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# Deep Brain Stimulation for Treatment-Resistant Depression: A State-of-the-Art Review

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## 1. Introduction

Depression is a common underdiagnosed, undertreated and costly mood disorder associated with substantial morbidity and mortality (1-3). It is related to the emotion of sadness or irritability and accompanied by several psychophysiological changes, such as disturbances in sleep, appetite or sexual desire; constipation; loss of the ability to experience pleasure in work or with friends; crying; suicidal thoughts; and slowing of speech and action (4-6). Approximately 5% of the population has major depression at any given time, with men experiencing a lifetime risk of 7%-12%; and women 20%-25% (3, 5).

Depressive mood is one of the most common – and potentially dangerous – psychiatric complications of every chronic disease because it often worsens the overall clinical condition. The prevalence of depression in patients with chronic conditions ranges from 25 to 33 percent and is frequent among people hospitalized with cancer, who have had a recent heart attack or stroke, or have diabetes or Parkinson's disease (7). Besides, even between non-hospitalized patients, depression has an important effect on life and may limit the social activities of individuals. People who are depressed tend to be more withdrawn from their community, friends and family, are less likely to work, present a decreased productivity and retire earlier. The relevant social-economic and clinical impacts of mood disorder, especially depression, on patient's life have drawn attention to possible therapeutic mechanisms that could improve the quality of life and outcomes of depressive patients.

The clinical approach of patients suffering of depressive mood has evolved considerably throughout years and includes mainly supportive care combined with pharmacotherapy and psychotherapy (8, 9). Globally, treatment planning requires coordination of short-term strategies to induce remission associated with longer term maintenance designed to prevent recurrence. The wide variety of drugs available to treat depressive patients has given the physician a large spectrum of therapeutic possibilities for a rationale approach.

Approximately 35 million adults in United States population, at least once in lifetime, experience an episode of major depression (3). The essential feature of a major depressive event is defined as a persistent period of at least two weeks in which there is either depressive mood or the loss of interest or pleasure in nearly all activities (DSM-IV). The available treatment currently used includes selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), selective norepinephrine reuptake inhibitors (NRI) and monoamine oxidase inhibitors (MAOI). However, only 47% of patients respond well to antidepressant treatment and only 33% of patients achieve remission in the first line of treatment with a widely used selective serotonin reuptake inhibitors (10). Additionally, relapse within 6-12 months is verified in approximately 50% of those who remit (11). Therefore, while currently available treatments are amongst the most widely prescribed drugs, they fail to have an effect on many patients and have incomplete effects for many others. Treatment-resistant depression has an estimated prevalence of 2-5% and continued depressive symptoms are directly responsible to ongoing functional impairment, increased utilization of health care resources, a high risk of suicide and an overall increased mortality (12-14). An effective treatment is then necessary, but there is very limited evidence for the efficacy of any specific therapeutic intervention in chronic, treatment-refractory depression.

Electroconvulsive therapy (ECT) is the main procedure indicated to patients resistant to antidepressive medications and consists of the induction of convulsive crises by means of applying an electric current through the brain for therapeutic purpose (15). The remission rate of depression with electroconvulsive therapy varies, generally, from 50% to 80% (15). However, ECT may have important side effects, especially cognitive impairment, that can limit its clinical use (16) and it is associated with a high relapse rate (15, 17).

Repetitive transcranial magnetic stimulation (rTMS) was recently approved by FDA (Food and Drug Administration) for the treatment of depression that has not responded to one antidepressant medication. This procedure is well-tolerated and has few side effects. Its mechanism of therapeutic action is linked to the principle of electromagnetic induction discovered by Faraday in 1831 by which electrical energy and magnetic fields are related. According to Pascual-Leone, an increased neuronal excitability linked to the increase of magnetic field may produce electrical currents in certain areas of the brain, especially the left prefrontal cortex, and reduce the depressive symptoms (18). rTMS has been described as a generally safe technique with consistent statistically significant antidepressant results (19, 20), however is associated with relatively low response rate and the maintenance of benefits over time is relatively unknown (21).

Vagus nerve stimulation (VNS) was approved in 2005 for the treatment of patients failing to respond to, at least, four antidepressant drugs and refers to electrical stimulation of the cervical portion of the left vagus nerve through a surgically implanted electrode and pulse generator. Surgical risks are relatively minor and long-term treatment is usually well tolerated. However, it has been noted that only a substantial minority of patients with extremely difficult-to-treat depressive disorder benefit from VNS and 21%-50% of patients who responded to VNS failed to maintain at least a 40% decrease in baseline depression severity over 1-2 years (22-24).

Deep brain stimulation (DBS) has been described as a promising therapy to severe and treatment-resistant depression. Since 2005, when Mayberg and colleagues (25) have

reported that the subgenual cingulate region (Brodman area 25) is a potential target to electrical stimulation with effective reverse of symptoms in patients suffering treatment-resistant depression, a large number of studies have been conducted to explore other potential sites in the brain that could be involved on the mechanisms of depressive mood disorders.

This procedure is characterized by a stereotactical implantation of an intracranial electrode that is connected to a pulse generator/battery pack (26). In 1947, at Temple University in Philadelphia, the neurologist Spiegel and the neurosurgeon Wycis first described a stereotactic apparatus and its use in humans to perform ablative procedures (27). The great knowledge achieved from the treatment of patients with movement disorders with DBS, such as Parkinson's disease, primary dystonia, and essential tremor, allowed its experimental use also on patients with treatment-resistant depression with encouraging results. Due to its reversible, revisable and adjustable potential, DBS represents an alternative and additional therapeutic approach to treatment-resistant depression.

The initial evidence that a focal disrupting pathological activity in limbic-cortical pathways was present in patients with negative mood was observed by Mayberg and colleagues, in 1999 (28). Using functional neuroimaging studies, they consistently demonstrated the involvement of the subgenual cingulate (Cg25) (Brodman area 25) in both the acute sadness and antidepressant treatment effects. A markedly increased blood flow was noted to the Cg25 during induction of transient normal sadness and, in contrast, a decreased activity was reported with clinical response to different antidepressant treatments, which suggested a critical role for this region in modulating negative mood states. This scientific observation raised the hypothesis that a therapeutic intervention on specific sites of the limbic-cortical circuits could effectively reverse the symptoms of otherwise treatment-resistant depression. Mayberg and colleagues, in 2005 (29), on an open-label study, applied bilateral DBS on the subcallosal cingulate white matter in six patients with treatment-resistant depression and observed a clinically significant antidepressant response in four after 6 months, which is known as the first published report of DBS for treatment-resistant depression.

Based on the presence of neuronal dysregulation in limbic-cortical circuits and positive lesional effects, various target areas for depressive disorders have been discussed. Schlaepfer and colleagues, in 2008 (30), stimulating the nucleus accumbens of 3 patients, observed after one week, 42% reduction in symptoms. Malone and colleagues, in 2009 (31), stimulating the ventral internal capsule and ventral striatum of 15 patients, noted a distinct reduction in symptoms by 57% during 12 months. Lozano and colleagues, in 2008 (32), stimulating the subgenual area of cingulum of 20 patients, observed reduction in symptoms by an average 48% during 12 months, with 2 non-responders and 7 remission. Other targets for DBS in treatment resistant depression have been proposed, including globus pallidus internus, inferior thalamic peduncle, lateral habenula and the rostral cingulate cortex (33, 34) (Table 1).

The ideal patient that may benefit from DBS is still a matter of controversy. The failure to two antidepressant treatments in the current episode appears to have a predictive validity. In STAR\*D, remission rates in successive stages of treatment were 36.8% in the first treatment, 30.6% in the second treatment, 13.7% in the third treatment, and 13.0% in

YEAR	REFERENCE	PLACE	PATIENTS	STIMULATION SITE	SYMPTOMS REDUCTION
2005	Mayberg <i>et al</i> (28)	Canada	6	Subgenual area of cingulum	71%
2008	Schlaepfer <i>et al</i> (29)	Germany	3	Nucleus accumbens	42%
2008	Lozano <i>et al</i> (31)	Canada	20	Subgenual area of cingulum	48%
2009	Malone <i>et al</i> (30)	USA	15	ventral internal capsule/ventral striatum	57%
2011	Puigdemont <i>et al</i> (35)	Spain	8	Subgenual area of cingulum	50%
2011	Kennedy <i>et al</i> (36)	Canada	20	Subcallosal cingulate gyrus	64.3%

Table 1. deep brain stimulation in patients presenting treatment-resistant depression.

the forth treatment (11). Additionally, the likelihood of remission is markedly lower for patients for whom two or more adequate antidepressant trials failed (11). Therefore, in some studies, to qualify for DBS, patients had to be in an episode of major depression for at least 1 year and had to have failed to respond to at least four treatments (32). Exclusion criteria usually includes substance abuse, severe personality disorder and psychotic depression (35).

The potential for adverse effects from DBS for treatment-resistant depression has not been completely studied. Lozano and colleagues, in 2008 (32), reported increased depression in 10% of patients that underwent DBS of the subgenual area of cingulum. Moreover, Malone and colleagues, in 2009 (31), describe hippomanic episodes, increased suicidility and syncope on patients submitted to DBS of internal capsule/ventral striatum. Future studies must carefully point the most commons adverse effects and complications, and the specific targets related to it as well.

DBS is a recently proposed therapeutic approach to treatment-resistant depression and, therefore, remains with many unsolved questions. Future investigations must correctly address which patient benefits most from the surgical procedure and which is the best therapeutic target or, if not possible, which target best correlates to specific symptoms of depression. Large, randomized placebo-controlled studies of DBS for treatment-resistant are necessary to describe the potential risks and complications from operation. Additionally, as the study of DBS progresses, complementary information must put into evidence which is



the best adjunctive therapy, the potential interactions of pharmacotherapy and the relative safety and efficacy of the various DBS targets.

This review aimed to describe the context in which DBS has emerged as an experimental therapy for refractory depression, present a brief historical note, discuss the different targets in these pathological neuro-psychiatric disorder, review the preliminary results of some clinical studies, and discuss the pros and cons of the method, as well as the possible adverse effects and future perspectives.

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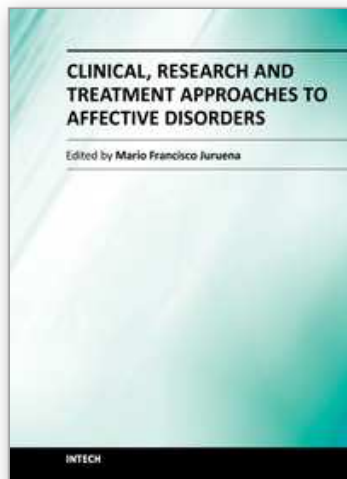
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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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