Deep Brain Stimulation:

Treatment for Clinical Depression

by

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Abstract

Depression is the most common mental disorder in the United States [1]. A person with this disorder is generally described as feeling sad, discouraged and in general, disinterested in life. Deep brain stimulation (DBS) is a method of electrically stimulating a specific part of a brain using implanted electrodes. Since the symptoms of major depressive disorder have been linked to the dysfunction of the reward circuitry system of which the NAcs are the major players of, DBS to these neurons have been one suggested method to improve patients' symptoms [2]. In 2013, DBS of the NAcs had given a promising result when patients treated by DBS had shown an improvement with little to no side effect [2]. This paper will discuss the advantages to DBS as an anti-depressant by the assessment of available studies and will further discuss the current as well as future challenges facing DBS.

I. Introduction

Before the 1950s and 1960s, depression was considered a rare disorder [3]. During these years, the understanding of "depression" was very limited, and the disease was thought to be only of a psychotic rather than neurotic nature. Therefore, the condition and symptoms were lumped together with that of anxiety and the development of any relevant treatment was directed towards the symptom of anxiety [3]. The drug Miltown, was introduced as an anti-anxiety drug in the 1960s and was replaced by benzodiazepine Librium which was also followed by Valium [3].

But after the 1970s, depression had gained focus and has now became the most common mental disease [3]. Behavioral therapy, drug therapy or the combination of the two had remained the common modalities in treating Depression. Currently, there are several classes of antidepressants classified based on their mechanisms of action are clinically available; of which the most prescribed include SSRIs, SNRIs and TCAs [4]. However, each class of therapeutic drugs come with their own downsides and plenty of side-effects. SSRIs have been linked to cause anxiety sleep disturbance, sexual dysfunction as well as gastrointestinal cramps and diarrhea [4].

Although these drugs are promising, not all patients respond to their antidepressant properties. During these occasions, TCAs are used. The use of TCAs has been linked to the blockage of histamine and muscarinic acetylcholine M receptors causing weight gain, constipation, blurred vision, drowsiness and dry mouth [4]. They also block α1 causing decrease in blood pressure [4]. They are also difficult to use and are lethal if one overdosed [4].

These findings together with the increased understanding of the neurological pathways and pathophysiology of the disorder combined with the improved precision of deep brain stimulation techniques, DBS have been suggested as another alternative to treat treatment resistant major depressive disorder. The procedures of DBS include implanting electrodes into a specific part of the brain and stimulating the region with a high frequency continuous electric signal

generated by an externally programmable generator [5]. Although deep brain stimulation's exact mechanism of action remains a mystery, the technique has been used and brought promising results in treating several neurological and neuropsychiatric disorders [5]. This paper will discuss clinical approaches and studies where the antidepressant property of DBS has been demonstrated.

II. Methods and Results

Mayberg et. al implanted electrodes in six patients that were labelled to have a treatment resistant depression (TRD) according to the criterions listed on the DSM IV-TR as well as had a minimum score of 20 on the scoring system used in the Hamilton Depression Rating Scale (HDRS) [6]. Each patient failed to show any significant improvement in a minimum of four types of antidepressant treatments which included medication, and psychotherapy [6]. The team used microelectrode mapping using electrodes that were made from parylene-C-insulated tungsten wires that were plated with gold and platinum, to locate the final target for DBS electrode implantation [6]. The DBS electrodes were then implanted in the middle of the gray and white matter region (Cg25WM) with the aid of MRI [6]. After implantation, the patients' immediate response to the effects of a single electrode stimulation with a 60 micro-second pulse-width at 130 Hz was observed without giving the patients any cues to when the signal is on or off [6]. Depending on the response and tolerance of patients, the voltage was incremented by 1 V every half a minute with a 15-20 second delay in between adjustments until reaching 9 V [6]. The patients were closely and carefully evaluated weekly for the first three months and then every two weeks for the months following that for a total of 6 months [6].

Initially, right after the electrodes were implanted, and stimulation was initiated, without any type of suggestion to let the patients know whether the device was on or off, all patients expressed a feeling of what they described as, "disappearance of the void", "sense of heightened awareness and also claimed to see the room brightening up all of a sudden [6]. It was also clear to see an increased speed in the patients' motor function and speech; however, as the voltage increased, at around 7 V, they could observe that the patients were experiencing lightheadedness [6]. During the 6 months, the patients received a DBS to the Cg25WM with an average voltage of 4 V, 60 micro-second pulse-widths at a frequency of 130 Hz [6].

Five out of the six patients showed improvements over the first two months of DBS [6]. This was evaluated using the HDRS-17 scoring system. As the trial continued, four out of the first five showed increased improvements through out the coming 5 months and finally three were evaluated to have a near complete remission of TRD [6]. During the initial weeks of DBS, most patients and their families had reported an increased energy, interest and a better overall quality of life; however there also were patients that described their feeling as "void" [6]. Two patients also developed infections and another a skin erosion due to implanted devices; All of which were treated using antibiotics [6].

Malone et. al. also demonstrated the antidepressant effects of DBS in 2008 by stimulating the ventral capsule/ventral striatum (VC/VS) of fifteen patients with a severe refractory depression [8]. All fifteen patients received a continuous stimulation which was observed for a time ranging from six months to four years [8]. The evaluation

similarly was made by using HDRS scoring system [8]. By the end of the study, there was a 20% remission rate amongst the patients. Moreover, during the first 6 months, the average HDRS scores of patients declined from 33.1 to 17.5 during the firsts 6 months and reached 14.3 by the last check-up [8].

Moreover, the antidepressant effect DBS of the VS region in particular, the nucleus accumbens (NAc), was demonstrated in three patients with TRD again in 2008 [7]. In this study, Medtronic model 3387 leads, with four electrodes of length 10.5 mm, spaced 1.5 mm apart were implanted to the NAc region with the guided help of an intraoperative X-ray [7]. A 4 V square-wave, with a 90 micro-second pulse-width was applied at a frequency of 145 Hz [7]. Similarly, they used the HDRS assessment method to evaluate the patients throughout the stages. Immediately after about a minute of stimulation, the researchers had noticed positive behavioral responses they described as “a sharp increase in exploratory motivation” in the two patients [7]. Given the condition the patients were in before the surgery, and as lack of motivations and interest being the most common symptom of depression, then this immediate response could be significant. After about a week of monitoring, and evaluation, the HDRS baseline score that was 33.7 dropped to 24 and after the first week of non-stimulation the scores increased to 29.3 [7]. They noticed that there was a direct correlation to the stimulation being on and off with the improving or worsening of the depressive symptoms; and this happened with no adverse side-effects whatsoever [7].

III. Discussion

The understanding of the signs and symptoms of major depressive disorders being at least in part related to the dysfunction of a specific brain reward-circuitry systems together with the advancement in surgical capabilities lately allowed for the use of DBS in a novel means to tackle this illness. The results above show the remarkable effectiveness of targeted DBS of the Cg25WM, VC/VS (specifically the NAc) regions and further suggest DBS to be very promising to treat patients with the illness that have exhausted all the other means to get well. Although DBS is an invasive procedure, it was demonstrated to be having much less adverse side-effects (compared to anti-depressant drugs currently in the market) in the above clinical trials (even though it is hard to speculate the chronic effects of DBS). Further exploration into the pathophysiology of major depression disorder is important to make targeting more specific as well as knowing the right tuning parameters to use for the device to increase effectiveness while decreasing the unwanted side-effects related to DBS.

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