Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Treatment-Resistant Depression: A Decade of Clinical Follow-Up

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ABSTRACT

Objective: Deep brain stimulation (DBS) is an emerging therapy for treatment-resistant depression (TRD) that has shown variable efficacy. This report describes long-term outcomes of DBS for TRD.

Methods: A consecutive series of 8 patients with TRD were implanted with ventral capsule/ventral striatum (VC/VS) DBS systems as part of the Reclaim clinical trial. Outcomes from 2009 to 2020 were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). Demographic information, MADRS scores, and data on adverse events were collected via retrospective chart review. MADRS scores were integrated over time using an area-under-the-curve technique.

Results: This cohort of patients had severe TRD—all had failed trials of ECT, and all had failed a minimum of 4 adequate medication trials. Mean ± SD follow-up for patients who continued to receive stimulation was 11.0 ± 0.4 years (7.8 ± 4.3 years for the entire cohort). At last follow-up, mean improvement in MADRS scores was 44.9% ± 42.7%. Response (≥ 50% improvement) and remission (MADRS score ≤ 10) rates at last follow-up were 50% and 25%, respectively. Two patients discontinued stimulation due to lack of efficacy, and another patient committed suicide after stimulation was discontinued due to recurrent mania. The majority of the cohort (63%) continued to receive stimulation through the end of the study.

Conclusions: While enthusiasm for DBS treatment of TRD has been tempered by recent randomized trials, this small open-label study demonstrates that some patients achieve meaningful and sustained clinical benefit. Further trials are required to determine the optimal stimulation parameters and patient populations for which DBS would be effective. Particular attention to factors including patient selection, integrative outcome measures, and long-term observation is essential for future trial design.

Trial Registration: ClinicalTrials.gov identifier: NCT00837486

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Major depressive disorder (MDD) is a very prevalent and debilitating psychiatric disorder, and numerous treatment modalities are currently available.[1,2] Traditional treatment options include pharmacotherapy, psychotherapy, transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT).[3–9] MDD refractory to two or more adequate treatment trials is termed *treatment-resistant depression* (TRD), also known as MDD with a treatment resistant course.[5,8,10–12] Approximately 30%–40% of patients with MDD are ultimately identified as having TRD, so there is a significant unmet clinical need for the development of alternative and more effective treatment modalities for major depression.

Deep brain stimulation (DBS) is an established US Food and Drug Administration (FDA)–approved treatment for movement disorders such as Parkinson's disease and essential tremor.[13,14] DBS achieves therapeutic neuromodulation via implanted intracranial electrodes, and it has also been investigated as a therapy for psychiatric disorders. Indeed, DBS has received a Humanitarian Device Exemption (HDE) from the FDA for obsessive-compulsive disorder (OCD).[15]

In addition, DBS has been explored as a therapy for TRD. Multiple brain regions have been targeted, including the inferior thalamic peduncle (ITP),[16] lateral habenula,[17] medial forebrain bundle (MFB),[18,19] subcallosal cingulate (SCC),[20–25] ventral anterior limb of the internal capsule (vALIC),[26] and the ventral capsule/ventral striatum (VC/VS).[27] While initial reports were promising,[28,29] subsequent short-term randomized trials[20,27] did not demonstrate efficacy of active over sham stimulation. Despite these results, multiple meta-analyses[30–33] have revealed that DBS is an effective treatment for TRD. Furthermore, several long-term studies[23,34–36] have shown that the efficacy of DBS for TRD improves over time, highlighting the importance of long-term stimulation and longer-term observation. Here, we detail our decade-long follow-up of TRD patients treated with DBS of the VC/VS to investigate the long-term efficacy and utility of this treatment.

METHODS

Patient Selection

We obtained approval from our institutional review board to retrospectively identify all consecutive patients at

Clinical Points

- Deep brain stimulation (DBS) has been explored as a therapy for treatment-resistant depression (TRD); however, prior work has yielded varying reports of clinical efficacy.
- In patients with TRD, DBS therapy may result in long-term symptomatic improvement. Further studies are indicated to explore the patient populations that would benefit most from this treatment.

our institution who underwent DBS implantation for TRD. These patients were implanted with bilateral Medtronic 3391 electrodes in the VC/VS along with bilateral Medtronic Kinetra implantable pulse generators (IPGs) as part of the Reclaim clinical trial (NCT00837486).[27] These procedures were performed in 2009–2010. All eligible patients were included in the study.

Clinical Data Collection

Once the target patient population was identified, we collected relevant data from medical records, both paper and electronic (Epic; Epic Systems Corporation). Data on demographics, indication for DBS treatment, psychiatric symptom severity at baseline, psychiatric medications, and longitudinal treatment response to DBS as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) were collected. Patient records were reviewed from January 1, 2009, to December 28, 2020. DBS treatment parameters and adverse events were also reviewed.

Patients in the Reclaim trial underwent a short stimulation survey over the course of several days 4 weeks after DBS implantation. After the stimulation survey, patients were randomized to receive either active or sham (0 V) stimulation for a 16-week blinded period.[27] Half of the patients in the present study received sham stimulation and half received active stimulation during the blinded phase (n = 4 in each arm). Due to the limited number of patients in our cohort and the fact that these patients were included in the previously published Reclaim trial data,[27] we did not compare outcomes between the active and sham stimulation groups during the blinded phase. The intent of the present study was to describe long-term patient outcomes, so we have focused our analysis on the open-label period during which all of our patients received active stimulation. For the first 6 months after study enrollment, patients were evaluated every 2 weeks. From 6 months to 1 year, patients were seen every month. After 1 year, patients were evaluated every 1–3 months.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2019 (Microsoft Corporation), GraphPad Prism 7 (GraphPad Software, Inc), and R 4.0.2 (R Foundation for Statistical Computing). Longitudinal depression outcomes were obtained using the trapezoidal rule to compute the area under the curve (AUC) of MADRS scores over time. For each year of follow-up, the AUC was then divided by time to obtain time-averaged, yearly MADRS scores. This computation has been dubbed the Illness Density Index (IDI).[34,37] Using this method allows for all available data to be used to assess a patient's disease severity over time. Since most patients have a fluctuating disease course, especially severely ill patients with TRD, single snapshots in time of disease severity do not faithfully represent true disease burden. The AUC analysis integrates disease severity over time, so patient outcomes are more meaningfully measured. Averages are presented as mean ± SD unless stated otherwise. For analyses that included patients who discontinued stimulation, the last-known MADRS IDI scores were carried forward.

To examine the effects of time and stimulation intensity (averaged between the two hemispheres) on MADRS scores, a linear mixed model fit by restricted maximum likelihood (REML) was generated using the lme4 package in R. Time and stimulation intensity were modeled as fixed effects, and patient intercepts were modeled as random effects. We used type-II Wald *F* tests with Kenward-Roger degrees of freedom correction (car package in R) to test the significance of the model predictors.

RESULTS

Patient Demographics

We implanted DBS systems targeting the bilateral VC/VS in 8 patients with severe TRD (Table 1). Half of the patients were male and half were female. The average age at time of DBS implantation was 46.1 ± 8.1 years. This cohort of patients had severe TRD—all had failed trials of ECT, and all had failed at least 4 adequate medication trials. The average baseline MADRS score was 36.5 ± 3.0, consistent with severe depression. Furthermore, half of the patients had persistent MDD with failure to respond to vagus nerve stimulation (VNS) device implantation. All VNS devices were removed at time of DBS implantation. For the entire cohort, average follow-up time was 7.8 ± 4.3 years, and the average age at last follow-up was 53.9 ± 7.8 years. Sixty-three percent of patients (n = 5) elected to keep their devices and continue to receive stimulation. Among the patients who continued to receive stimulation, average follow-up time was 11.0 ± 0.4 years.

Long-Term Outcomes of DBS of the VC/VS for TRD

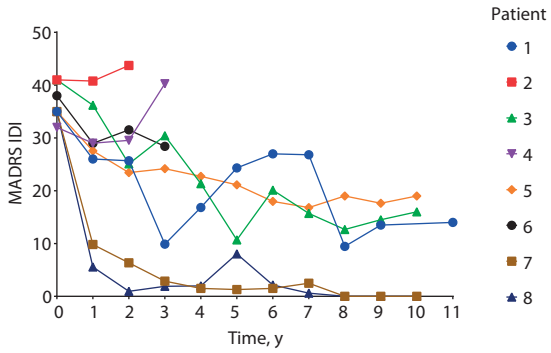
Depression severity was measured over time using the MADRS IDI. After the short blinded phase, all of our patients entered the long-term open-label phase. The vast majority of our patients (75%, n = 6) improved with active stimulation (Figure 1). Two patients did not experience improvement with DBS of the VC/VS, so they elected to have their devices removed. Another patient (patient 6) experienced improvement with stimulation; however, stimulation was discontinued due to recurrent manic episodes despite stimulation parameter adjustment. This patient committed suicide 26 days after stimulation was discontinued (additional details in the Adverse Events section).

Table 1. Patient Demographics

Patient	Sex	Age at Implant	Baseline MADRS Score	Follow-Up Duration, y	Age at Last Follow-Up, y	ECT	VNS	Currently Receiving DBS
1	M	55	35	11.91	67	Yes	No	Yes
2	F	50	41	1.67	52	Yes	Yes	No
3	F	31	41	10.73	42	Yes	Yes	Yes
4	M	47	32	2.53	49	Yes	No	No
5	M	47	35	10.92	58	Yes	Yes	Yes
6	M	53	38	2.75	55	Yes	Yes	No
7	F	51	35	10.71	62	Yes	No	Yes
8	F	35	35	10.95	46	Yes	No	Yes

Abbreviations: DBS = deep brain stimulation, ECT = electroconvulsive therapy, F = female, M = male, MADRS = Montgomery-Åsberg Depression Rating Scale, VNS = vagus nerve stimulation.

Figure 1. Individual Patients' MADRS IDI Scores Over Time[a]



[a]Each patient's MADRS IDI score is presented over at least 10 years of follow-up.
Abbreviations: IDI = Illness Density Index, MADRS = Montgomery-Åsberg Depression Rating Scale.

Improvement in severity of depression was sustained over time (Figures 1 and 2). A robust, positive response to DBS is seen in the cohort of patients (63%, n = 5) who continued to receive stimulation (Figure 2). Even when long-term outcomes of the entire cohort are considered (with last-known MADRS IDI scores carried forward for the patients who discontinued stimulation), a clear improvement in MADRS IDI scores is observed (Figure 2). At last follow-up, mean improvement in MADRS scores was 44.9% ± 42.7% for the entire cohort of patients.

We also tracked therapeutic response (defined as a > 50% decline in MADRS total score relative to baseline) and remission (MADRS total score ≤ 10) rates over time (Figure 3). At last follow-up, 25% of our patients (n = 2) had achieved remission and 50% (n = 4) achieved therapeutic response to DBS. Interestingly, it took 7 years until 50% of the cohort (n = 4) demonstrated response to DBS (Figure 3). This phenomenon was driven partly by fluctuations in some patients' disease severity (eg, patient 1, see Figure 1). Other patients (eg, patients 3 and 5), however, did not achieve full benefit until after 5–6 years of stimulation (Figure 1).

To further assess the relationship between MADRS score, time, and stimulation intensity, we constructed a linear mixed model (see Methods section). Both time and stimulation intensity were inversely related to MADRS score (coefficients of −1.2 and −0.5, respectively), and both were significant predictors of MADRS score ($F = 43.3$, $P < .0001$ and $F = 9.5$, $P = .002$, respectively).

Stimulation Parameters and Battery Life

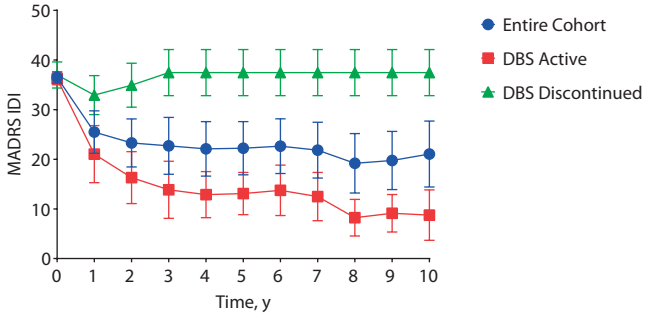
The Reclaim trial provided fairly flexible stimulation parameter selection guidelines.[27] The stimulation settings for the patients that continued to receive stimulation as of the study endpoint are shown in Table 2. All patients received bilateral VC/VS stimulation at 130 Hz. The majority (80%, n = 4) received stimulation set to a pulse width of 210 ms, while 1 received stimulation at a pulse width of 90 ms (Table 2). Bipolar stimulation was more commonly employed (60%, n = 3) compared to monopolar stimulation. Most patients (80%, n = 4) received continuous stimulation, while 1 patient received stimulation during the daytime only. We found that high stimulation intensities were necessary for therapeutic benefit (Table 2). The average stimulation amplitude was 7.2 ± 2.6 V. Despite having a separate battery for each lead, frequent battery replacements were necessary. Of the patients who continued to receive stimulation, the average battery lifespan was 1.2 ± 0.9 years with the Medtronic Kinetra IPGs. Following the introduction of the Activa RC rechargeable IPG, we replaced all of the patients' IPGs with rechargeable devices. Through the study endpoint, these rechargeable devices have lasted for an average of 7.7 ± 0.2 years without replacement.

Further supporting the efficacy of VC/VS DBS for TRD, 60% of patients who continued to receive stimulation through the study endpoint (n = 3) experienced mood deterioration upon battery depletion or inadvertent device deactivation. These patients experienced clinical improvement after resumption of stimulation.

Adverse Events

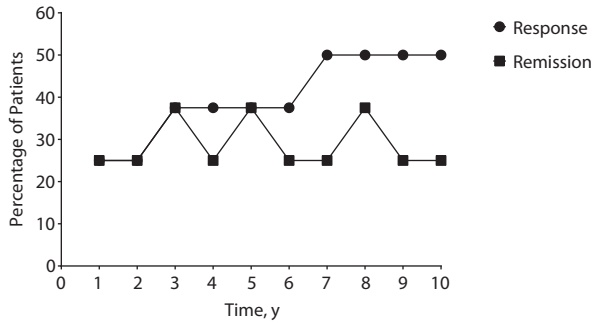
DBS of the VC/VS was largely well tolerated; however, some adverse events were noted throughout the study period. The most common adverse event was hypomania (62.5% of patients, n = 5) and mania (12.5% of patients, n = 1), despite a diagnosis of unipolar depression at baseline. In the patients with hypomania, stimulation parameter adjustment was sufficient to resolve the hypomania. Despite improvement in depression severity (Figure 1), patient 6 experienced stimulation-induced manic episodes. These episodes continued despite stimulation parameter adjustment, and

Figure 2. MADRS IDI Scores Over Time[a]



[a]The mean ± SEM MADRS IDI scores are presented for the entire patient cohort, the subgroup that continued to receive stimulation, and the subgroup in which DBS was discontinued. For the patients that no longer received stimulation, their last MADRS score before exiting the study was carried over.
Abbreviations: DBS = deep brain stimulation, IDI = Illness Density Index, MADRS = Montgomery-Åsberg Depression Rating Scale, SEM = standard error of the mean.

Figure 3. Percentage of Patients Achieving Remission or Response Over Time[a]



[a]Of the entire patient cohort, 50% of patients achieved response (> 50% decline in MADRS score relative to baseline) by the seventh year. At last follow-up, 25% of patients had achieved remission (MADRS score ≤ 10).

Table 2. Stimulation Parameters

Patient	Bipolar	Frequency, Hz	Pulse Width, μs	Voltage, V	Continuous
1	No	130	210	10.5	Yes
3	Yes	130	210	4.2/8[a]	Yes
5	No	130	210	6	No
7	Yes	130	210	9.5	Yes
8	Yes	130	90	4	Yes

[a]Patient 3 received 4.2 V on the left and 8 V on the right.

turning the stimulation off resolved the mania. Due to the frequency of the manic episodes, the stimulator was turned off. The patient committed suicide 26 days later.

Regarding surgical adverse events, there were 2 infections (25%) requiring electrode and battery removal and replacement. One patient (12.5%) had high impedances noted on a clinic visit, so they underwent replacement of the lead adapters. The impedances did not completely normalize; however, stimulation settings were modified to provide adequate and safe stimulation. All of the patients who continued to receive stimulation as of the study endpoint have been implanted with rechargeable IPGs. Two patients required charger replacement, 1 due to malfunction and 1 due to loss of the charger. One patient has presented with left arm tremor and difficulty with gait. This patient has been evaluated by movement disorder specialists, and these symptoms are thought to be medication induced, not an adverse effect of stimulation. Unscheduled follow-up appointments due to device malfunction were rare (average = 1.8 ± 1.7 visits).

DISCUSSION

We investigated the long-term efficacy of bilateral VC/VS DBS in patients with TRD because prior studies have demonstrated that the efficacy of DBS for TRD improves over time.[23,34–36] In the present study, we analyzed the long-term outcomes of these patients for over a decade. To our knowledge, this study represents the longest follow-up report of DBS for TRD to date.

Our data demonstrate that DBS of the VC/VS is effective for TRD. Remarkably, the vast majority of patients (75%) derived benefit from stimulation despite the severity of their refractory depression. Furthermore, symptomatic improvement was durable and improved over time in many patients. Remarkably, 50% of patients achieved a clinically meaningful decline in their depression scores of at least 50% (responder status) and 25% achieved remission. For a disease with no compelling treatment options, these numbers are very encouraging.

The large multicenter randomized trials of DBS for TRD[20,27] have used blinded periods of 4–6 months. Our data demonstrate that the full effect of DBS for TRD many not be seen for up to 6 years. Efficacy of VNS, another neuromodulatory therapy for TRD, also improves over time, and long-term results are encouraging.[38] Aaronson and colleagues[38] compared depression severity in patients treated with VNS to depression severity in patients undergoing "treatment-as-usual" in a longitudinal fashion. They demonstrated that while some symptomatic improvement is seen in the "treatment-as-usual" group, a much greater percentage of patients achieved response/remission in the VNS group. While the logistics of a multiyear trial are daunting, a long-term trial may be necessary to definitively prove the efficacy of DBS, or any neuromodulatory therapy, for TRD.

Stimulation parameter optimization is difficult when DBS is used to treat psychiatric conditions.[39] For movement disorders, motor symptoms such as tremor or rigidity may be used to titrate stimulation.[40,41] For psychiatric conditions, symptoms do not respond as rapidly, and stimulation adjustment is much more challenging. Trials of DBS for TRD have provided some guidelines regarding stimulation parameter selection, but it is ultimately the treating clinician's and patient's response that determine the chosen parameters. Furthermore, many studies do not rigorously report

the final stimulation parameters used. Ramasubbu et al[39] reviewed the stimulation parameters employed in previous studies and found that high frequency stimulation was nearly uniformly used and that lower amplitudes were used with longer pulse widths. Those authors also conducted a randomized trial[42] to compare efficacy of longer pulse width with lower amplitudes and shorter pulse width with higher amplitudes and found that clinical outcomes were largely equivalent. In the present study, we most commonly treated patients with high-frequency, high-amplitude, and long–pulse width stimulation. While some groups have employed high stimulation intensities, most studies place limits on stimulation intensity or have charge density cutoffs.[17,39] A charge density of 30 $\mu C/cm^2$ is commonly reported as the maximal safe tissue dose, however the relationship between tissue damage and charge density is complex and a true safe dose is not entirely known.[43] Furthermore, prior studies of DBS for TRD have employed charge densities greater than 30 $\mu C/cm^2$ with no obvious detrimental effects.[16] Our data suggest that higher stimulation intensities may be necessary to achieve therapeutic benefit in some patients. This phenomenon is also observed when using psychopharmacologic agents in some patients with TRD. A full range of stimulation intensities (ie, adequate trial dose and duration) should be trialed before deeming DBS therapy unsuccessful.

Many centers may limit stimulation intensities due to concerns regarding IPG battery life and the need for frequent battery replacements. Indeed, the stimulation parameters we employed resulted in short IPG lifespans (average = 1.1 ± 0.9 years). In all of the patients that received stimulation through the end of the study period, we implanted rechargeable IPGs. These IPGs have had an average lifespan of 7.7 ± 0.2 years so far and are rated for up to 15 years of usage. We have previously reported that rechargeable IPGs result in greater patient satisfaction and lower cost.[44] In the case of DBS for TRD, rechargeable IPGs may decrease the likelihood of premature treatment discontinuation, because the decision between IPG replacement versus explanation would not need to be made early on in the treatment course (~ 12 months post-operatively before complete treatment response). Furthermore, others have reported success with rechargeable IPGs for OCD.[45] Here, we demonstrate that these IPGs may be used to treat TRD as well.

DBS for TRD is typically well tolerated, and most adverse effects resolve with adjustment of stimulation parameters.[33] In the present study, the most common adverse event was hypomania. In all but 1 patient, decreasing stimulation intensity and/or pulse width resolved the hypomania. In 1 patient, however, the manic episode did not resolve with stimulation down-titration, so the device was turned off. This patient unfortunately committed suicide soon after. The patient's mood at the time of suicide is unknown, and the patient did not endorse suicidal ideation during the last clinical assessment. This patient's medication regimen included lithium and quetiapine before the device was switched off. More data are needed to better explore the role of stimulation intensity adjustments and concomitant use of mood stabilizers to prevent or treat affective switches in the context of DBS. For patients who experience uncontrollable hypomania, hospitalization may be considered for close monitoring of patients during stimulation discontinuation.

The risk of suicide is high in patients with MDD and even greater in patients with TRD.[46,47] The suicide rate in this study (12.5%) is within the range of suicide rates reported in studies of patients with MDD not receiving DBS.[48] In the present study, the suicide occurred while the stimulator was off, suggesting that the suicide was not directly due to stimulation. DBS is an invasive and experimental therapy, so patients may consider DBS their last resort for recovery. Hence, patients who do not respond or are unable to tolerate DBS may experience increased hopelessness. Continuation of existing stable psychotherapy may also be important to mitigate hopelessness. Careful prior discussion of potential alternate treatment options and psychoeducation are also necessary to alter these perceptions and to mitigate risk of suicide.

The VC/VS is one of several DBS targets being explored as a therapy for TRD.[16–27] Among the various previously studied targets, the SCC has received the most attention.[20–25] When comparing targets, it is important to consider efficacy in the context of adverse effects. The current study reveals hypomania as a relatively common adverse effect of VC/VS stimulation. This adverse effect is not frequently encountered with SCC stimulation.[20,33] On the other hand, worsening depression severity and visual disturbances are some adverse effects seen more commonly with SCC stimulation.[20] These differences illustrate that the optimal treatment strategy likely involves patient-specific target selection. For example, SCC stimulation may be preferred in patients with bipolar features while VC/VS stimulation may be preferable in patients with severe anhedonia.

A major limitation of this study is its small sample size, thus the findings presented here may not generalize to the broader TRD patient population. Future studies with larger patient cohorts are necessary to ensure generalizability. Other limitations of this study include its open-label, retrospective design and the flexible use of concomitant antidepressant treatments during the long-term observation period. While we have not compared active to sham stimulation, this study does provide evidence that DBS is therapeutic for TRD. We have also demonstrated that long-term stimulation may be necessary to achieve maximal benefit. Furthermore, our data show that stimulation intensities may be titrated higher to achieve clinical benefit without adverse effects. Stimulation intensity should not be limited by concerns such as battery life, because patients with TRD may be implanted with rechargeable IPGs. This study demonstrates that TRD patients do tolerate recharging their devices.

Given the high degree of treatment resistance in this cohort of patients (ie, medication, psychotherapy, VNS, and ECT) it is not expected that the sustained clinical improvement observed in this sample is a direct result of the use of concomitant medication and psychotherapy

during the observation period. Furthermore, despite the presence of concomitant treatments, 60% of the patients who continued to receive stimulation experienced mood deterioration upon battery depletion or inadvertent device deactivation with subsequent improvement after resumption of stimulation.

While these results are encouraging, future larger studies are critical to verify the efficacy of DBS for TRD. Careful attention to trial design is essential.[18,49] Prior studies have suggested that longer trials are needed,[34] and our results confirm these findings. Furthermore, because symptom severity changes over time, future trials should employ outcome measures that integrate depression scores over time instead of using snapshots of disease severity at specific timepoints. The area-under-the-curve methodology used here and elsewhere[34] can be applied to any longitudinal outcome measure (eg, Hamilton Depression Rating Scale instead of the MADRS). Crossover trial design has been employed in some DBS studies[33] and may enhance the likelihood of success of clinical trials compared to a parallel trial design. In agreement with prior reports,[26] we observed mood deterioration in some of our patients upon cessation of stimulation. These results suggest that if implemented, crossover trials will have to be carefully designed to monitor for potential deterioration during the crossover period.

CONCLUSIONS

While enthusiasm for DBS of the VC/VS as a therapy for TRD has been tempered by recent randomized trials, this long-term open-label study demonstrates that many patients achieve meaningful and sustained clinical benefit from DBS. Further trials are required to determine the optimal stimulation parameters and patient populations for which DBS would be effective. Particular attention to factors that include patient selection, integrative outcome measures, stimulation parameters, and long-term observation is essential for future trial design.

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