Deep Brain Stimulation for Treatment-Resistant Depression: A Review

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Abstract: Treatment-resistant Depression (TRD) is the failure of pharmacological treatment, with or without psychotherapy or electroconvulsive therapy, in major depressive disorder patients. Over the past years, various trials of Deep Brain Stimulation (DBS) in TRD patients have been performed. By means of a systematic Pubmed search, the reports on these trials were gathered and critically appraised. Even though the reported research methodology was flawed, the combined study outcomes (of a total of fifty patients, 58% (95% CI = [44.2%; 70.6%]) showed a response to treatment and 26% (95% CI = [15.8% ; 39.7]) were considered being in remission) are promising. Nonetheless, further research is required to evaluate the most beneficial stimulation areas in the brain, the stimulation parameters, and the possible long-term therapeutic and side-effects.

Keywords: Treatment-resistant depression, deep brain stimulation, DBS, depression, major depressive disorder.

INTRODUCTION

Major depression is a mental illness characterized by an all-encompassing low mood, profound sadness, or anhedonia, which is the loss of interest or pleasure in what was before enjoyable and gratifying activities. In addition to the aforementioned symptoms, depression is often accompanied by a battery of other arduous symptoms such as sleep disturbances, changes in appetite, fatigue, feeling of worthlessness, executive dysfunction, psychomotor agitation/retardation and worst of all suicidal intentions [1]. Moreover, depressed patients are prone to a greater susceptibility to medical illnesses, which result in shorter life-expectancy. Furthermore, major depression patients may experience stigmatization in their social surrounding. This disease is a world-wide burden and has a life-prevalence of about 8-12% [2-4] with females seemingly being affected twice as often as males [5]. Many patients can be helped with psychotherapy, antidepressant medication, electroconvulsive therapy, or a combination of the aforementioned. However, 15-33% of all patients do not respond adequately to the aforesaid treatments [6]. The term 'treatment-resistant depression' (TRD) was coined for this phenomenon. Table **1** gives an overview of a common classification of TRD. For the TRD patients, deep brain stimulation (DBS) has been proposed as a possible treatment.

DBS is a surgical treatment that utilizes a so called brain pacemaker; a device that sends electrical signals to specific areas of the brain through implanted electrodes. The mechanism of DBS is still not completely understood, though five general hypotheses exist: depolarization blockage, synaptic inhibition, synaptic depression, stimulation-induced modulation of pathologic network activity, and a combination of the aforementioned hypotheses [7]. Based on the idea that dysfunction in monoamine brain-circuits are the basis of the pathophysiology of depression, several structures have been proposed as potential stimulation sites [8]. This review has the intention to give a summation of the findings of the clinical studies on DBS and TRD that have been concluded thus far.

Table 1. Thase and Rush Classification Scheme of TRD

Stage	Treatment Response
0	No single adequate trial of medication
1	Failure to respond to an adequate trial of 1 medication
2	Failure to respond to 2 different monotherapy trials of medications with different pharmacologic profiles
3	Stage 2 plus failure to respond to augmentation of 1 of the monotherapies
4	Stage 3 plus failure of a second augmentation therapy
5	Stage 4 plus failure to respond to ECT

Table 2. Oxford Quality Scoring System Calculation

Item	Score
Was the study described as randomized?	0/1
Was the method used to generate the sequence of randomization described and appropriate?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate.	0/-1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate.	0/-1

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MATERIAL AND METHODS

A Medline search (PubMed) was performed using the following 'Mesh' and free terms, and their combinations: 'Major Depressive Disorder', 'Depression', 'Treatment-resistant Depression', ' Deep Brain Stimulation', and 'DBS'. All 916 articles published before March 2010 were screened as available by their titles and abstracts. Clinical studies on deep brain stimulation that were carried out exclusively on unipolar depressed patients were included. Case studies [9-11] were excluded due to their high risk of publication bias. Reports on ethical issues concerning DBS were also ignored. Additionally, studies performed on obsessive-compulsive disorder or Parkinson's disease patients receiving DBS were excluded due to potential differences in pathophysiology [12]. Likewise, studies on epidural stimulation were not taken into account [13]. Conclusively, of the 916 articles, five clinical studies with a total of 50 patients were seen fit for inclusion and critically appraised (Table **5**) with the Oxford Quality Scoring System (Table **2**) [14] as a basis. One article, an update [15] from Malone *et al*. that was published four months after performing the literature search, was recommended by peers and therefore included. An overview of all articles and their results is displayed in Table **4**.

Only the results of the Hamilton Depression Rating Scale (HDRS) were used to evaluate and compare the effect of the treatment. This was done for two reasons: First, HDRS was often the only results presented quantitatively in the papers; secondly, HDRS is considered the gold standard in psychiatry for diagnosing major depressive disorder [16, 17]. A HDRS of 0-3 is considered not ill and a score above eight is established as mildly ill; the severity of the disease increases with the number. HDRS is a multiple-choice questionnaire performed by a clinician, the number stated after HDRS indicates how many items were used in the specific test. Here, and in most evaluated articles, a response to therapy is defined as a reduction of HDRS of more than half and remission is defined as a HDRS of lower or equal to eight. The confidence intervals were calculated using the adjusted Wald method.

RESULTS

Mayberg *et al.* [18] were the first to experiment with DBS in depressive patients in 2005. They performed DBS of the subgenual cingulate white matter in six TRD patients. Two of these patients showed a reduction of more than 50% in HDRS-24 within six months. Even more notable, two patients had a HDRS-24 lower than eight. However, the prevalence of side-effects was high; two patients had an infection on device implantation site, another patient had complaints of skin erosion. The reported methodology is acceptable. Downsides of the experiment are small sample-size and inclusion of a bipolar II patient. Aside from that, mere single-blindation on patient level increases the risk of reporter's bias. Another article (McNeely *et al.*) [19] stated that the same patient group showed no adverse changes in neuropsychological testings at 12 months, with the exception of slower motor speed. Depression ratings were not re-evaluated in this report.

In 2008 Lozano *et al*. [20] reported on subcallosal cingulate gyrus DBS in twenty TRD patients. Of these 20 patients, six were already described by Mayberg *et al.* in 2005. In total, eleven patients showed a decrease in HDRS-17 of more than 50%, of which seven patients even achieved a score lower than eight of the HDRS-17. Complications included five wound infections, consequently, pacemakers needed to be removed in three patients; one peri-operative seizure and other, minor complications. Blindation to stimulation settings was performed only on patient level.

Schlaepfer *et al.* [21] implemented DBS of the nucleus accumbens in three TRD patients in 2007. One of these patients showed a reduction of more than 50% in HDRS-17. Alleviation of anhedonia was found in all patients. This report however was flawed by apparent methodological weaknesses: Sample size was extremely small and patients were not followed-up longer than five, eight and 22 weeks, respectively. Inclusion criteria were few and no exclusion criteria were stated. Moreover, no description of blindation methods was given.

Bewernick *et al.* [22] also evaluated DBS of the nucleus accumbens in ten TRD patients in 2010. It is not certain if the three patients of Schlaepfer *et al*. were part of the sample-size. Of these patients, five showed a reduction of at least 50% in HDRS-28. Two patients dropped out of the study before twenty months, one of them due to suicide after non-compliance by refusing any changes of parameter settings. The reason for drop-out of the other patient was not given. A long list of physical and psychological side-effects was reported, of which most were parameter setting dependent. An example is stimulation induced increase of anxiety, agitation and hypomania. Methodological weaknesses include no blindation and no reasons were given for loss to follow-up.

Malone *et al.* [23] performed DBS of the ventral capsule/ventral striatum in 15 TRD patients and described their findings in an article published in 2009. Larger leads than the standard leads were used in this study. Six subjects had a reduction in HDRS-24 of more than 50%; of these patients, three had a score lower than eight at six months. Four patients were lost to follow-up without any reasons given. Reported side-effects included pain at incision site, one lead fracture, and reversible, stimulation induced hypomania. Furthermore, in this study, blindation only occurred on patient level.

An update on the findings by Malone *et al.* [15] was published July 2010 and reported on the total outcome of 17 TRD patients, two more than in 2009. The focus of the article lies on summarizing the experiments done by Malone *et al.* thus far, with a minimum follow-up of the patients of 14 months. However, only the mean outcomes of the Montgomery-Åsberg Depression Rating Scale (MADRS), another widely used psychiatric diagnostic questionnaire for depression, were stated. Since HDRS and MADRS have been proven to correlate [24], therefore, the equation (Table **3**) by Heo *et al.* was used to convert the MADRS to HDRS-17. Of the 17 patients, twelve showed a response of more than 50% at last follow-up. Six of the twelve responding patients were considered being in remission. In addition to the above stated side-effects, infections, adverse cosmetic effects, frequent

Table 3. Equation to Convert MADRS to HDRS17

$HDRS17 = -1.58 + 0.86 \times MADRS$

Table 4. Overview Results

Year	Author(s)	Stimulation Target	Number of Patients	Oxford Qlinical Scoring System Score	Outcome HDRS	Other Outcomes	Complications (Percentage of Patients)	Minimum Follow-Up	Other Remarks
2005	Mayberg *et al.*	Subgenual Cingulate White Matter	6	4	2 responders (33%), above that 2 in remission (33%) (HDRS-24)	Significant decreased MADRS, reduction in CGI, improvement in neuropsychological testings	2 infections with as a result hardware removal (33%), 1 skin erosion (17%)	6 months	One bipolar II patient included, one patient without prior ECT, 12 month neuropsycho-logical follow-up of these patients reported in McNeely et al. 2008
2007	Schlaepfer *et al.*	Nucleus Accumbens	3	1	1 responder (33%)	Significant decrease in MADRS, morphine-benzedrine score after operation for all patients 0 unrelated to stimulation parameters (thus diminishment of anhedonia)	None	5 weeks	The monozygote twins showed similar results
2008	Lozano *et al.*	Subcallosal Cingulate Gyrus	20 (of which 6 were described by Mayberg *et al.* 2005)	2	11 responders (60%), of which 7 in remission (35%)	Significantly decreased BDI, significant reduction in CGI, significantly decreased BAI	5 infections (25%), 1 seizure, 4 perioperative headaches (20%), 1 pain at pulse generator site (5%), 2 worsening of mood/irritability (10%)	12 months	One patient was later diagnosed as bipolar II, 2 patients showed no improvement
2009	Malone *et al.*	Ventral Capsule/ Ventral Striatum	15	1	6 responders (40%), of which 3 in remission (20%) (HDRS-24)	Decreased MADRS, significant increased GAF, significant reduction in IDSSR, significantly decreased CGI	1 pain at incision site (6.7%), 1 lead fracture (6.7%), one stimulation induced hypomania (6.7%)	6 months	One bipolar I patient included, leads used larger than standard DBS leads
2010	Malone. (Update from 2009)	Ventral Capsule/ Ventral Striatum	17 (of which 15 were described in 2009)	0	12 responders, of which 6 in remission	Decreased MADRS	Surgical adverse effects: infections, adverse cosmetic effects; stimulation induced acute adverse effects: paresthesias, mood changes, autonomic effects	14 months	

(Table 4). Contd…..

Year	Author(s)	Stimulation Target	Number of Patients	Oxford Qlinical Scoring System Score	Outcome HDRS	Other Outcomes	Complications (Percentage of Patients)	Minimum Follow-Up	Other Remarks
2010	Bewernick *et al.*	Nucleus Accumbens	10	1	5 responders (50%) (HDRS-28)	Significant decrease MADRS, significant reduction in IDSSR, significant decrease HAMA, significant rise in Hautzinger (thus improved anhedonia)	6 swollen eyes (60%), 4 erythema (40%), 3 dysphagia (30%), 3 induced increase in anxiety (30%), 3 increased sweating (30%), 3 pain (30%), 2 induced hypomania (20%), 2 disequilibrium (20%), 2 paresthesia (20%), 2 induced increase in agitation (20%), 1 headache (10%), 1 muscle cramps (10%), 1 oculomotor problem (10%), 1 induces psychotic symptoms (10%), 1 lead dislodgement (10%)	12 months	Listed side-effects are mostly adjustable to stimulation parameters

Remission = Hamilton Depression Rating Scale score < 8.
Response = Decrease in HDRS of > 50%.
MADRS = Montgomery-Åsberg Depression Rating Scale.
CGI = The Clinical Global Impression - Severity scale.
BDI = Beck Depression Inventory.
BAI = Beck Anxiety Inventory.
GAF = Global Assessment of Function.
IDSSR = Inventory for Depressive Symptomatology-Self-Rated.
HAMA = Hamilton Anxiety Scale.
SCL-90 = 90-Item Symptom Checklist.
Hautzinger = List of Positive Symptoms modified according to Hautzinger.

surgeries due to depleted batteries and stimulation induced but reversible acute adverse effects were reported.

DISCUSSION

Summarizing the findings of the fifty patients together, a staggering 58% (95% confidence interval (CI) = [44.2%; 70.6%]) of all patients showed a response. Of all patients, 26% (95% CI = [15.8% ; 39.7]) were even considered being in remission. Thus, the numbers implicate that the chances of improving depression with DBS are favorable, whilst the chance of a complete cure is slim. Positively, it seems as if the procedure causes no adverse neuropsychological effects besides slower motor speed [19]. However, sample-sizes for the different target areas are small and no long-term outcomes are available. Moreover, despite the fact that relapses of depressive symptoms had occurred in at least one patient, they weren't mentioned in the articles [25]. Henceforth, more research is needed to determine the most beneficial stimulation areas, including hypothetical target areas that haven't been evaluated by experiments yet, examples being the lateral habenula as seen in a case study [11] and stimulation of the ventral tegmental area that alleviated depressive behavior in rats [26]. Moreover, the most beneficial stimulation parameters, and the risks of DBS in TRD patients must be properly assessed. Although improbable, a possible placebo effect hasn't been ruled out entirely. What is more, co-morbid psychiatric disorders of the patients were not taken into account. Evaluating response differences in patients with co-morbid psychiatric disorders are of particular interest, as can be seen in the clinical course of one included bipolar I patient that was reported to be very variable with episodes of stimulation induced hypomania [23]. It should be mentioned, as with all psychiatric diseases, that diagnosing major depressive disorder can be difficult. HDRS, the gold standard for depression, has been criticized in the past for having poor interrater and retest reliability [16] and content validity [16, 17]. Barring that, different item HDRSs used could lead to differences in scores. However, at least for the results of remission, these differences are certainly negligible. Lastly, it is noticeable that most researchers report conflicts of interest by accepting grants and funds from firms such as Medtronic. This, together with no blindation on an examiner level, increases the risk of a reporter's bias.

CONCLUSIONS

Although only a moderate percentage of patients gained relief, one must keep in mind that these were the patients in

Table 5. Critical Appraisal of Articles Sortet by Author

	Mayberg *et al.*	**Schlaepfer *et al.***	**Lozano *et al.***	**Malone *et al.*2009**	**Malone. 2010**	**Bewernick *et al.***
Oxdord Quality Scoring System Items:						
Randomization?	randomization for blinded off-on-off-on trials	no	no	no	no	no
Blindation?	single-blind on patient level by means of sham and subthreshold stimulation	double-blind and placebo controlled, no description	single-blind on patient level, no description	single-blind on patient level, no description	not described	blindation broken due to worsening of symptoms in three patients; other patients not blinded
Drop-outs?	no drop-outs	no drop-outs	3 hardware removals due to infections	yes, no description of reasons	no reports	2 drop-outs, 1 due to suicide, the other no reasons mentioned
Other appraisal criteria:						
In-/Exclusion criteria and their description	excellent	ok, very little description of inclusion criteria, no description of exclusion criteria	good	good	good	excellent
Confounding	one bipolar II patient included; one patient without previous ECT	too little sample size to evaluate	no	one bipolar I patient; 2 patients with previous narvus vagus stimulation	not elaborated	no
Compliance	yes	yes	yes	several visits missed by some patients	not mentioned	no for at least 1 patient
Co-interventions	psychopharmaca, no report on changes	no changes in medications; no other concamitant treatment allowed	minor changes in medications; no new drugs added	psychopharmaca, medication changes in 4 patients during first six months of stimulation; leads used larger than standard leads	not exampli-fied	psychopharmaca, no report on changes

which standard therapy had failed them. Under this aspect, therefore, the results are indeed very promising. However, sample sizes were small and a lack of proper research methodology was apparent; as a consequence, the most beneficial stimulation areas, parameters and its side-effects are not yet determinable.

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