Response and Safety Outcomes in Treatment-Resistant Depression After Subcallosal Cingulate Gyrus Deep Brain Stimulation: Long-term Follow-up Study

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ABSTRACT

Objective: To replicate previous findings and to investigate related clinical factors of long-term benefits and safety of subcallosal cingulate gyrus deep brain stimulation (SCG-DBS) for treatment-resistant depression (TRD).

Methods: Sixteen patients with TRD (with either major depressive disorder or bipolar disorder, *DSM-IV* and *DSM-5* criteria) receiving chronic SCG-DBS were followed for up to 11 years (January 2008 to June 2019). Demographic, clinical, and functioning data were collected pre-surgery and during the follow-up. Response was defined as a ≥ 50% decrease from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D_{17}) score, and remission was defined as ≤ 7 in the HAM-D_{17} score. The Illness Density Index (IDI) was used as a longitudinal measure of treatment effects. Survival analyses were performed for response outcomes and relapses.

Results: Depressive symptoms were significantly decreased over time ($F = 2.37$; $P = .04$). Response and remission rates were 75% and 62.5% at individual endpoint. Based on Kaplan-Meier curve analysis, 55% of patients reached remission in 139 days. IDI curves showed sustained clinical improvements as measured with HAM-D_{17} and Clinical Global Impression and sustained functioning improvement as measured with Global Assessment of Functioning scores. The procedure was generally safe and well tolerated (122 adverse events across 81 patient-years, of which 25 were related to SCG-DBS). Two patients committed suicide long after surgery.

Conclusions: SCG-DBS produced a robust and protracted improvement in most patients, which reinforces the possibility that SCG-DBS could be an alternative for patients with treatment-resistant unipolar or bipolar depression. Identification of clinical and neurobiological response predictors should guide the continuation of DBS for TRD, to obtain its indication soon.

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Although common antidepressants and psychotherapy are effective first-line tools for many patients with affective disorders, there is a high proportion of patients experiencing recurrences or poor response. It is estimated than one-third of patients with major depressive disorder (MDD) will have a treatment-resistant depression (TRD) and up to 20% will present a chronic course.[1] Moreover, some follow-up studies indicate that up to 22% of patients with bipolar disorder (BD) may have prolonged depressive episodes[2] and 11% of patients remain chronically depressed for 5 years or more.[3] Beyond the sustained emotional suffering, patients with TRD have disproportionately higher rates of recurrences, disability, morbidity and mortality, and suicidality, and higher economic costs.[4,5]

Besides the combination of antidepressant drugs and psychotherapy, there are other proven pharmacologic strategies, but the efficacy remains limited for a good proportion of patients, and there are ketamine or esketamine[6] or electroconvulsive therapy (ECT),[7] but long-term efficacy and safety issues are still a matter of debate. Deep brain stimulation (DBS) has been investigated as one of the strongest alternatives for those patients with the most severe and refractory forms of TRD.[8–11]

Different targets have been tested for DBS in TRD, such as ventral capsule/ventral striatum,[12] nucleus accumbens,[10,13] lateral habenula,[14] medial forebrain bundle,[10] and subcallosal cingulate gyrus (SCG), with this latter area the most frequently studied.[9,15–17] Several studies have reported promising short-term antidepressant benefits of SCG-DBS, with 12-month response rates ranging from 43% to 62.5%.[18–21] Longer term outcomes have been scarcely investigated on this target. An open-label long-term follow-up study (4–8 years)[18] showed that TRD patients treated with SCG-DBS experienced a robust and sustained antidepressant response. Yet, given the episodic nature of MDD, the effects of SCG-DBS on the progression of the illness, ie, the potential occurrence of new episodes, relapses, and the impact of SCG-DBS on recovery, are to be further addressed.

This is an observational study of the long-term outcomes of SCG-DBS in patients with TRD followed for a range of 2–11 years. The aims are 3-fold: to replicate the previous findings on long-term benefits and safety of SCG-DBS in refractory depression; to explore potential clinical variables associated with long-term benefits; and to document the

Clinical Points

- Management of patients with treatment-resistant depression can be challenging when the available therapeutic alternatives do not work.
- Though invasive, subcallosal cingulate gyrus deep brain stimulation (SCG-DBS) seems to be a safe long-term strategy for treatment-resistant depression.
- Clinical remission and functional recovery are achieved with SCG-DBS by a considerable number of patients for whom conventional treatment options had not been successful.

relapses/recurrences along chronic stimulation by means of survival analyses.

METHODS

Participants

Sixteen patients diagnosed with severe and highly refractory depression (MDD or BD type I or II, *DSM-IV* or *DSM-5* from 2014) treated with SCG-DBS with at least 2 years of follow-up were included in the present study. The timeframe of implantation of this sample ranged from January 2008 (first implanted patient) to June 2017 (last patient). For the present analyses, patients were followed up until 2019. The first 12 patients underwent SCG-DBS implantation within a clinical trial (NCT01268137), and the remaining 4 patients underwent SCG-DBS as part of a compassionate treatment program. Inclusion criteria for eligibility to DBS can be found elsewhere.[17] In summary, patients were aged 18 to 70 years and were in a current depressive episode of at least 12 months' duration that was resistant to pharmacologic treatment, in at least stage IV of the Thase and Rush scale,[19] with lack of or partial response to ECT or lack of tolerance to maintenance ECT. Patients in the study also had an admission score on the 17-item Hamilton Depression Rating Scale (HAM-D_{17})[20] ≥ 18. Patients could not have modified their antidepressant treatment in the month previous to inclusion, and no medication changes were permitted during the stabilization period of chronic DBS stimulation.

Surgical considerations and detailed stimulating parameters are described elsewhere.[21] Briefly, the surgery was carried out with local anesthesia, and no intraoperative microrecording was performed. Two quadripolar leads (model 3387S-28/40 with stimloc, Medtronic, Inc.) were bilaterally implanted in SCG in all patients and were connected to a non-rechargeable impulse generator (IPG) (model Activa PC, Medtronic Inc, Minneapolis, MN) that was implanted into the abdominal subcutaneous tissue under general anesthesia. IPG replacements were scheduled when the battery signal was depleted or nearing end of life; rechargeable IPGs were later implanted in 11 of the 16 participants. SCG-DBS stimulation was initiated 48 hours after surgery in all patients. Gradual voltage increases were carried out when response was not achieved (see below the criterion for response). In the first 5 days after surgery, stimulation parameters (voltage, frequency, and pulse width) were adjusted prior to chronic stimulation commencement. Continuous monopolar stimulation (3.6 V, 135 Hz, 90 ms) was used in the first implanted patients using the most ventral electrode contacts. Because of no response, stimulation was shifted to bipolar in these first patients. The next 10 patients were then stimulated with bipolar stimulation (same parameters). The sequence of changes to maximize therapeutic effects was (1) to increase voltage up to 5 V; (2) to increase pulse width up to 240 ms; and (3) to change active contacts (and starting with initial voltage and pulse width values). The last 3 patients received monopolar stimulation, using individualized preoperative tractography. After post-surgery clinical stabilization, which was defined as a HAM-D_{17} score < 8 maintained for at least 3 months (9 months on average), 5 patients participated in a 6-month crossover double-blind clinical trial between 2009 and 2010.[22]

Patients were seen by their psychiatrist every 2 weeks after clinical stabilization. Visits were then tapered to every 1–2 months from year 2 to last follow-up point (ranging from 2 to 11 years). Adverse events were tracked and reported according to regulatory requirements of the Spanish Regulatory Drug and Medical Devices Agency. The present study was approved by the local ethics committee (N°366/10/EC). All patients were fully informed about all procedures and gave written informed consent.

Variables

Clinical data of the approved studies were used for the current analyses.[17,22] Response to treatment was defined as a 50% decrement from baseline in the HAM-D_{17} score, and remission was defined as a HAM-D_{17} score below 8. Clinical severity was measured using the Clinical Global Impression (CGI)[23] scale, while psychosocial functioning was assessed using the Global Assessment of Functioning (GAF)[24] scale, in which scores above 70 points indicated functional recovery.

Patients were classified according to subsequent symptom response and functional recovery. Therefore, 3 groups were established: responders/recovered (R/R; HAM-D_{17} score decrement ≥ 50% and GAF score ≥ 70); responders/nonrecovered (R/NR; HAM-D_{17} score decrement ≥ 50% but GAF score < 70); and nonresponders/nonrecovered (NR/NR; HAM-D_{17} score decrement < 50% and GAF score < 70).

Analyses of Data

Demographics and clinical characteristics were analyzed with descriptive and qualitative statistics, and comparisons of treatment outcomes were analyzed with quantitative nonparametric statistics.

The Illness Density Index (IDI) proposed by Kelley and colleagues[25] was applied. This index is calculated as the area under the curve of the plot of the repeated measure of interest (HAM-D_{17} in our case) by time within a subject, adjusted by time under observation to be comparable across subjects. Yearly summaries were calculated for each

participant's available data on the HAM-D_{17}. IDI scores for HAM-D_{17} had the same range as the original scale and are easy to interpret and use as remission cutoffs in descriptive analyses. Instead, IDI scores adjusted for baseline HAM-D_{17} were used for the remaining analyses. Provided that at least 2 years of follow-up was available for all participants, individual IDIs could be calculated with no restrictions. A repeated-measures analysis of variance (ANOVA) was run to compare percentage of change in IDI scores among the 3 groups, ie, R/R, R/NR, and NR/NR.

To estimate the probability of response and remission over time, survival analyses were used. The last-observation-carried-forward (LOCF) approach was used for missing follow-up values. Kaplan-Meier method was used to estimate the cumulative incidence of response over time (time-to-event) for the whole sample. Log-rank tests were performed to compare the cumulative incidence between groups of subjects according to the following qualitative factors: diagnosis (MDD vs BD), response to ECT in previous episodes (yes/no), pre-intervention HAM-D_{17} scores, number of suicide attempts before DBS, duration of illness before DBS and age at DBS intervention, and classification based on response and recovery as previously explained. Univariate Cox proportional-hazard regressions were performed to test the association between quantitative factors and the occurrence rate of response and remission. Univariate Cox regression models for recurrent events (counting process model of Andersen-Gill[26]) were performed to evaluate the association between clinical factors previously described and the occurrence rate of relapses. Those subjects who had not responded to DBS during the follow-up were not included in these analyses. The last observation for the subjects who did not have a relapse of their disorder (depressive, manic, or mixed episode) was May 31, 2021.

The statistical package Stata 13.1 (StataCorp, College Station, TX) and the Excel software were used to run all the analyses. Significance level was set at 5% (2-tailed) and confidence intervals to 95%.

RESULTS

Baseline Parameters

Sixteen participants (12 females) with TRD and a mean pre-surgery age of 48.6 years were included in this data set. Ten patients were diagnosed with unipolar MDD, 4 patients with BD type I, and 2 with BD type II (see Table 1 for further details). A total of 1,075 time points and 81 patient-years of data (112 patient-years using LOCF) were collected and combined for follow-up analyses.

Table 1. Baseline Characteristics of All Patients With Treatment-Resistant Depression Included in the Study[a]

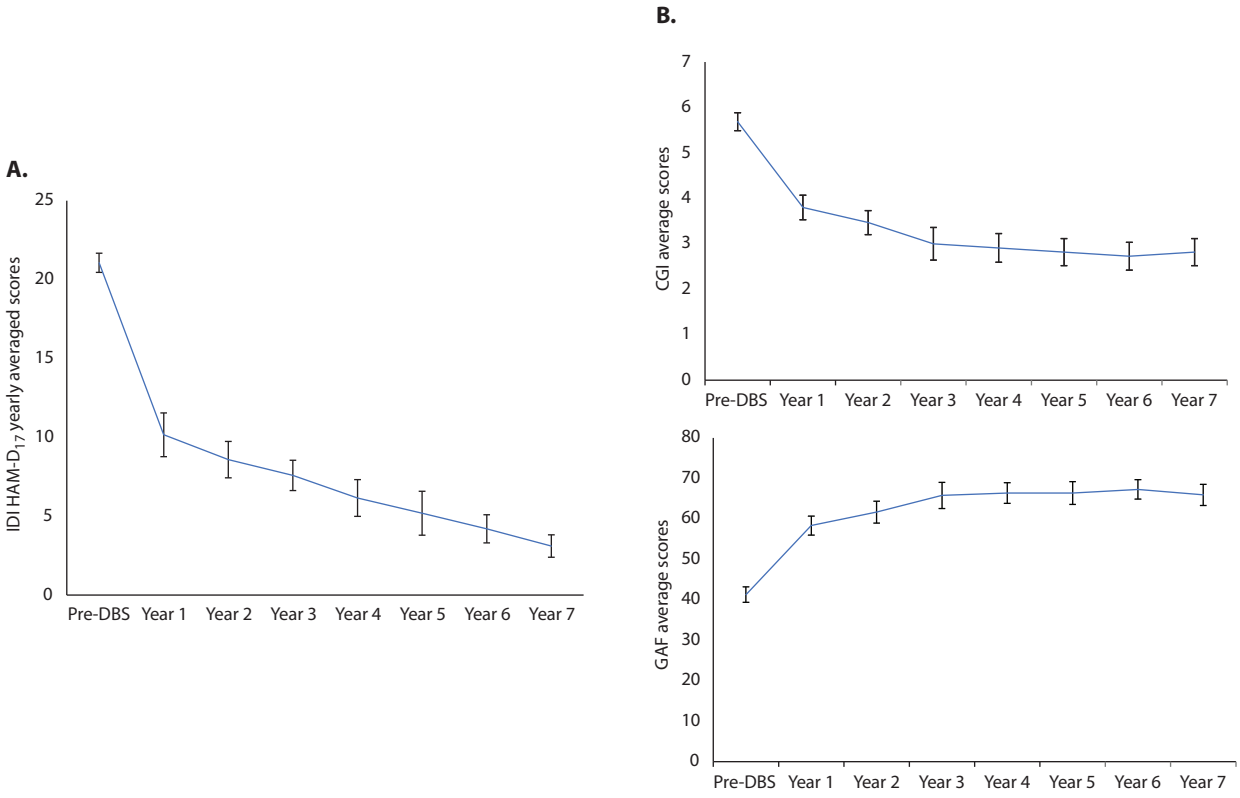
	All participants (n = 16)	MDD (n = 10)	BD (n = 6)
Gender, %			
Female	75.0	80.0	66.7
Male	25.0	20.0	33.3
Age at surgery, y	48.6 (±9.8)	46.5 (±9.8)	52.2 (±7)
	34–70	34–63	49–70
Years of schooling	12.6 (±4.1)	12.6 (±4.2)	12.7 (±3.9)
	6–16	6–16	6–16
Marital status, %			
Single	43.8	40.0	50.0
Married or in a stable relationship	43.8	50.0	33.3
Divorced	18.8	10.0	16.7
Age at illness onset, y	24.4 (±7)	21.9 (±4.7)	28.5 (±8.1)
	15–41	15–30	15–41
Patients with melancholic characteristics, %	56.3	60	50
Length of current episode, mo	64.9 (±76.1)	87 (±89)	28.2 (±8.6)
	17–302	24–302	17–42
Previous suicidal attempts	1.4 (±1.4)	2.0 (±1.3)	0.3 (±0.5)
	0–4	0–4	0–3
Family history of affective disorders, %	93.8	90	100
No. of previous episodes	5.0 (±3.5)	4.3 (±3.7)	6.2 (±2.7)
	1–14	1–14	3–11
No. of medications at time of implantation	4.8 (±1.6)	4.9 (±1.9)	4.5 (±0.5)
	2–8	2–8	4–5
$HDRS_{17}$			
Pre-DBS	21.1 (±2.4)	21.1 (±2.4)	21 (±2.4)
	17–25	17–24	18–25
Follow-up endpoint	5.8 (±5.2)	4.1 (±1.9)	8.5 (±5.4)
	0–17	0–14	1–17
CGI			
Pre-DBS	5.7 (±0.8)	5.6 (±0.7)	5.8 (±0.9)
	5–7	5–7	5–7
Follow-up endpoint[b]	2.9 (±1.1)	2.5 (±0.8)	3.7 (±1.2)
	1–5	1–4	2–5
GAF			
Pre-DBS	41.2 (±7.1)	41.4 (±3.8)	40.8 (±10.6)
	25–55	38–50	25–55
Follow-up endpoint	63.4 (±13)	67 (±12.7)	57.5 (±11.1)
	40–80	40–80	40–75

[a]Values represent mean (SD) unless otherwise specified. Values listed immediately below mean (SD) values represent ranges.
[b]Follow-up endpoint corresponds to the last value of every individual to calculate the mean.
Abbreviations: BD = bipolar disorder, CGI = Clinical Global Impression, DBS = deep brain stimulation, GAF = General Assessment of Functioning, $HDRS_{17}$ = 17-Item Hamilton Depression Rating Scale, MDD = major depressive disorder.

Group and Individual Outcomes by Illness Density Index for Depressive Symptoms

Patients with TRD receiving chronic SCG-DBS were followed for up to 11 years (14 participants completed ≥ 3 years of follow-up and 12 participants ≥ 7 years). The drop-off in the sample size at later time points was of 56.25% (because patients had not yet reached those time points), and thus the group analysis was performed with the 7 first years of study participation. Whenever dropouts were due to lack of response or adverse events, the LOCF was used to handle missing values for these individuals. The repeated measures ANOVA of IDI HAM-D_{17} showed a

Figure 1. (A) Annual Averages of IDI Scores for HAM-D_{17} and (B) Average Scores for CGI and GAF During the Follow-up Period[a]



[a]Bars represent SEM.
Abbreviations: CGI = Clinical Global Impression, DBS = deep brain stimulation, GAF = Global Assessment of Functioning, HAM-D_{17} = 17-item Hamilton Depression Rating Scale, IDI = Illness Density Index, SEM = standard error of the mean.

Table 2. Response Percentage by Patient Through the Follow-up Period (Green = Years With Clinical Response, Red = Years With No Response, Pink = Last Observed Percentages Carried Forward)

Participant	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
1	42%	41%	37%	50%			
2	57%	75%	59%	78%	81%	82%	86%
3	50%	60%	51%	69%	68%	73%	80%
4	78%	44%	53%	89%	78%	55%	16%
5	95%	80%	86%	86%	99%		
6	36%	29%	48%	72%	57%	89%	98%
7	48%	52%	62%	34%	53%	72%	86%
8	47%	44%	44%	44%	44%	44%	44%
9	47%	68%	84%	84%	94%	83%	84%
10	57%	70%	76%	74%	72%	63%	73%
11	41%	76%	66%	79%	88%	83%	75%
12	22%	22%	41%	41%	41%	41%	41%
13	36%	92%	81%				
14	31%	59%					
15	91%	90%	78%	82%			
16	25%	38%	38%	38%	38%	38%	38%
Responders	**37.5%**	**62.5%**	**66.7%**	**71.4%**	**75.0%**	**72.7%**	**63.6%**

significant time effect (Wilks lambda $F_{7,49} = 2.37$; $P = .04$; see Figure 1A). Particularly, at year 1, the mean HAM-D_{17} score decreased more than 50%, and the improvement continued over subsequent years, reaching up to 85% of decrement at year 7. From year 2 onward, the response and remission rates reached 62.5% and 43.75%, respectively, and in the last 2 years of the follow-up of each patient, the response and remission rates were 75% and 50%, respectively (Tables 2 and 3).

The mean CGI score at baseline was 5.7 (SD = 0.8; markedly ill) and improved to 2.9 (SD = 1.1; mildly ill or better) from year 1 to year 7. In the same line, the mean GAF score at baseline was 41.2 (SD = 7.1), indicating serious impairment in several areas, which improved to 63.4 (SD = 13) within the 61–70 range, indicating mild symptoms with overall good functioning (Figure 1B).

Seven patients were considered as R/R, 6 patients were considered as R/NR, and only 3 patients were classified as NR/NR. Figure 2 displays percentages of change in IDI HAM-D_{17} for each group. The repeated measures ANOVA showed a significant main effect ($F_{7,14} = 4.39$; $P < .004$) and a significant group effect ($F_{2,13} = 13.42$; $P = .001$) where NR/NR differed from R/NR ($P = .028$) and from R/R ($P = .001$), showing higher scores across the follow-up. IDI individual HAM-D_{17} curves are displayed in Figure 2 (right panels).

Table 3. Remission Criterion Met by Patient Through the Follow-up Period (Green = Years in Remission, Red = Years Not in Remission, Pink = Last Observations Carried Forward)

Participant	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
1	No	No	No	No	No	No	No
2	Yes	Yes	No	Yes	Yes	Yes	Yes
3	No	No	No	Yes	Yes	Yes	Yes
4	Yes	No	No	Yes	Yes	Yes	No
5	Yes	Yes	Yes	Yes	Yes		
6	No	No	No	Yes	No	Yes	Yes
7	No	No	No	No	No	Yes	Yes
8	No	No	No	No	No	No	No
9	No	Yes	Yes	Yes	Yes	Yes	Yes
10	No	Yes	Yes	Yes	Yes	Yes	Yes
11	No	Yes	Yes	Yes	Yes	Yes	Yes
12	No	No	No	No	No	No	No
13	No	Yes	Yes				
14	No	No	No	No	No	No	No
15	Yes	Yes	Yes	Yes			
16	No	No	No	No	No	No	No
Remitters	**18.75%**	**43.75%**	**37.5%**	**60.0%**	**50.0%**	**61.5%**	**53.8%**

Survival Analyses and to Clinical Variables Time to Response/Remission and Recurrences

Based on Kaplan-Meier survival analysis, half of the sample had responded 139 days after SCG-DBS. The comparisons of survival curves showed that patients with MDD responded faster than patients with BD ($\chi^2 = 4.51$; $P = .034$; see Figure 3). Age, baseline severity, illness duration, response to ECT in previous episodes, and suicide attempts had no effect on either the time to response or the occurrence of response. Half of the sample achieved remission 303 days after SCG-DBS implantation. Only baseline severity showed a significant effect upon the time to remit in Cox regression models ($\chi^2 = 4.4$; $P = .04$).

The mean number of depressive relapses/recurrences per year in responders was 0.4, ie, 1 in 3 years (0.3 for R/R group and 0.6 for R/NR group; $\chi^2 = 5.95$, $P = .05$). Only the number of previous suicide attempts revealed a significant effect on the risk of subsequent relapse/recurrence ($\chi^2 = 8.14$; $P = .004$) in which the risk of relapse was increased by 1.34-fold (95% CI, 1.09 to 1.63).

Long-term Management and Safety

Currently, 11 patients continue in the long-term follow-up. One patient withdrew from the study after 3 years because she exhibited no significant symptom improvement during the follow-up. Another participant dropped out after 7 years of DBS because of comorbid cluster B personality disorder and relapse into cocaine use disorder that compromised follow-up and treatment outcomes. Three participants died in the second, sixth, and seventh years of follow-up after DBS implantation; 1 due to nonpsychiatric medical circumstances (myocardial infarction) and the other 2 due to suicide, as further detailed in Supplementary Appendix 1. One hundred twenty-two adverse events were recorded across 81 patient-years, but only 25 were related to SCG-DBS (Supplementary Table 1). One patient required lead repositioning to reach the desired stimulation site, which was carried out 2 days after the initial because post-operative brain magnetic resonance imaging (MRI) (as proceeded in 2013), after coregistration with the pre-operative MRI, indicated that the right electrode was out of the planned target. Another patient required an IPG replacement 7 months later due to hardware dysfunction. Four of the first patients in our cohort presented some accidental disconnections, which were solved by turning off the magnet control circuit of the IPG.

There were 12 medical hospitalizations and 25 psychiatric hospitalizations. However, 16 of these psychiatric hospitalizations corresponded to 2 participants, those who have presented a worse clinical evolution after SCG-DBS, while the other 14 participants accumulated a total of only 9 subsequent psychiatric hospitalizations, 70% of which occurred in the first year post-intervention. There were 44 psychiatric adverse events, which included 5 patients with MDD who attempted suicide and 2 who died by suicide, as noted before. Five patients (4 with BD and 1 with MDD and psychotic depression) received ECT at least once after SCG-DBS (see Supplementary Appendix 1 for details). Although up to 6 mania/hypomania episodes occurred involving 5 different patients, none of them were considered to be induced by the surgery procedure or stimulation; they were spontaneous or coincided with antidepressant adjustments. Four patients had a prior diagnosis of BD. The other patient (later reclassified as BD) suffered 2 transient hypomanic episodes 3 and 9 years after DBS implantation, after periods of sustained recovery.

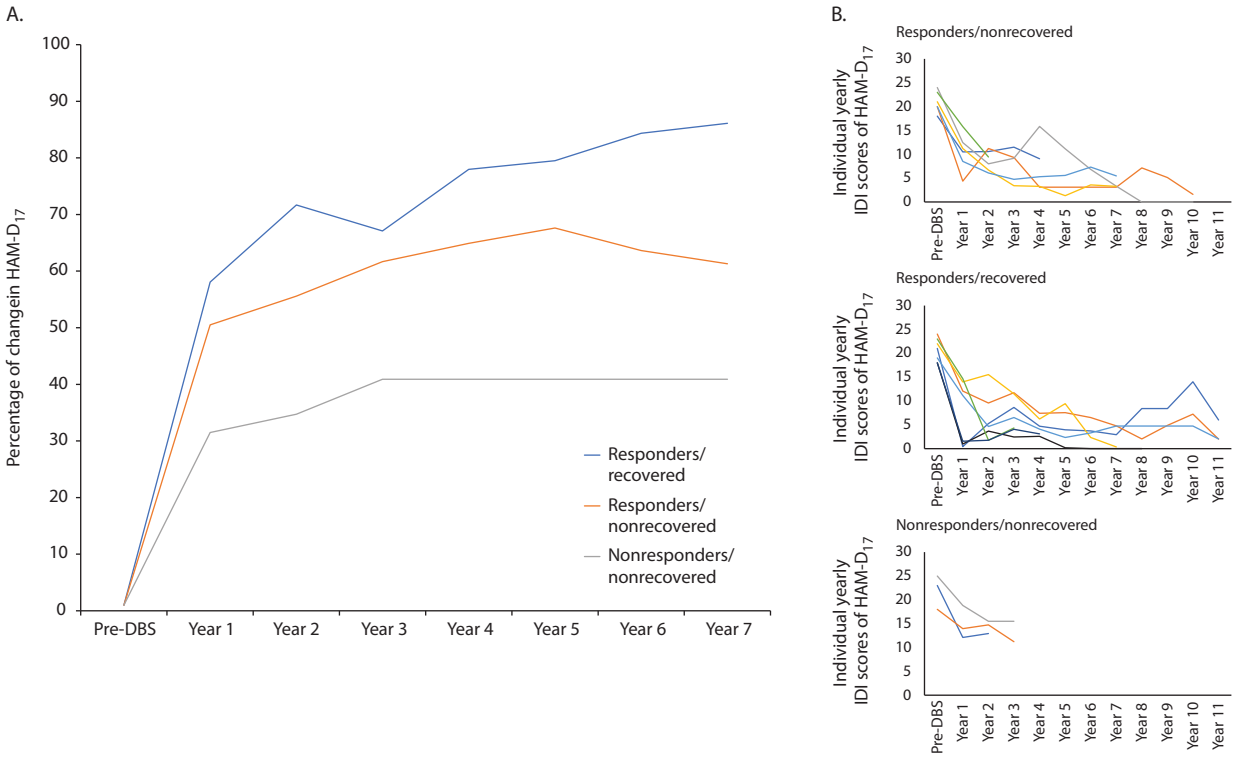
Stimulation and Device Considerations

Stimulation parameters were maintained during the follow-up within these ranges: frequency 130–135 Hz, amplitude 3.5–5 V, and pulse width 90–240 ms. The average life of a non-rechargeable implantable IPG in our cohort was 26.2 months (SD = 7.1), requiring an average of 2.4 replacements per patient (range, 1 to 7). Eleven patients were finally implanted with a rechargeable IPG; 3 of them had recurrent problems handling battery recharging, and 2 requested a switch to a conventional IPG.

DISCUSSION

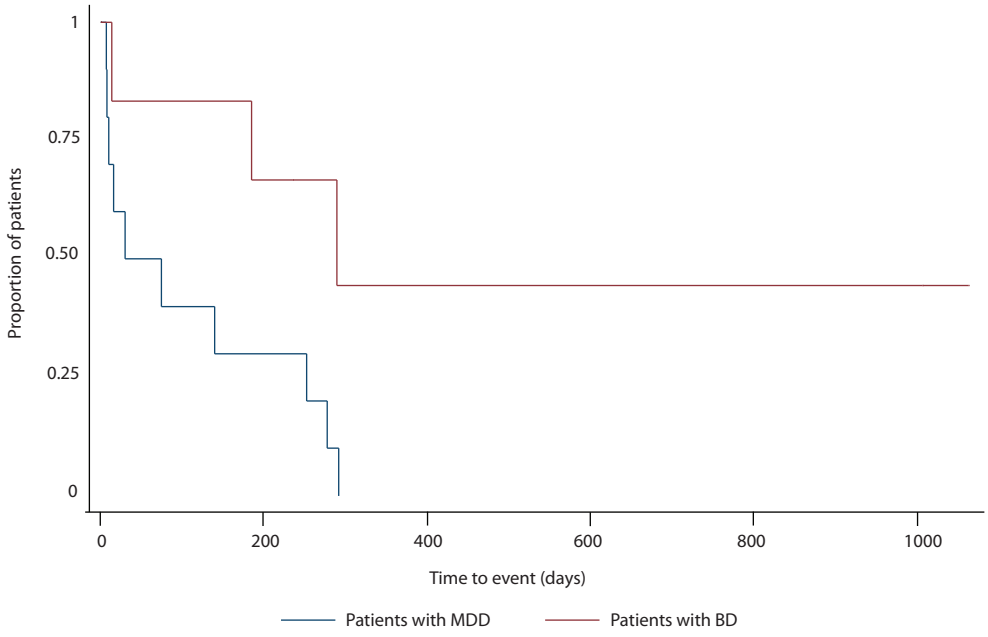
The results confirm and extend previous observations on the usefulness of DBS to treat patients suffering from severe TRD. The follow-up data support the long-term safety and sustained benefits of SCG-DBS for both unipolar and bipolar depression. Twelve of the 16 patients in our cohort (75%) responded to SCG-DBS, and 10 of them (62.5%) achieved complete sustained remission. The improvement after more than 7 years of follow-up was evident at both symptomatic and functional levels, with an average decrease of 85% on the $HAM\text{-}D_{17}$ with respect to the initial levels and a significant increase in the GAF scale scores so that more than 40% of the patients could be considered finally recovered.

Figure 2. (A) Comparison of Percentage of Changes in HAM-D_{17} During Follow-up per Group and (B) Individual Yearly Average IDI Scores for HAM-D_{17} by Response and Recovery Groups and the Last Observation of Each Participant



Abbreviations: DBS = deep brain stimulation, HAM-D_{17} = 17-item Hamilton Depression Rating Scale, IDI = Illness Density Index.

Figure 3. Survival Kaplan-Meier Curves Comparing Patients With Major Depressive Disorder and Bipolar Disorder[a]



[a]Median days to respond was significantly different between groups.
Abbreviations: BD = bipolar disorder, MDD = major depressive disorder.

Our results are in line with previous findings from the longest follow-up studies of patients treated with SCG-DBS. Kennedy and colleagues[27] reported average response and remission rates of 64.3% and 42.9%, respectively, in patients followed up to 3–6 years after intervention. Crowell and coauthors,[18] using the yearly IDI scores for HAM-D_{17}, reported average response and remission rates above 50 and 30%, respectively, in patients followed for at least 8 years. All of these studies are open label without long-term control groups, but the sustained response and remission rates over time are remarkable considering the long-lasting episodes (> 5 years on average in our cohort) with no response before DBS. In contrast, the largest multicenter, randomized, controlled trial with sham SCG-DBS published by Holtzheimer and colleagues[28] showed no significant differences between groups. Half of our cohort responded to the intervention within the first 5 months and achieved remission within the first 11 months. Nevertheless, individual trajectories show that the response is rapid and sustained for only a few patients, while others present a more gradual evolution until the response is stable. Notably, long-term results of their study at 2 years were promising in the open-label phase.[28] This could explain the lack of efficacy for DBS in short-term clinical trials. Future trials in the field should probably consider longer study periods and alternative control arms to validate long-term results.

Still, not all patients benefit from neuromodulation, and not all achieve optimal functional recovery. Apart from neurobiological factors, some aspects related to disease chronicity; previous family, social, and occupational maladjustment; persistent psychosocial stressors; cognitive impairment; maladaptive personality traits; substance misuse; and other psychiatric and nonpsychiatric comorbidities may seriously impact the outcomes of DBS, even when depression is clearly improved. This entails another difficulty for short-term DBS clinical trials. As has been previously highlighted in studies of DBS for TRD, obsessive-compulsive disorder, and other nonpsychiatric indications,[29–31] neurosurgery and neurostimulation can be a key starting point in the recovery process but should be encompassed in a broader therapeutic approach including psychopharmacologic, psychotherapeutic, and rehabilitation interventions.

R/R patients had fewer recurrences than the rest of patients. The number of previous suicide attempts was significantly related to the risk of subsequent relapse/recurrence in our cohort, confirming an association between suicidality and greater clinical burden in affective disorders.[32,33] Most of the recurrences were moderate and easily manageable through optimization of stimulation parameters and other psychotherapeutic interventions (including ECT). Thus, neuromodulation of key brain circuits with SCG-DBS may provide sustained improvement in TRD or attenuate its recurrences but also facilitate the therapeutic action of other antidepressant strategies. A previous case series supports that ECT can be applied effectively and safely in patients with implanted neurostimulators.[34]

Identification of response predictors to SCG-DBS is still challenging, given the small sample sizes and the tremendous variability of TRD. Previous studies have suggested melancholic features, prefrontal cognitive dysfunction, good response to ECT, or periods of good functional recovery in previous episodes as potential markers of DBS response.[18,35,36] In a recently published paper on the 5-year follow-up of our cohort, no clear associations between lead position or electrical parameters and treatment outcomes were found,[21] but in the present series it has been revealed that patients with MDD responded faster than those with BD and higher baseline severity was associated with longer time to remission. In any case, analyses in larger samples with detailed clinical characterization and the recent widespread use of preoperative tractography to plan surgery and guide postoperative programming will likely provide better opportunities to identify prognostic biomarkers.

The DBS procedure itself was generally safe and well tolerated. Most recorded adverse events were unrelated to surgery or DBS device, and none of them was directly attributable to short- or long-term neurostimulation. No serious surgical complications occurred, with no cases of intracranial hemorrhage or infections in our cohort, improving the numbers of other reports.[37] Hardware-related events were mainly unintentional disconnections (with associated risk of relapse) during the first months after substitution by rechargeable IPGs. The need for reintervention is clearly reduced with rechargeable devices, especially considering the higher voltages used in TRD, although some patients find the charging process cumbersome, and age seems to be negatively related to satisfaction with rechargeable stimulators.[38,39]

Switches to hypomania/mania were not related to SCG-DBS and occurred in patients with BD who had reached euthymia after the intervention. For the management of these episodes, instead of interrupting stimulation and increasing the risk of depressive relapse, it is much more advisable to focus on psychopharmacologic adjustments, especially with mood stabilizers.

Seven suicide attempts (mainly mild to moderate) and 2 completed suicides occurred. In these 2 cases, suicide occurred in patients with BD in a period of mood cycling that needed psychiatric hospitalization. The risk of suicide attempt and suicide mortality is particularly high in patients with TRD and BD in direct relation to severity, need of hospitalization, insufficient response, and longer time in symptomatic disease states.[40–42] Unrealistic expectations of quick and sustained improvement can also increase the risk of suicide in these patients.[43] SCG-DBS has reduced suicidality in those patients who achieved response to neurostimulation, but greater vulnerability to stressors can remain and DBS cannot guarantee a full reduction in suicidal risk in such advanced TRD stages. Our data reinforce the need for patients to be aware that the stabilization process can be slow and tortuous and for clinicians to be extra vigilant during periods of illness instability, disabling symptoms, proximity to hospitalizations, and increased environmental stressors.

The first limitation of this study is the limited sample size. This is common to most of the studies of DBS for TRD, and thus interpretation of the results should be cautious. However, detailed reports on the existing studies and trials are of exceptional value to gather evidence and information to continue this line of research. In any case, larger sample sizes are needed to affirm categorically the safety and the clinical efficacy of DBS as a therapeutic alternative in the treatment of TRD. A second limitation is the use of LOCF in longitudinal studies.[44] To avoid bias in data, this approach was uniquely used for dropouts due to lack of response or adverse events, and thus the estimation of response and remission rates would be, in any case, inferior. Finally, it should be noted that the results after the DBS implantation could not be compared with a control group, which is a limitation common to all the studies of DBS in TRD.

While randomized, controlled studies with larger samples, longer follow-up periods, and finer predictors of response are indeed mandatory and welcome, the pragmatic results presented here provide evidence for the long-term efficacy and safety of SCG-DBS as a viable strategy for patients with the most severe and refractory forms of both unipolar and bipolar TRD.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Response and Safety Outcomes in Treatment-Resistant Depression After Subcallosal Cingulate Gyrus Deep Brain Stimulation: Long-term Follow-up Study

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Appendix 1** Long-term Management and Safety
2. **Table 1** Adverse Events in Patients Receiving Deep Brain Stimulation of the Subcallosal Cingulate Gyrus for Treatment-Resistant Depression

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APPENDIX 1

Supplementary Material. Long-term management and safety

Suicide commitment: Two patients with BPD committed suicide long time after surgery. In one of these two cases, suicide occurred during a depressive relapse. This patient, diagnosed with a BPD and a very chronic and refractory index depressive episode (more than 10 years), responded to DBS for up to 6 months, even achieving remission criteria. Nevertheless, this participant had to be considered as part of the NR/NR group, because symptom amelioration occurred at the borderline of the first and second year after SCG-DBS, and the final improvement according to the IDI-HAM-D_{17} scores was less than 50% in either of these years. Afterwards and undertreated with mood stabilizers, she experienced a manic episode for which the professionals conveyed in turning off the IPG as a precautionary measure. Soon after she suffered a depressive relapse, was hospitalized for 5 months and SCG-DBS was gradually re-started up to 3V. Given the symptomatic severity, she also received 10 ECT sessions with good response (but not remission). Two months after discharge and being in a fragile stability, she committed suicide. In the second case, suicide occurred 7 years after the intervention, when there had been a gradual sustained response without functional recovery. Here, the suicide also occurred in close proximity to a manic episode in a patient with a BD but this time in the absence of a subsequent depressive shift, and surrounded by environmental stressors although in circumstances that could not be fully clarified. This case was unrelated to DBS hardware dysfunction or recent parameter changes.

ECT: Five patients received ECT at least once after SCG-DBS. Before surgery, all of them had previously been on maintenance ECT without sufficient response and/or with unbearable cognitive problems. After intervention, ECT was indicated because of the severity of depressive symptoms (in some cases associated with intense suicidal ideation) in those patients who had shown no response to SCG-DBS yet (n=3, in whom a change of parameters or electrode repositioning was subsequently considered) or in patients who experienced a severe recurrence months or even several years after achieving

sustained remission with SCG-DBS (n=2; one of whom in up to 4 episodes, one shortly after DBS implantation and two shortly after rechargeable battery had been depleted, mainly following delirium with pre-existing cognitive impairment and infections). Bifrontal ECT was administered in variable series of 6-12 sessions at a frequency of 2-3 sessions per week; in one case, ECT has been maintained for 5 years at an average rate of 1 session/week due to poor response to SCG-DBS (311 sessions so far). DBS devices were turned off prior to ECT courses or immediately before each session, turning them back on. ECT was effective in all cases (even in patients in whom it had ceased to be efficacious prior to SCG-DBS) without any unexpected adverse effect to the patients or to the DBS hardware. Only low impedances between two ipsilateral contacts were found in the IPG of the patient on maintenance ECT, suggesting a potential short-circuit; nevertheless, the remaining impedances were within normal range not affecting current therapeutic stimulation.

Supplementary Table 1. Adverse events in patients receiving deep brain stimulation of the subcallosal cingulate gyrus for treatment-resistant depression (TRD). DBS= deep brain stimulation; IPG= impulse generator.

Adverse Events	Number of events
Non-psychiatric	78
DBS IPG replacement due to system failure	1
DBS reimplantation to improve targeting	1
Infection related to DBS system	0
DBS accidentally disconnected in non-rechargeable IPG	8 (involving 4 patients), 4 of which associated with serious worsening/relapses
DBS disconnected in rechargeable IPG	15 (involving 6 patients)
Rash	2
Subdural hematoma after mild traumatic brain injury (3 years after DBS)	1
Spinal arachnoid cyst	1
Senile cognitive impairment	1
Neuroleptic-induced movement disorders	3 (involving 3 patients)
Focal epileptic seizures (7 years after DBS)	1
Restless legs syndrome	1
Headache	4
Mild renal insufficiency	1
Urinary tract infection	20 (18 of which in 1 patient)
Gastrointestinal	3 (involving 2 patient)
Eyelid oedema/cellulitis/ptosis	3 (involving 3 patients)
Pulmonary embolism	1
Deep venous thrombosis	4 (involving 1 patient)
Iron-deficiency anaemia	3 (involving 2 patients)
Gynaecologic	2 (involving 2 patients)
Subclinical hypothyroidism induced by lithium salts	1
Meniscal injury	1
Death (non-suicide)	1
Psychiatric	44
Suicidal ideation	5
Suicide attempt	7 (involving 5 patients)
Suicide commitment	2
Auditory hallucinations	1
Relapse into cocaine use	1
Mania/hypomania	6 (involving 5 patients)
Serious depression worsening/recurrences	21 (16 involving 2 patients)
Total	122
Surgery-related	1
Device-related	24