efficacy of DBS at the ventral capsule/ventral striatum (VC/CS)

The antidepressant effects of VC/VS DBS was first noticed with its use in OCD patients where it showed significant reduction in depressive symptoms regardless of changes in the OCD symptoms themselves [29]. In patients with depression, a response rate of 40% was recorded at 6 months, while a remission rate of 20% were recorded at about the same time interval [30]. A follow-up of the same patients recorded response and remission rates of 71% and 35%, respectively, after about 14 to 67 months post-therapy. A similar study on patients with unipolar depression recorded response rates of 53.3% using VC/VS DBS after about 6 to 51 months post-stimulation [30]. Both studies highlighted an improvement in the symptoms – improved moods, reduced anxiety, improved awareness, and spontaneous smiling. At the same time however, there were negative effects such as increased anxiety, tachycardia, and perseverative speech; although the magnitude of these effects were not stated. It has been suggested that these negative effects can be tempered down with fine changes in stimulation parameters [29].

Efficacy of DBS at the Nucleus Accumbens (NAcc)

The nucleus accumbens' influence on reward and motivation pathways has been established in various reports, which makes its modulation with DBS a rational move [31,32]. It has been shown that modulation of the NAcc can eliminate the occurrence of anhedonia which is a fundamental depressive symptom [33]. A study showed a significant improvement in hedonic response and depression ratings in three patients with treatment-resistant depression (TRD) after active stimulation of NAcc with DBS, and whose improvement reversed after cessation of active stimulation [34]. An antidepressant response of 50% was recorded after 12 months of continuous active stimulation of the NAcc, when the same cohort was widened to 10 patients with similar symptom characteristics. These results suggest an acute positive response which is not indicative of a long term outcome. It is important to note that the negative effects recorded in this study were similar to that noticed with VC/VS DBS, with a case of suicide which was later proved to be unrelated to DBS use [29]. In addition, the similarity between the results of studies with VC/VS DBS and NAcc DBS is congruent with the fact that the location of electrode placement in the brain tends to overlap in both cases since the NAcc is a group of neurons which are located within the VS [30,35].

Efficacy of DBS at the inferior thalamic peduncle (ITP)

The stimulation of the ITP with DBS was first reported in a case study of a female patient with TRD that coexisted with bulimia and borderline personality disorder [22]. A significant response was achieved with chronic stimulation for nearly 24 months. Notably, she experienced a mild resurgence of depressive symptoms when active stimulation was stopped after eight months for a double-blind testing period. Negative effects such as tachycardia, anxiety, dyspnea, nystagmus and sweating were associated with the acute ITP DBS. However, there were no recorded adverse effects associated with chronic stimulation [22]. Similarly, studies have shown the effect of focal stimulation of the LHb in two patients who had refractory depression, unresponsive to medications and ECT [36,37]. Both patients recorded significant reduction in their HDRS scores, although cessation of stimulation caused an immediate relapse in both cases, and which gradually resolved with resumption of stimulation. It was also pointed out that the one of the patients needed a voltage increase to 10.5V from 5V in order to reach full remission; which suggests that there will be a faster consumption of battery power and frequent changes in battery will be required [19]. In both cases, there were no negative effects with either acute or chronic stimulation.

Table 1. Major clinical studies on the use of DBS for unipolar depression and bipolar disorder

Study	Number/type	Target	HDRS (%)	Follow-up period	Remarks
Mayberg et al.(2005) [47]	6 (unipolar)	SCC	55.0% response	6mo	
Lozano et al. (2008) [63]; Kennedy et al.(2011) [58]	20 (unipolar)	SCC	64.3% response	72 mo	
Holtzheimer et al.(2012) [27]	11 (unipolar) 7 (bipolar)	SCC	69.0% response	24mo	92% response
Malone et al.(2009) [30]	15 (unipolar)	VC/VS	53.3% response	48mo	40% remission
Dougherty et al. (2014) [64]	30 (unipolar)	VC/VS	23% response	24 mo	
Schlaepfer et al.(2013) [21]	7 (bipolar)	MFB	-	6 mo	
Bewernick et al.(2010) [34]	11 (unipolar)	NAcc	41.7% response	48mo	9% remission
Jiménez et al.(2005) [22]	1 (unipolar)	ITP	Remission	N/R	No adverse events
Kiening et al.(2013) [36]; Knapp et al.(2009) [62]; Sartorius et al.(2007) [37]	1 (unipolar)	LHb	Remission	N/R	

Type signifies whether the form of depression is unipolar/bipolar; SCC =Subcallosal Cingulate; VC/VS = Ventral Capsule/Ventral Striatum; MFB = Medial Forebrain Bundle; NAcc= Nucleus accumbens; ITP = Inferior Thalamic Peduncle; mo= months; HDRS = Hamilton Depression Rating Scale; N/R = Not Reported.

Discussion

The effectiveness of the DBS in BD further strengthens the hypotheses that mood disorders are caused by the pathologic disruption of neural networks that moderate varying aspects of human emotional behavior. Evidences brought forward via brain imaging from fMRI, PET scans, and diffusion tractography have shown reduced gray matter volume in the broadman area (BA) of the brain in the orbital BA11 & BA47,and ventrolateral prefrontal cortex (PFC) BA45& BA47 [38,39]; superior temporal gyrus; and posterior cingulate cortex in patients with BD [40]. These have been associated with abnormal circuitry, especially within the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuits [41]. The LCSPT circuit which has been associated with emotional behavior is particularly implicated in the causation of depression. Since disruption of these circuits affects proper neural transmission through them, it is easy to relate how the dysfunction can lead to the pathological affective states that are seen in BD [42].

The resulting neuroanatomical, neurophysio-logical, neuropathological, and neurochemical abnormalities that has been presented with evidences converges under the neurocircuitry models of depression and mania. The abnormal discharges and metabolism in the amygdala, SCC, NAcc, and medial thalamus forms the rationale behind the application of DBS as a therapeutic modality [41,43]. In simple terms, DBS acts to inhibit activity in the gray/white matter that it stimulates, although its mechanism of action has been shown to be quite more complex [44,45]. Its results depend largely on the location of electrodes in the brain and the magnitude of stimulation. In addition, the efficacy of DBS also depends on the level of activity of the brain area and the capacity of DBS to effectively modulate this activity [29].

The use of DBS has been tilted more towards patients with both unipolar and bipolar depression, in which significant positive response has been noted as compared to mania [16]. However, a few studies also point to its usefulness in patients with actual bipolar disorders [27,28]. In addition to these studies, there is a case report of a patient suffering from intractable bipolar disorder, alternating and progressively worsening depression and mania, which was unresponsive to pharmacotherapy, ECT, and even nerve stimulation (VNS) [46]. The study reported a 2.5 year follow-up decrease in the HRSD score from 32 to 8 after 6 months of chronic stimulation of the SCC with DBS.

Quite a number of studies have reported significant results with SCC DBS, pointing to the usefulness of SCC modulation in treating both unipolar and bipolar affective disorders [24-28]. The SCC is an important neural circuitry for the

regulation of mood and has been established as a significant target for DBS in depressive patients [47,48]. The results so far suggests the positive role, the SCC (BA-25) can play in managing patients that have both manic and depressive episodes within the context of a bipolar disorder considering the reduced risk of causing mania unlike the other DBS targets [27,28,46]. However, the minute possibility of triggering manic episodes in patients with unipolar depression still needs to be considered. This is because one case report has reported a female patient being managed for OCD with DBS of the NAcc and the anterior limb of the internal capsule, who subsequently exhibited a manic episode [49]. Transient mania has also been reported in a few other cases after the use of DBS [50-52].The cause of this stimulation-induced mania might have been caused by spread of stimulation from the target sites to areas around the frontal and limbic regions [20,53]. The management of BD with DBS requires further exploration of the brain areas which needs to be stimulated, so that undesired symptoms caused by DBS can be prevented.

The usefulness of the other DBS targets such as the VC/VS, NAcc, ITP, and LHb. All have reported varying successes on patients with unipolar depression that cannot be underestimated in patients with BD. Even though there have been minimal inquests into their relevance in managing BD patients, the success reported with the Medial Forebrain Bundle (MFB) DBS in 6 out of 7 bipolar patients suggests the use of other DBS targets is worth considering [21]. All these other potential target areas have been shown to share substantial linkages within their circuitry, and they are also known to play important roles in the pathophysiology of BD based on results from neuroimaging, morphologic, and metabolic studies [46].

Overall, these evidences suggest that DBS is indeed an effective treatment modality for bipolar disorders, even though it is skewed towards the treatment of depression [27,28,30,47]. BD is a heterogeneous disorder consisting of a wide range of symptom patterns that have been shown to arise from one or more dysfunctional mood-influencing neural circuits [7,18,54]. Nevertheless, targeting one or more of these circuitries have resulted in significant positive response in patients with unipolar depression as well as those with bipolar disorders, but with extended depressive states. Better results can be obtained with optimal stimulation settings, more precise electrode positioning, improved voltage selection, and modulation of specific microstructural targets [55-57]. It is difficult to categorically state that DBS is effective for the treatment of manic states as there is limited evidence to back this up.

Limitations and Future Recommendations

It is clear that the structural and functional changes that take place in the brain after acute or chronic DBS still needs to be further elucidated. It is necessary to clearly iron out the neurophysiological and neuroanatomical modifications that are precipitated by DBS in order to be able to refine stimulation parameters, and significantly reduce negative effects or brain damage. A lot of studies do not give information about what happens several years after cessation of stimulation, whether there is a relapse, or whether response/remission continues stably. One hypothesis is that DBS induces some form of endogenous plasticity so that normal brain mechanisms take over when stimulation stops [16]. In patients where this was tested, many of them required resumption of stimulation to maintain their response [27]. Whether these set of patients will require adjuvant therapy to remain symptoms-free is yet to be clarified.

In the treatment of both unipolar and bipolar depression, the use of higher voltages resulted in improved outcomes [58]. However, this translates to rapid depletion of battery power, more frequent replacements via surgery, and therefore, increased risk of surgical complications. There needs to be innovative solutions such as the use of rechargeable batteries or intermittent pacemaker-like mode of stimulation [59-61].

Conclusion

The use of DBS can bring much needed symptomatic relief to the depressive state of BP patients. However, more research still needs to be done to show the efficacy of this treatment modality that blends neurosurgery with interventional psychiatry. Particularly, the dearth of information concerning the use of DBS in mania points at the need for more case reports, blind and randomized trials in order to clearly establish the efficacy of DBS in manic patients. Also, the question of which patients will benefit maximally from DBS is yet to be established. For this purpose, large multicenter collaboration and exchange of information to encourage improved patient selection for DBS is required.

Even though DBS is still considered as a form of experimental therapy for now, its acceptance by leading figures in the field that are saddled with the task of developing protocols for its clinical use will help hasten its status as a recommended line of therapy for patients with mood affective disorders. It is hoped that it will gradually work its way to becoming either a second-line or first-line treatment for depressive state of bipolar disorder.

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