PSYCHOSURGERY - USE OF DEEP BRAIN STIMULATION FOR DEPRESSION

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Abstract

Major depressive disorder (MDD) is a prevalent neuropsychiatric condition with significant implications for one's well-being. Despite advancements in conventional treatments, a substantial portion of patients experience treatment-resistant depression (TRD). The historical evolution of psychosurgery, from ancient trepanation to the controversial lobotomy era, lead to skepticism and criticism of the methods. However, MDD's severe and chronic nature, often refractory to standard therapies, has yet again spurred interest into psychosurgery. This time, the focus is turned to a new psychosurgical technique – deep brain stimulation (DBS). Targeting the cortico-striato-thalamo-cortical mood circuit, DBS involves precise electrode implantation to modulate dysfunctional brain circuits. DBS is a less invasive and reversible technique, representing progress over historical lesioning methods. Potential ethical concerns and risks of implementing this new psychosurgical procedure necessitate thorough regulation, controlled trials, and informed consent to ensure safety and efficacy. Despite what was previously stated, the evolving landscape of neuropsychiatric interventions brings hope for individuals contending with the significant impact of TRD and holds an exciting potential for challenges in treating TRD.

KEYWORDS: deep brain stimulation, lobotomy, major depressive disorder, psychosurgery, treatment-resistant depressive disorder

INTRODUCTION

Major depressive disorder (MDD) is a common neuropsychiatric disorder affecting around 3% of the overall population, at least once in their lifetime.[1–4] It clinically presents as low mood or extreme sadness, anxiety, lack of interest and pleasure from previously enjoyed activities, as well as low energy, cognitive deterioration and suicidal thoughts.[5,6] Affecting women more than men and occurring at any age, MDD has a recurring nature in as many as 50% of patients. Each depressive episode may progressively lengthen, having serious repercussions on both physical and mental wellbeing of patients.[5] It impacts every aspect of a person's life, including relationships, ability to work and may lead to many chronic illnesses, especially cardiovascular disease and stroke.[7] Since it is a severe and chronic disorder that infiltrates one's whole life, it unfortunately puts those suffering at great risk of suicide, with one in six patients suffering from severe MDD eventually committing suicide.[8,9]

With the earliest accounts during the Hippocratic era, when it was described as a dysfunction of the melancholia, one of four humors, MDD has been known throughout most of human history[10] and the approach to treating MDD has changed variously, as has medicine. Today, with tremendous progress being made in pharmacotherapy, treatment most commonly includes a wide array of antidepressant drugs, psychotherapy, electroconvulsive therapy and other psychosocial measures.[5] Although more than half of patients will respond to some combination of conventional therapies, regardless of optimal care, up to a third will not achieve a clinically adequate response and may be classified as having treatment-resistant depression (TRD).[11] TRD is defined as failure to respond to three different treatment options: antidepressants, psychotherapy, or electroconvulsive therapy, given in the right amount and at the right time.[12,13] Keeping in mind the grave tone and potentially grievous character of TRD represented by a high number of suicide in patients, and taking into account that around 20-30%[14] of patients are refractory to pharmacotherapy, and that 60%[14] do not respond adequately to existing treatment options, the focus of the scientific community has shifted to psychosurgery.[6,11]

PSYCHOSURGERY - AN EVOCATIVE HISTORY

'Evocative is our history but exciting is our future'
— Lazarus Takawira

Trepanation is a procedure requiring either that parts of the cranium be removed or holes in the skull be made. When a well-preserved cranium of a man showing clear

evidence of two successful trepanations was found in a neolithic archeological site in France, it was the earliest physical confirmation of a triumphant cranial intervention in humans dating all the way back to the Stone age approximately 5100 BC. It is now believed to be the oldest recorded surgical procedure ever performed.[22] In the course of later periods, trepanation continued to be used even during the ancient Greek and Roman civilizations with discovered artifacts suggesting the likes of Hippocrates, Galen and many others not only carried out the procedure but also perfected tools specifically for penetrating the skull, the terebra serrata.[23,24] By the end of 18th and 19th centuries, the use of trepanation as a treatment of neurological or psychiatric conditions greatly declined.[24]

In November 1935, operating under the directions of the neurologist Antonio Egas Moniz, neurosurgeon Pedro Almeida Lima performed the first ever prefrontal leucotomy or better known today as lobotomy.[25] The duo carried out the operation on a total of first ever 20 patients with disorders such as anxiety, depression or schizophrenia and promptly published their reports in following months. They soon coined the term *psychosurgery* thus announcing the era of frontal lobotomy. First they used injections of absolute alcohol but dissatisfied with the method, Moniz quickly developed a leucotome, surgical instrument consisting of a rod with a retractable loop wire designed specifically for severing the connections between the frontal lobes and the rest of the brain.[25]

In 1936, closely following Moniz's and Lima's work, neurologist Walter Freeman along with neurosurgeon James Watts conducted the first frontal lobotomy in America using a modified version of the leukotome.[26] Surgeries were deemed a success and the pair went on to perform around 200 operations by 1942 reintroducing a variation of transorbital lobotomy, a procedure originally developed by the Italian psychiatrist Amarro Fiamberti.[27]

Regardless of its perceived usefulness and beneficial reported results, by 1949 disbelief regarding lobotomy's efficacy and safety began to rise[28] as more and more patients manifested with frontal lobe syndrome (apathy, impulsivity and blunted effect), sometimes even epilepsy, intracerebral hemorrhage and death.[27,29] Utilization of the procedure finally began to wane with the introduction of chlorpromazine in 1953, the first truly effective antipsychotic drug.[25]

After the arrival of chlorpromazine, similar antipsychotics soon appeared, approval of antidepressants and then anxiolytics quickly followed.[30] Despite the fact these new drugs were safe and cost- effective, before long it became evident certain individuals did not benefit from pharmacologic treatment, a reality that soon restored interest in surgical approaches. Techniques polished during this period laid the foundation for present-day stereotactic microsurgery.

Today, psychosurgery pertains to neurosurgical treatment of a psychiatric illness which is not responding to other forms of treatment.[15] Ablative psychosurgical procedures include lesioning of the white mater tracts of the brain to treat a psychiatric illness. There are four such procedures currently used in the world: cingulotomy, limbic leucotomy, anterior capsulotomy, and stereotactic subcaudate tractotomy.[16] However, with better understanding of the pathophysiology of MDD, less invasive methods, which are also reversible in comparison to the ablative methods, are taking the reins. One of them is deep brain stimulation (DBS) which is defined as a procedure in which electrodes are implanted precisely in previously defined brain regions which are then stimulated.[6] DBS sends electric impulses to modulate neuronal activity and dysfunctional brain circuits, and is used today as a therapy for various neurological disorders.[17] Developing parallel to stereotactic microsurgery in the 1950s, DBS evolved and the concept of long-term high-frequency electric stimulation was introduced.[31] An important step was the observation that stimulation with frequency greater than 100Hz continually gave rise to an apparent functional ablation of target area.[32] In the 1980s and 1990s DBS was first approved for humans in essential tremor[23] and later became widely used as a treatment option for Parkinson's disease as well as other movement disorders.[33] It was first tested as a new treatment for MDD in 2005.[18] Since MDD is considered to be caused by a dysfunction in the cortico-striato-thalamo-cortical (CSTC) mood circuit,[19,20] recently refined psychosurgical procedures, including DBS, offer high precision in targeting those regions. With an interesting history, and an even more exciting future, psychosurgery imposes itself as a new way in treating the most despairing depressed patients.[21]

DBS – AN EXCITING NEW POTENTIAL FOR DEPRESSION

Following the approval of DBS in movement disorders, interest peaked regarding possible uses in other neuropsychiatric conditions, such as obsessive compulsive disorder (OCD) and MDD in which safety and efficacy have been best established.[23] Given its nondestructive and reversible nature, DBS provides an alluring substitute to older lesioning methods. Several different areas of the brain have been proposed as promising targets for treatment of TRD. Overall, defined as the percentage of patients with >50 % improvement on the Hamilton Depression Rating Scale, the published response rate to DBS therapy is reported to be 40-70%, and outcomes were comparable across studies.[14]

In 2005, the subcallosal cingulate gyrus (SCG) was the first target proposed for the treatment of TRD by Helen Mayberg et al. in a study on six patients of which four had experienced remission at 6 months.[18] A number of trials followed with relatively satisfactory results illustrated by overall expected responder rates of 55% to 75%.[20,35,36] In a trial by Puigdemont et al., after six months of stimulation four out of five patients were remitted and none experienced relapse.[37] Lozano et al. reported an immediate antidepressant result of SCG-DBS after a bilateral electrode implantation and overall 62% response rate after 12 months.[38] Moreover, in a long-term follow-up study with 28 participants, most experienced robust and sustained antidepressant response. There were no side effects of acute or chronic stimulation and the procedure was overall safe and well tolerated.[39] Meanwhile, in a study by Merkl

et al., merely 33% of participants showed improvement in 24-26 weeks.[40] In addition, two more trials failed to show an improved response at all.[13,40] All in all, SCG remains a valid DBS target for TRD but more research is needed for an improved responder rate.

The medial Forebrain Bundle (MFB) aptly acts as both the center of the reward pathway and a specific stimulation target. The first clinical antidepressant effect of MFB-DBS was reported by Schlaepfer et al. in 2013.[41] In a study by Fenoy et al. two out of three patients continued to show a significant response after more than 26 weeks with some displaying immediate signs of increased energy and motivation upon stimulation, thus replicating similar rapid antidepressant effect as initially reported by Schlaepfer et al.[42] Furthermore, an acute and sustained antidepressant effect was suggested after 50% of patients reached remission after 12 months and some were revealed to be stable results after four years.[43] These results suggest a possibility to induce a rapid and robust antidepressant effect even in a small sample of TRD patients, rendering the MFB an attractive target for future studies.

The nucleus cccumbens (NAcc) is divided both anatomically and functionally into the core and the shell, each respectively receiving information from motor and limbic system.[44] In a 2014 trial, three out of four patients showed significant simultaneous mood improvement.[45] Additionally, 50% of patients reported change for the better one year after implantation with a significant increase in number of hedonic activities. In comparison to other TRD studies, this one also displayed an antianxiety effect.[46] Although the successfulness of NAcc has been documented, more research is needed to prove the precise effective stimulation localization as the clinical outcome and mechanism of NAcc- DBS remain disputable.

The ventral capsule/ventral striatum (VC/VS) are crucial in the cortico-striatal-pallidal neural circuits and are key in reward and motivation.[47] Despite the fact these targets were first used in treating OCD, participants' consequential improvement in their comorbid depressive symptoms was quickly noted.[48,49] These results prompted new research with following trials showing favorable outcomes with a 40% improvement at six months and 53% at the last follow up.[50] On the other hand, some contradictory results have followed suggesting that the VC/VS may not be convenient targets with response rates being 20%, 26.7%, and 23.3%[51] at 12, 18, and 24 months, respectively, here defined as 50% or greater improvement on the Montgomery-Åsberg Depression Rating Scale from baseline.

Another location being investigated as potentially suitable for TRD is the bed nucleus of the striata terminalis (BNST). It is part of the limbic system located at the immediate proximity of the VC/VS and NAcc with a number of projections associated with reward, anxiety and stress processing.[52] A careful and detailed dissection of the structure is of immense significance to unravel its role in depression. Another target is the lateral habenula, a compact nucleus receiving afferent neural pathways from the limbic system and providing efferent pathways to the BNST amongst others. The connectivity of this nucleus suggests that it plays a part in emotional regulation. While most of the clinical trials show promising results for each proposed target, it is evident further research is warranted for providing more compelling evidence of not only efficacy but also safety of DBS in TRD patients. In addition, for suboptimal outcomes, lack of personalized targeting is another important factor with individual clinical characteristics and specific abnormalities that should be taken into account.

ETHICAL ASPECTS OF DBS IN TREATING DEPRESSION

Undoubtedly the word psychosurgery itself will kindle strong, mostly negative emotions in many, so it is perhaps worth mentioning and reasonable to presume that history might have taken a different course if, in the past, had there been strict regulations, adequately controlled trials to prove its safety and efficacy, as well as informed consent. While there is an ongoing debate whether DBS should be classified as a form of psychosurgery, Stahl et al. contend that it indeed falls within that category, albeit as a more precise and refined method than its predecessor.[53] Nevertheless, certain ethical and legal questions must be raised and discussed.

In contrast to lesioning methods, where a part of the brain is either destroyed or removed, DBS involves neuromodulation. Specifically, brain activity is modulated via electrical impulses and, as impulses can easily be turned off, DBS is considered reversible.[53] Adjustability and reversibility of current psychiatric neurosurgery procedures are cited by some as the two primary improvements over earlier forms.[16,21,54] However, the potential for unintentional damage during insertion of electrodes remains, posing a risk of causing irreparable damage in the process.[55] Several aspects distinguish modern psychosurgery from its earlier forms. Advancements in neurosurgery, stereotactic, and imaging techniques contribute to much more precise lesion locations, resulting in considerably lower complication rates.[56,57] Side effects such as seizures, apathy, confusion, and poor attention, which were common in early psychosurgeries, are now much rarer in psychiatric DBS procedures.[58] Nonetheless, hardware related adverse effects, such as lead isolation, lead fracture, and infection, along with stimulation-induced effects like aggression, worsening of depression, and suicide, are still possible.[54] Another important distinction is that psychiatric DBS is currently experimental only and as such is mostly used in context of clinical trials. In contrast, early psychosurgeries were often performed without strong scientific data or justification.[53]

Regardless of the perceived advantages of DBS over lesioning methods, its absolute superiority remains undisputed.[54] While the lack of robust evidence regarding safety and effectiveness, as well as the absence of established targeting and stimulation parameters, is undeniable,[14,59] DBS is not only being researched for its therapeutic potential but also to gain a better understanding of the intricate circuitry of the brain, with the goal of designing less invasive treatments.[59,60]

CONCLUSION

MDD is a prevalent neuropsychiatric disorder that poses a significant challenge to the overall well-being of individuals. Despite the progress made in conventional treatments, up to 30% of patients experience TRD and new treatment options are needed.

Though the historical methods of psychosurgery fell short, they have paved the way for the current era of DBS. Though DBS represents improvement over earlier psychosurgical methods, different targets have demonstrated varying degrees of success in alleviating depressive symptoms, with response rates ranging from 40-70%. Still, the emergence of DBS in the field of neuropsychiatry has shown promising results in targeting specific brain regions associated with depression and the need for further research to enhance responder rates and identify optimal stimulation parameters cannot be overemphasized.

While ethical concerns persist, the evolving landscape of neuropsychiatric interventions provides a beacon of hope for individuals grappling with the profound impact of TRD.

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PSIHOKIRURGIJA - PRIMJENA DUBOKE MOZGOVNE STIMULACIJE U LIJEČENJU DEPRESIJE

Sažetak

Veliki Depresivni Poremećaj (MDD) raširen je neuropsihijatrijski poremećaj sa značajnim posljedicama za pojedinca. Unatoč napretku u konvencionalnim metodama, značajan dio pacijenata pati od depresije otporne na liječenje (TRD). Povijesna evolucija psihokirurgije, od drevne trepanacije do kontroverznog razdoblja lobotomije, dovela je do skepticizma i kritiziranja metoda lezioniranja. Ipak, teška i kronična priroda MDD-a, često otporna na standardne terapije, ponovno je potaknula interes za psihokirurgiju. Ovaj put fokus je usmjeren na novu psihokiruršku tehniku - duboku moždanu stimulaciju (DBS). Ciljajući kortiko-striatalno-talamo-kortikalni krug, DBS podrazumijeva preciznu ugradnju elektroda radi modulacije disfunkcionalnih moždanih krugova. DBS je manje invazivna i reverzibilna tehnika, predstavljajući tako napredak u odnosu na povijesne metode. Kako bi se osigurala sigurnost i učinkovitost, te etička korektnost, DBS zahtijeva rigoroznu regulaciju, kontrolirane studije i informirani pristanak. Unatoč prethodno navedenom, evoluirajući pejzaž neuropsihijatrijskih intervencija donosi nadu pojedincima koji se suočavaju sa značajnim utjecajem TRD-a i nosi uzbudljiv potencijal za izazove u liječenju TRD-a.

KLJUČNE RIJEČI: duboka moždana stimulacija; lobotomija; depresivni poremećaj, veliki depresivni poremećaj, otporan na liječenje; psihokirurgija