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Safety and Efficacy of Deep Brain Stimulation (DBS) in Patients with Treatment-Resistant Depression (TRD): A Review

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ABSTRACT

Deep Brain Stimulation (DBS) is a promising, though still experimental, treatment for treatment-resistant depression (TRD) in patients who have failed standard forms of pharmacotherapy. The main objective of this study is to comprehensively analyze the safety profile of this method in light of the latest scientific reports from 2019–2025. A review of the literature shows that the use of DBS is associated with the risk of technical complications (e.g., infections, equipment failure) and neuropsychiatric complications (e.g., hypomania, anxiety, impulsivity). It has been shown that a key risk factor is the lack of precision in the location of electrodes relative to individual white matter tracts, which undermines the validity of using universal anatomical coordinates. The paper presents evidence that the implementation of modern technologies, such as preoperative tractography and closed-loop stimulation systems, can significantly reduce the risk of adverse effects while maintaining therapeutic efficacy. The conclusions point to the need for a multidisciplinary approach to patient qualification and monitoring, using objective electrophysiological and behavioral biomarkers.

Keywords: deep brain stimulation (DBS), treatment-resistant depression (TRD), safety, neuroimaging, closed-loop stimulation, complications

1. Introduction

Deep brain stimulation (DBS) is one of the most promising methods of treating treatment-resistant depression (TRD) developed in recent years [1, 2]. TRD affects 20–30% of patients with major depressive disorder (MDD) and is characterized by resistance to conventional antidepressant therapy or therapy in combination with psychotherapy and electroconvulsive therapy [1, 2]. Due to its high morbidity, TRD requires the search for new therapeutic methods, including interventions targeting deep limbic circuits [1, 3, 4].

The technique of DBS involves modulating neuronal activity, but the exact mechanism is not yet fully understood [5, 6]. Studies suggest that the effectiveness of DBS in TRD depends on the proximity of white matter pathways responsible for regulating emotions and reward in a similar manner [7]. The subcalosal gyrus (SCG), ventral capsule/ventral striatum (VC/VS), anterior limb of the internal capsule, nucleus accumbens (NAc), medial forebrain bundle (MFB), inferior thalamic peduncle, and lateral habenula (LHb) are key anatomical targets of DBS in mood regulation in patients with MDD [2].

Early case series of DBS for treatment-resistant depression showed significant improvement in symptoms in patients in selected areas [1, 8]. Subsequent large randomized clinical trials, such as BROADEN (for the Cg25 target) and RECLAIM (for the VC/VS target), were terminated due to a lack of statistically significant difference in efficacy between active and sham stimulation [1, 5, 7]. Recently, there has been an increasing focus on analyzing white matter architecture and brain network organization to predict response to DBS in the treatment of treatment-resistant depression [9].

Modern technologies, such as directional stimulation systems and closed-loop DBS, are being developed to tailor DBS therapy to the current state of the patient's brain [10, 11, 12]. Personalized neuromodulation has the potential to increase treatment efficacy [9, 13].

The safety of DBS is of fundamental importance when considering this method as a potential treatment for TRD [14, 15]. Surgical complications include infections, intracranial bleeding, and technical problems related to electrodes and pulse generators [1]. Stimulation of limbic structures may cause undesirable behavioral effects such as transient agitation, anxiety, hypomania, and, in rare cases, Tourette-like reactions [1, 16].

The literature also describes a case of a manic episode following stimulation of the habenula in a patient with TRD [17]. The safe use of DBS therefore requires careful patient selection, precise electrode placement, and systematic monitoring of treatment effects [1, 17]. The most important barrier remains the high clinical heterogeneity of TRD and variability in response, which highlights the need to integrate data from neuroimaging, network biology, and clinical psychiatry [1, 8].

This paper aims to comprehensively discuss the safety profile of Deep Brain Stimulation (DBS) in the treatment of treatment-resistant depression (TRD), going beyond the analysis of clinical efficacy. Based on the latest scientific evidence, the paper analyzes the risk of surgical complications and specific neuropsychiatric adverse events. Particular emphasis is placed on the role of modern neuroimaging techniques and network biology in predicting and minimizing risk, which is a key step in the transformation of DBS from an experimental method to a standard clinical procedure [1, 7, 16].

2. Mechanisms of action of DBS in TRD

Deep brain stimulation (DBS) in the treatment of TRD is defined as a selective intervention on neural circuits, involving the modulation of nodes located at the intersection of critical white matter pathways that connect cortical and subcortical regions [1, 8]. Although the exact therapeutic mechanism is not fully understood, there is evidence that DBS affects the circuits responsible for mood regulation, reward processing, and cognitive control [18, 19]. Targets used in TRD, such as the cingulate gyrus (Cg25), nucleus accumbens (NAcc), ventral capsule/ventral striatum (VC/VS), and habenula, exhibit different network modulation profiles, which explains the variability in clinical response [1, 2].

Neuroimaging studies have shown that the effectiveness of DBS depends largely on the activation of specific white matter pathways that connect the target to the prefrontal cortex, amygdala, and hippocampus [9, 13]. Tractography and brain connectivity analysis can predict which neural connections are responsible for improving depressive symptoms and which may cause adverse effects [9, 20].

At the functional level, DBS can alter neural oscillations in the theta and gamma bands, modulate limbic-striatal network synchronization, and influence the processing of emotional stimuli [11, 21]. Some studies suggest that the effects of DBS are partially “state-dependent,” meaning that the effectiveness of stimulation may depend on the patient's current emotional state and neural activity [11, 20].

Bilateral stimulation of the habenula may lead to rapid mood improvement in patients with TRD, although manic episodes have been reported in isolated cases [17]. In the case of the VC/VS and NAcc, DBS modulated the activity of areas responsible for motivation and reward processing, which is crucial in the treatment of anhedonia in patients with treatment-resistant depression [1, 8].

Modern approaches also use closed-loop systems that allow stimulation to be adjusted to current network activity, increasing therapeutic precision and minimizing side effects [11, 15]. In addition, intracranial EEG recordings and local field potential (LFP) analysis allow the identification of biomarkers of response to DBS, enabling personalization of therapy [11, 22,

23]. It should be emphasized that a precise understanding of the anatomy of the pathways is crucial for safety, as stimulation of adjacent white matter tracts can lead to physical side effects, such as oculomotor disorders (diplopia) observed with stimulation of the medial forebrain bundle (MFB) [14].

3. Anatomical targets and DBS targets in TRD

In the treatment of TRD, various anatomical targets are most commonly used to modulate the limbic-frontal networks responsible for mood and motivation regulation [1, 2]. The most commonly used targets include the subgenual cingulate cortex (Cg25), nucleus accumbens (NAcc), ventral capsule/ventral striatum (VC/VS), and habenula [1, 2]. Another important target is the medial forebrain bundle (MFB), which is the main dopaminergic pathway. Its stimulation can produce a rapid antidepressant effect through direct activation of the reward system and connections with the frontal cortex [24].

The cingulate gyrus (Cg25) is one of the most studied targets in TRD. Stimulation of this area leads to modulation of limbic-striatal network activity and a reduction in the fronto-limbic hyperactivity observed in patients with treatment-resistant depression [1, 7]. Studies indicate that the response to Cg25 stimulation depends on the individual architecture of the white matter, which allows the effectiveness of therapy to be predicted using tractography [9, 13].

The nucleus accumbens (NAcc) is an important hub for reward and motivation processing. DBS in this area improves anhedonia and motivation in patients with TRD by modulating connections with the prefrontal cortex and limbic system [1, 8].

The ventral capsule/ventral striatum (VC/VS) is a target connecting the frontal cortex with the striatum. Stimulation of this area affects mood and impulse regulation and may also reduce anxiety symptoms associated with TRD [2, 12]. Tractographic analyses indicate that the effectiveness of VC/VS DBS depends on the activation of appropriate connections with the prefrontal cortex and amygdala [9, 11].

The habenula is a key structure in the processing of negative stimulus value and the regulation of the reward system. DBS in this area can lead to rapid improvement in depressive symptoms, although manic episodes have been reported in individual cases [2, 17].

Other targets, such as the precuneus or frontal regions associated with the default mode network (DMN), are being investigated in the context of experimental interventions designed to modulate emotional and cognitive pathways [15, 18].

The selection of the DBS target is crucial for the effectiveness and safety of the therapy. The use of tractography and network analysis allows for the personalization of electrode placement, increasing the chance of a therapeutic response while minimizing side effects [9, 11, 12, 15]. Studies suggest that despite anatomical differences, effective stimulation of different targets (e.g., MFB and Cg25) may in fact affect a common neural network, converging in areas of the frontal lobe white matter (so-called HUB regions) [24].

4. Safety and adverse effects of DBS in TRD

4.1. Surgical and technical complications

The implantation of DBS electrodes carries a risk of surgical complications, which can occur both during the procedure and in the postoperative period [1, 5]. The most serious complications include intracranial hemorrhages, which can lead to neurological symptoms and, in rare cases, permanent damage [1, 5, 25]. Infections are another serious risk, including both infections at the pulse generator implantation site and in the brain tissue surrounding the electrodes [25, 26]. Technical problems, such as electrode displacement, generator failure, or lead disconnections, may require additional surgical procedures [25, 26].

The risk of surgical complications is significantly related to the experience of the neurosurgical team and the precision of electrode placement in the target area of the brain [17, 26]. Modern imaging techniques, including MRI and tractography, minimize the risk of damage to important brain structures and improve the safety of the procedure [9, 26]. Despite the optimization of surgical procedures, complications remain a significant factor limiting the widespread use of DBS in TRD [1].

4.2. Neuropsychiatric and behavioral complications

Stimulation of deep brain structures can cause mood changes, including transient agitation, anxiety, or depression [1]. Some patients have experienced episodes of hypomania or mania,

particularly when stimulating the habenula or other limbic areas [1, 17]. Less commonly, atypical impulsive behaviors have been reported, including increased aggression, impulsivity, or changes in social behavior control [1, 16, 17].

Cases of Tourette-like symptoms following VC/VS stimulation have also been described, indicating the possibility of unintended activation of motor circuits [16]. Behavioral and emotional reactions are often dependent on stimulation parameters such as amplitude, frequency, and directionality of pulses [10, 20]. Studies indicate that these effects may be reversible after adjusting the parameters or temporarily turning off the stimulation [1, 16].

Individual patient susceptibility plays a key role in the risk of neuropsychiatric complications, highlighting the need for careful preoperative qualification [1, 5]. Despite advances in neuroimaging, current meta-analyses indicate that no single preoperative clinical or demographic indicator is sufficiently reliable to predict the response to DBS on its own, necessitating a multifactorial approach [27]. Monitoring the patient's condition during and after stimulation allows for early detection of adverse effects and appropriate therapeutic intervention [1, 25]. Personalization of DBS, including the use of closed-loop systems and intracranial EEG recordings, minimizes the risk of behavioral complications while increasing the effectiveness of therapy [11, 22].

4.3. Long-term complications and risk factors

Long-term complications of DBS can include both technical and biological problems that arise months or years after electrode implantation [1, 26, 28]. The most common technical problems include pulse generator malfunctions, lead breaks, or electrode displacement, which often require surgical intervention [25, 26]. Infections at the site of generator or electrode implantation may also occur in the long term and require antibiotic therapy or removal of the DBS system [25, 26].

Long-term neuropsychiatric complications include persistent or recurrent hypomania, anxiety episodes, agitation, or changes in impulsive behavior [1, 17]. The risk of adverse effects is related to individual brain architecture, white matter connections, and the location of the electrode in relation to adjacent structures [9, 16]. Long-term stimulation may also affect

cognitive functions, especially in cases of inappropriate targeting or excessive pulse amplitude [5, 16].

Factors that increase the risk of complications include previous neurological disorders, comorbidities, and unstable stimulation parameters [16, 26]. Monitoring the patient's condition and regular follow-up visits allow for early detection of complications and optimization of DBS parameters, reducing the risk of permanent side effects [1, 28]. In addition to traditional clinical scales, digital behavioral tests (e.g., affective assessment tasks) are increasingly being used in the monitoring process, as they can serve as objective indicators of mood changes in real time [23].

An important safety aspect is suicide risk monitoring; although patients with TRD are at high risk, meta-analyses have not shown that DBS treatment alone increases the suicide rate compared to standard care [5]. The use of modern technologies, such as directional stimulation and closed-loop systems, minimizes the risk of complications while maintaining the effectiveness of therapy [10, 11].

5. Conclusions

A review of the literature confirms that Deep Brain Stimulation (DBS) is an effective alternative for patients with treatment-resistant depression, but the method still has the status of experimental therapy. The main clinical challenge remains the safety profile, which includes both technical complications (equipment failure) and specific adverse effects. Analysis of studies shows that this risk is largely due to a lack of precision in electrode placement, confirming the need to move away from universal anatomical targets. A solution to improve safety is to personalize the procedure using tractography and closed-loop stimulation systems, which allow for precise control of therapy based on biomarkers. Ensuring patient safety therefore requires an interdisciplinary approach and close monitoring of treatment effects [1, 9, 11].

Disclossure

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