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Considering eligibility for studies of deep brain stimulation for treatment-resistant depression: insights from a clinical trial in unipolar and bipolar depression

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Abstract

Background—While electroconvulsive therapy (ECT) is the most effective treatment for major depression (MDD), deep brain stimulation (DBS) has shown efficacy in patients who have not received benefit from ECT. Studies of DBS are small, and a better understanding of which eligibility criteria lead to exclusion may help achieve a more appropriate balance between scientific rigor and generalizability in future trials. We assessed the rate and reasons for exclusion from a study of DBS for treatment-resistant MDD and bipolar type-II depression (BPII).

Methods—1,098 adults were screened for a study of DBS for MDD or BPII. Reasons for exclusion were documented. Descriptive statistics were calculated for each reason for exclusion for the entire sample as well as the self-reported MDD and BPII subgroups.

Results—Ninety-eight percent (98%) of patients screened were excluded. Exclusion due to lack of interest or inability to relocate to the study site was high (41%). Following this, primary reasons for exclusion were lack of prior electroconvulsive therapy (ECT) and presence of psychiatric/general medical comorbidity. MDD patients were more likely to be excluded due to inadequate ECT, while BPII patients were more likely to be excluded for comorbid psychiatric diagnoses and not meeting minimum severity criteria.

Conclusions—A surprisingly high number of potential participants were excluded due to lack of adequate ECT. This suggests that many patients self-identifying as “treatment resistant” have not truly exhausted available, evidence-based treatments. Overall exclusion rate was high, with key

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differences in exclusion reasons between the MDD and BPII subgroups. These findings can inform design of future clinical trials for treatment-resistant unipolar and bipolar depression.

Clinicaltrials.gov Identifier: NCT00367003

Keywords

depression; bipolar disorder; deep brain stimulation; research patient recruitment; clinical trial design

1. Introduction

Electroconvulsive therapy (ECT) remains the most effective treatment for major depression, including treatment-resistant depression (TRD) [1]. Even so, many patients are either unwilling to undergo ECT or have an inadequate response. Over the last twenty years, efforts have been made to find other brain stimulation treatments for depression that are tolerable and equally or more effective. These efforts have led to the development of several alternatives. Transcranial magnetic stimulation (TMS), currently FDA-approved to treat depression, is likely less effective in highly treatment resistant populations and less effective in ECT non-responders [2-5]. Vagus nerve stimulation (VNS), is FDA-approved for treatment-resistant depression, though published response and remission rates are relatively low [6-8], and access has been limited due to widespread lack of insurance reimbursement.

Deep brain stimulation (DBS) is a more invasive brain stimulation approach to treating depression, and is currently only investigational; however, DBS of various brain regions has shown efficacy in patients who have not received benefit from ECT [9-12]. To date, studies of DBS have largely been limited to small open label trials. Given the small size of these studies, and the invasive nature of the intervention, eligibility criteria have typically been strict.

To optimize recruitment without sacrificing scientific validity, inclusion and exclusion criteria must be carefully considered. Stringent criteria allow for better interpretation of the final data, and are especially appropriate early in treatment development. However, such stringency makes recruitment more difficult and diminishes the generalizability of the data to the broader clinical population. Until treatment-specific biomarkers are identified for subtypes of depression or other psychiatric disorders are developed and generally available [13-15], strategies to increase the subject pool for a novel brain stimulation treatment trials are needed. Unfortunately, clinical trials for depression that have attempted to recruit from a clinical practice setting report a very low percentage of patients who are eligible [16-18].

A better understanding of which eligibility criteria most often lead to exclusion from specific clinical trials may help achieve a more appropriate balance between scientific rigor and generalizability. Further, it would be helpful to know if specific eligibility criteria lead to differential exclusion among subgroups of patients (e.g., unipolar vs. bipolar depressed patients). These issues are especially salient in studies of brain stimulation, especially invasive treatments such as DBS for treatment-resistant depression [TRD] where sample size

will likely be smaller, patients will be more ill with more complicated histories, and the proper evaluation of safety and efficacy will require high quality data.

In this study, we reviewed the reasons for exclusion from a study of DBS for treatment-resistant unipolar and bipolar depression [10]. Reasons for exclusion were ranked for all subjects seeking participation in the trial. In those subjects with adequate information, the differential reasons for exclusion in the unipolar and bipolar groups were compared.

2. Methods

This study included data from all patients who expressed interest in participating in the first cohort of an ongoing investigational clinical trial of DBS for TRD [10]. This study was fully funded through internal, non-profit foundation and federal funding (Dana Foundation, Emory Healthcare, NIMH, Stanley Foundation, Woodruff Foundation). All devices were donated by St. Jude Medical (St. Paul, MN). Therefore, patients were not required to have insurance and bore no financial burden from participating. Information about the trial was provided on clinicaltrials.gov (NCT00367003) and in letters sent to regional psychiatrists and other mental health providers. Potential participants were identified via physician, self or family referral.

Using a protocol approved by the Emory Institutional Review Board, a research coordinator first briefly assessed each patient (via telephone or email) to confirm that a set of minimum eligibility requirements were met: diagnosis of unipolar (MDD) or bipolar (BPII) depression, a history of electroconvulsive therapy (ECT) and ability/willingness to relocate to Atlanta for a minimum of 3 months. Patients who met these criteria then participated in a detailed 30-minute phone screen that collected information regarding patients' psychiatric and medical history. All phone screens were conducted by a trained experienced research coordinator in a semi-structured fashion to ensure consistency and reliability across patients. A study psychiatrist reviewed completed phone screens. In some cases, patients were re-contacted to resolve additional questions and limited records may have been requested. If still eligible, patients were asked to request that complete medical records (including ECT records) be sent for review by the study team with appropriate releases obtained by the patients. Patients who continued to be eligible after review of records were then invited to come for an in-person screening visit during which patients met with a study coordinator for administration of the Structured Clinical Interview for DSM-IV (SCID) [19] as well as the 17-item Hamilton Rating Scale for Depression (HRSD) [20] to evaluate current severity. Screening also included psychiatric evaluation by two board-certified psychiatrists, a physical exam, neurosurgical evaluation, magnetic resonance imaging (MRI) and blood and urine testing.

Full eligibility criteria for the study can be seen in Table 1. The Antidepressant Treatment History Form, a validated research instrument [21], was used to assess adequacy of current and prior antidepressant treatments, including ECT, psychotherapy and medication. Using the ATHF criteria, inadequate ECT was defined as no history of ECT or less than seven consecutive treatments (either unilateral or bilateral or a combination of the two). The psychiatric comorbidity exclusion category included depressed patients with diagnoses other

than MDD or BPII or those who had significant additional Axis I or II diagnoses such as post-traumatic stress disorder, obsessive-compulsive disorder, borderline personality disorder or history of substance abuse or dependence in the previous 12 months. Severity during the initial screen and phone screen stages was assessed by self-reported duration of current episode and self-reports of severity/level of dysfunction. This was corroborated by the medical records review and in-person evaluation stages. The HDRS-17 was used to assess severity during the in-person screening stage. Location was defined as exclusion for those subjects who chose not to participate due to the requirement to travel and/or relocate to the study site. Subjects who did not follow up at any screening stage, did not respond to follow-up phone calls/emails, or clearly stated they were not interested were labeled as excluded for “lack of interest”.

Statistical Package for the Social Sciences (SPSS) version 21.0 was used for all analyses. Descriptive statistics were calculated for each reason for exclusion for the entire group as well as the MDD and BPII subgroups. Chi-square and independent samples t-tests were used to assess for differences between MDD and BPII depressed subjects' reasons for exclusion. A p-value ≤ 0.05 was chosen *a priori* as the threshold for statistical significance.

3. Results

Patients from all 50 states as well as Canada, Europe, Central/South America and Australia/New Zealand inquired about participating in the study (Table 2). A flow diagram of the study including the number of subjects at each stage of screening can be seen in Figure 1. 1098 potential participants expressed interest in participating in the study. Gender data was available for 1034 patients (55.5% female, 44.5% male). 60.2% of the sample was self-reported MDD, 21.0% BPII and 18.8% with other or unknown diagnosis. The first point of contact was primarily self-referral (69.0%) followed by family member (23%) and mental health professional (8.0%).

Of the 1098 screened for the study, 1081 (98%) were excluded. Four hundred fifty (450; 41.0%) were excluded due to lack of interest in participating or inability to relocate. Of the remaining 648 (424 MDD, 163 BPII), 631 (97.4%; 57% of the original sample) were excluded for other reasons. For those patients with available data, there were no significant differences in age (p=.520), duration of episode (p=.076), number of depressive episodes (p=.060), duration of psychotherapy (p=.247) or number of ECT treatments (p= .913) between MDD and BPII patients. Clinical and demographic characteristics of patients with available data can be seen in Table 3. As seen in Figure 2, the primary reason for exclusion overall was inadequate ECT followed by psychiatric comorbidity. MDD patients were significantly more likely to be excluded for inadequate ECT than BPII patients (53.3% vs. 31.9%) (x^2 (1)= 21.63, p=.000). BPII patients were significantly more likely to be excluded for lack of adequate severity (20.9% vs. 6.8%) (x^2 (1)=24.15, p=.000) and psychiatric comorbidity (47.9% vs. 24.1%) (x^2 (1)= 31.36, p=.000) than MDD patients.

Of note, only 37 patients (24 MDD, 13 BPII) from this interested cohort met criteria for inclusion after completing the phone screen and records review stages. These patients were invited and completed the in-person screening. 20 (54%) patients were excluded at this stage

due to psychiatric comorbidity (60%) and/or not meeting the minimum severity requirement (50%). There were no significant differences in reason for exclusion between the MDD and BPII patients at this level of screening.

4. Discussion

This study addresses a current gap in knowledge by detailing reasons for exclusion from a study of DBS for TRD and highlighting differences in reasons for exclusion for MDD and BPII patients. No study has assessed differences in reason for exclusion in patients with unipolar versus bipolar depression, nor has any study assessed for primary reasons of exclusion in treatment studies of TRD. Outside of lack of interest and/or location, the most common exclusion factor was inadequate ECT followed by psychiatric and/or general medical comorbidity. Another important finding was the limited number of patients who were referred by treating physicians.

Of the 1098 patients, only 17 were enrolled, and of those, 6 were physician referrals, 8 self-referrals and 3 family referrals. Of the physician referrals, about 13% eventually enrolled in the study compared to 2% of self/family referrals. Although both percentages are small, this suggests that patients referred by their physician for such trials are more likely to qualify. However, it is notable that only a very small percentage of the patients screened were actually referred by their treating physicians; the reasons for this are not clear.

Across the sample interested and able to relocate for the study, MDD patients were more likely than BPII patients to be excluded due to inadequate ECT. Qualitatively (based on narratives from telephone screening), many patients had either never had ECT presented as a treatment option or were wary of it due to information obtained from the media, friends/family or their treatment providers. To highlight this, many patients excluded for not having received adequate ECT expressed the view that they would much prefer experimental invasive brain surgery than to undergo ECT. This is striking since ECT remains the most effective treatment for depression, including TRD [1].

Due to the high rate of psychiatric comorbidity in BPII patients [22-24], it is not surprising that BPII patients were more likely to be excluded for co-morbid diagnoses than MDD patients. They were also more likely to be excluded for lack of adequate severity (in both the whole sample and the phone screen sample). This is perhaps to be expected due to the fluctuations in mood states inherent in the disorder such that the minimum duration of current episode criterion might be more difficult to meet. However, it raises the important question of whether “minimum severity” might be defined differently for bipolar vs. unipolar depressed subjects (e.g., perhaps by percentage of time ill over a given time period).

The major limitation of this study is validity of the information collected. Of the interested sample, few progressed to the medical record review and/or in-person screening stage, and psychiatric diagnoses and other clinical data could not be confirmed in those that did not progress to and complete this stage. Importantly, for those patients that did have some degree of medical records review, data collected during the phone screens was occasionally found to be invalid or omitted (e.g. diagnoses of personality disorders). Therefore, the

validity of the data collected during the telephone screen is lower than those data collected at other stages in the screening process. However, these self-report data still have value, especially for the primary finding that many patients did not want to try ECT or were unwilling/unable to complete an adequate course.

In conclusion, this study was able to categorize reasons for exclusion in a large sample of self-identified TRD patients interested in participating in a clinical trial of DBS. The results showed that while many patients are initially interested in participating in the trial, the exclusion rate was very high largely due to the strict eligibility criteria. Given the large number of subjects excluded due to lack of prior or adequate ECT, presence of co-morbid psychiatric diagnoses (especially among the BPII subgroup), and failure to meet the minimum illness severity criteria, these elements might be reconsidered in the design of similar trials in the future. This study also highlights the ongoing stigma associated with ECT. Even decades after popular movies such as “One Flew over the Cuckoo's Nest” and negative press, patients are more willing to undergo experimental brain surgery and stimulation rather than a course of ECT. Better patient education especially by treating physicians may help temper these fears.

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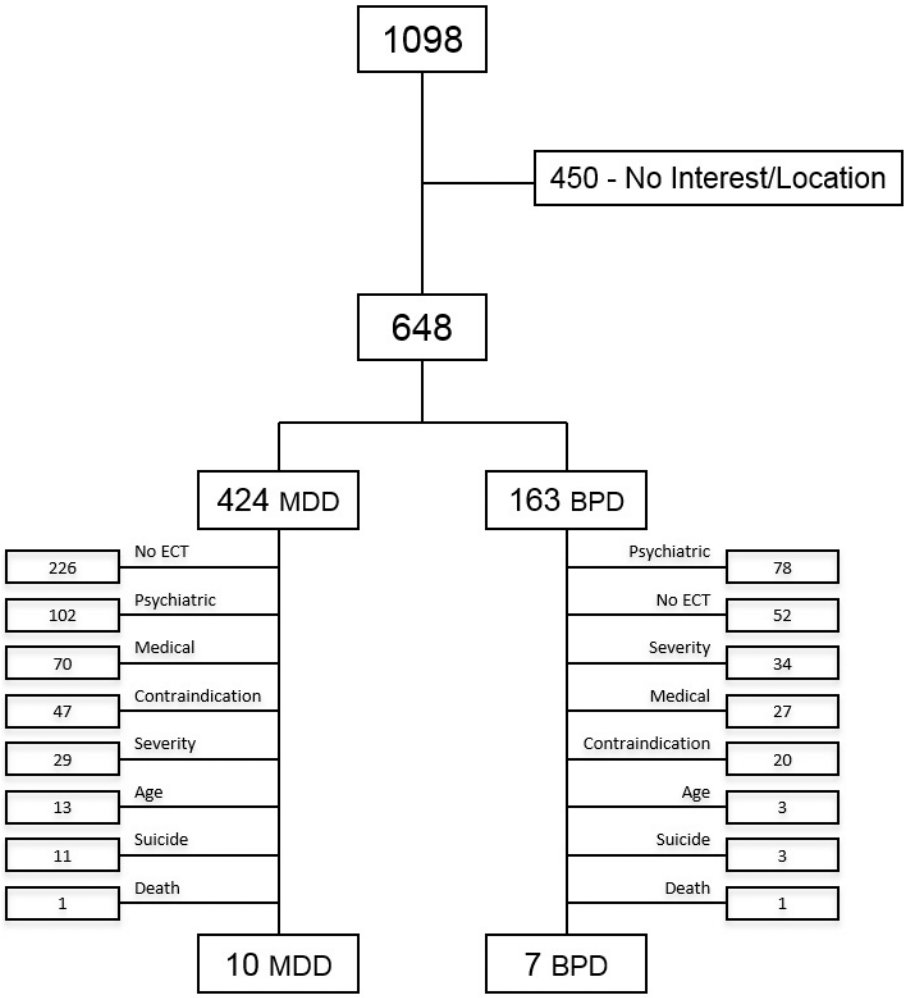

Figure 1.

Pre-Screening Flowchart for total sample (N=1098). Abbreviations: MDD: Major Depressive Disorder, BPD: Bipolar Disorder, ECT: Electroconvulsive Therapy.

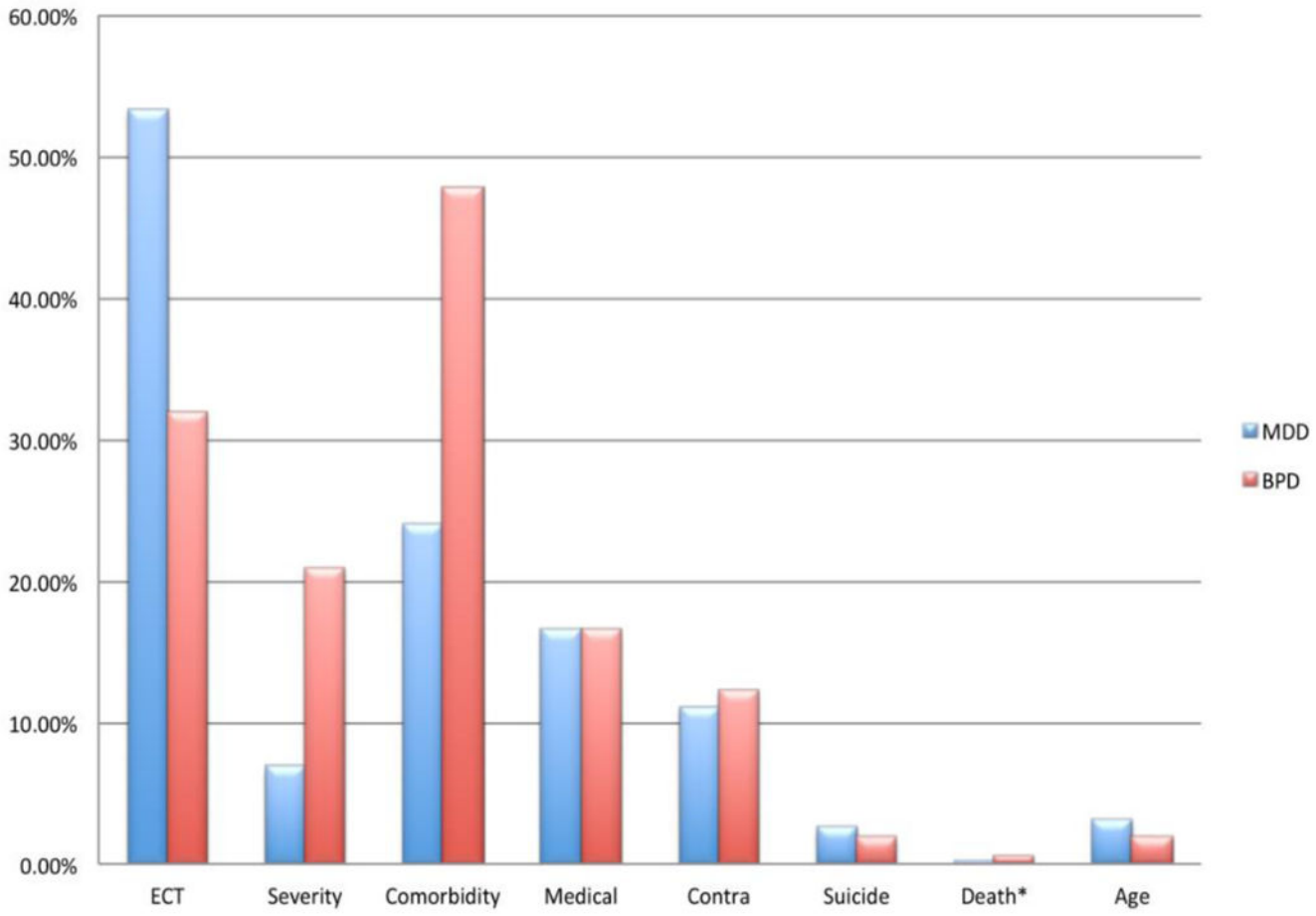

Figure 2.

Reasons for exclusion in N=648. Severity includes minimum severity criteria such as duration of current episode, level of disability and Hamilton Depression Rating Scale score at time of screening; patients were excluded if they did not meet minimum severity criteria.* Patient death as a result of age or general medical condition. ECT = Electroconvulsive Therapy

Table 1

Inclusion & Exclusion Criteria

Inclusion
Age 18-70 years old
Ability to provide informed consent
Current MDE: major depressive disorder or bipolar type II, current episode: depression
Currently meets treatment-resistant depression criteria:
•Failure to respond to at least 4 different AD treatments during the current episode
•Failure or intolerance of adequate course of ECT during any episode
Currently meets minimum severity criteria:
•Current MDE duration of at least 12 months or a history of more than 4 depressive episodes
•Minimum severity score at study entry of 20 on the 17-item HDRS
•Average pre-operative 17-item HDRS of 20 or greater (over 4 weekly evaluations)
•Average pre-operative 17-item HDRS no more than 30% lower than the screening score
•Maximum Global Assessment of Functioning of 50
Stable doses of psychotropic medications during the 4 weeks prior to surgery
Established outpatient psychiatrist
Exclusion
Significant medical or psychiatric comorbidity (e.g. cardiovascular risk, cognitive impairment, personality disorder, psychosis)
Substance abuse or dependence within the last year
Active suicidal ideation; suicide attempt within the last 6 months or 3 attempts within the last 2 years
Pregnancy or plan to become pregnant during the study period
General contraindications to DBS surgery (e.g. cardiac pacemaker/defibrillator, diathermy required, anticoagulant medications, requires repeated MRIs, anesthesia intolerance)
Inability or unwillingness to comply with long-term follow-up
History of intolerance to neural stimulation of any area of the body
Participation in another drug, device or biologics trial within the preceding 30 days
Terminal illness associated with expected survival of <12 months

Abbreviations: MDE (Major Depressive Episode), AD (Antidepressant), ECT (electroconvulsant therapy), HDRS (Hamilton Depression Rating Scale), DBS (Deep Brain Stimulation), MRI (magnetic resonance imaging)

Table 2

Regional Location of the Entire Sample

Variable	Total (N=1098)	MDD (N=660)	BPII (N=231)
United States	955	585	214
South	432	259	110
West Coast	94	63	14
New England	54	39	7
Mid Atlantic	124	73	32
Great Lakes	99	65	16
Southwest	84	49	19
Plains	48	29	10
Rocky Mountain	20	8	6
International	52	30	10
Canada	29	16	5
Europe	12	9	3
Central/South America	5	2	0
Australia/New Zealand	4	3	1
Africa	2	0	1
Unknown*	91	45	7

* Regional information for these patients was not obtained because either patients contacted via e-mail or phone and did not provide their location.

Abbreviations: MDD (Major Depressive Disorder), BPII (Bipolar Disorder – Type II)

Table 3
Demographic and Clinical Characteristics Sample (n=648)

Variable	MDD*	BP*	N (MDD/BP)
Gender(M%, F%)	41.5, 58.5	46.7, 50.3	410/161
Age (years) Mean±SD	45.8±11.5	46.5±11.9	146/93
Episode Duration (months) Mean±SD	100.5±113.2	73.7±97.3	132/83
Number of Episodes Mean±SD	7.2±12.7	12.5±19.8	104/62
Psychotherapy (%)	92.5	96.3	146/93
Time in Therapy (months) Mean±SD	83.4± 90.0	102.4±112.9	99/68
ECT (%)	77.5	84.3	146/93
Comorbid Diagnoses[a] (%)	37.9	49.1	146/93
Previous Suicide Attempts (%)	37.9	41.6	146/93
Past Substance Abuse[b] (%)	48.9	49.1	146/93
Current Substance Abuse (%)	20.4	28.6	186/53
Currently Working (%)	26.4	25	146/93
Disability (%)	38.5	44.4	146/93

Abbreviations: MDD (Major Depressive Disorder), BP (Bipolar Disorder), SD (Standard Deviation), ECT (Electroconvulsive Therapy) F (Female), M (Male), Due to exclusion at various stages during the screening process, the numbers of patients contributing to each category varied. The respective sample sizes are included for clarity.

[a]Patients were asked if they had ever been diagnosed with PTSD, GAD, Schizoaffective disorder, schizophrenia or panic disorder.

[b]Substance abuse included nicotine

*Diagnoses based on patient self-report