ORIGINAL ARTICLE

Deep Brain Stimulation of the Nucleus Accumbens for Treatment-Refractory Obsessive-Compulsive Disorder

Damiaan Denys, MD, PhD; Mariska Mantione, MSc; Martijn Figee, MD; Pepijn van den Munckhof, MD; Frank Koerselman, MD, PhD; Herman Westenberg, PhD; Andries Bosch, MD, PhD; Rick Schuurman, MD, PhD

Context: Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder that affects 2% of the general population. Even when the best available treatments are applied, approximately 10% of patients remain severely afflicted and run a long-term deteriorating course of OCD.

Objective: To determine whether bilateral deep brain stimulation of the nucleus accumbens is an effective and safe treatment for treatment-refractory OCD.

Design: The study consisted of an open 8-month treatment phase, followed by a double-blind crossover phase with randomly assigned 2-week periods of active or sham stimulation, ending with an open 12-month maintenance phase.

Setting: Academic research.

Patients: Sixteen patients (age range, 18-65 years) with OCD according to *DSM-IV* criteria meeting stringent criteria for refractoriness to treatment were included in the study.

Interventions: Treatment with bilateral deep brain stimulation of the nucleus accumbens.

Main Outcome Measures: Primary efficacy was assessed by score change from baseline on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Responders were defined by a score decrease of at least 35% on the Y-BOCS.

Results: In the open phase, the mean (SD) Y-BOCS score decreased by 46%, from 33.7 (3.6) at baseline to 18.0 (11.4) after 8 months ($P<.001$). Nine of 16 patients were responders, with a mean (SD) Y-BOCS score decrease of 23.7 (7.0), or 72%. In the double-blind, sham-controlled phase (n=14), the mean (SD) Y-BOCS score difference between active and sham stimulation was 8.3 (2.3), or 25% ($P=.004$). Depression and anxiety decreased significantly. Except for mild forgetfulness and word-finding problems, no permanent adverse events were reported.

Conclusion: Bilateral deep brain stimulation of the nucleus accumbens may be an effective and safe treatment for treatment-refractory OCD.

Clinical Trial Registration: isrctn.org Identifier: ISRCTN23255677

Arch Gen Psychiatry. 2010;67(10):1061-1068

Author Affiliations: Departments of Psychiatry (Drs Denys and Figee and Ms Mantione) and Neurosurgery (Drs van den Munckhof, Bosch, and Schuurman), Academic Medical Center, University of Amsterdam, Amsterdam; and Department of Psychiatry and Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht (Drs Koerselman and Westenberg), the Netherlands.

OBSESSIVE-COMPULSIVE disorder (OCD) is a psychiatric disorder characterized by persistent thoughts (obsessions) and repetitive ritualistic behaviors (compulsions). It has an estimated lifetime prevalence of 2% and affects men and women equally. If left untreated, OCD can destroy a person's capacity to function at work, socially, and even at home. Specific treatments for OCD have been developed, such as cognitive behavior therapy (CBT) and pharmacotherapy with selective serotonin reuptake inhibitors. It is estimated that these treatments provide a mean of 40% to 60% symptom reduction in half of the patients. However, even when the best available treatments are applied, approximately 10% of patients remain severely affected and experience treatment-refractory OCD.[1]

For a small proportion of treatment-refractory patients, deep brain stimulation (DBS) may be appropriate. This is a neurosurgical treatment involving the implantation of electrodes that send electrical impulses to specific locations in the brain, selected according to the type of symptoms to be addressed. There is evidence that DBS is effective in patients with treatment-refractory OCD when it is targeted to the anterior limb of the internal capsule, the ventral striatum, the nucleus accumbens, or the subthalamic nucleus.[2-7] Because there is evidence of dysfunction of the reward system

in OCD, DBS to the nucleus accumbens might be promising therapy.[8] In a pilot series, stimulation of the nucleus accumbens, which is thought to have a critical role in the pathogenesis of OCD, led to significant reduction in the severity of symptoms in 3 of 4 patients.[9]

The objective of the present study was to confirm these results in a larger series. We also assessed the efficacy and tolerability of bilateral DBS of the nucleus accumbens in severely disabled patients with treatment-refractory OCD.

METHODS

PATIENTS

Patients were recruited from the outpatient clinic for anxiety disorders at our university hospital. All patients consented to participate in this study and signed an informed consent form. The medical ethics review committee of our hospital approved the study, which was registered under trial number ISRCTN23255677 in the international controlled trial registry.

INCLUSION CRITERIA

Participants were female or male outpatients, aged between 18 and 65 years, who were diagnosed as having primary OCD according to *DSM-IV* criteria using the Structured Clinical Interview for *DSM-IV* Axis I disorders.[10] Only patients with a score of at least 28 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), measured twice at least 2 weeks apart, were included in the study. Patients were required to have at least a 5-year history of OCD and to experience substantial functional impairment according to *DSM-IV* criterion C and a Global Assessment of Function score of 45 or less. Refractoriness to therapy was defined as no response or insufficient response following at least 2 treatments with a selective serotonin reuptake inhibitor at maximum dosage for at least 12 weeks, plus 1 treatment with clomipramine hydrochloride at maximum dosage for at least 12 weeks with assessment of plasma levels to control for sufficient bioavailability, plus at least 1 augmentation trial with an atypical antipsychotic for 8 weeks in combination with an selective serotonin reuptake inhibitor, plus at least 1 CBT trial for a minimum of 16 sessions.

EXCLUSION CRITERIA

Except for those with major depressive disorder and mild anxiety disorders, patients with clinically significant comorbid *DSM-IV* diagnoses (such as schizophrenia, bipolar II disorder, alcohol or substance abuse in the last 6 months, current tic disorder, or body dysmorphic disorder) were excluded from the study. Patients with severe personality disorders, assessed using the Structured Clinical Interview for *DSM-IV* Axis II disorders,[11] were excluded. Other reasons for exclusion were clinically significant and unstable neurologic or medical illnesses.

STUDY DESIGN

The study consisted of 3 sequential treatment phases. After electrode implantation, patients entered an open phase of 8 months during which they were evaluated every 2 weeks for severity of symptoms and optimal stimulation parameters. Once an initial and substantial decrease (on average, 6 points) in Y-BOCS score had been obtained, which was usually after 8 weeks of stimulation, a standardized CBT program was added. Because OCD is a context-related disorder, it is common for patients to actively avoid stimuli or social contexts to cope with their disease. To realize the full potential of the DBS treatment, the program was designed to confront patients with their feared stimuli and consequently to force them to deal with their obsessive-compulsive symptoms. Treatment with CBT consisted of weekly individual sessions of 60 minutes for 24 weeks and was conducted by a CBT practitioner (M.M.) and a trained nurse.

After the open phase, patients entered a 1-month, double-blind, sham-controlled phase. Patients were randomly allocated to 2 periods of 2 weeks with the stimulators blindly turned on (active stimulation) in one period and turned off (sham stimulation) in the other period. Block randomization was used with computer-generated random sequence, providing adequate concealment. Patients were assessed 3 times (at baseline, after a 2-week period of active or sham stimulation, and after the second 2-week period of reversed active or sham stimulation). The assessor (M.M.) was blinded to stimulation conditions. Treatment with CBT was continued during the crossover period.

The ensuing maintenance phase lasted 12 months, during which patients were evaluated at 3-month intervals. The stimulators were turned on for all patients, and stimulation parameters were adjusted if necessary.

SURGICAL PROCEDURE

Implantation of the electrodes was performed according to standard stereotactic procedures using frame-based magnetic resonance imaging for target determination. All patients underwent bilateral implantation of 4 direct-contact electrodes (model 3389; Medtronic Inc, Minneapolis, Minnesota), with contact points 1.5-mm long and separated from adjacent contacts by 0.5 mm. The contacts are coded from 0 (ventral) to 3 (dorsal) and are independently programmable. Target coordinates for the electrode tip were 7 mm lateral to the midline, 3 mm anterior to the anterior border of the anterior commissure, and 4 mm inferior to the intercommissural line. Electrodes were implanted following the anterior limb of the internal capsule into the target nucleus, with an anterior angle of approximately 75° to the intercommissural line. The target coordinates were uniformly used in all patients, as there was not yet a rationale available for relative positioning within the nucleus accumbens given the individual variation of anatomy relative to the stereotactic atlases. Electrodes were connected via subcutaneous extensions to stimulators (Soletra, Medtronic Inc) placed bilaterally in an infraclavicular pocket under general anesthesia. Postoperative frame-based computed tomography images (n=9) or radiographs (n=7) were used to verify the position of the implanted electrodes, which were all located at a shorter distance from the intended target than the size of the electrode contact, with an error within the limits of precision of the imaging technique. To restrict variability of the study design, stimulation parameters were standardized to a frequency of 130 Hz and a pulse width of 90 microseconds. Optimization was limited to changes in active contact points and voltage, ranging to a maximum 5.0 V.

OUTCOME MEASURES

Obsessive-compulsive symptoms were measured using the Y-BOCS,[12,13] with scores ranging from 0 to 40; higher scores indicated more severe symptoms. Patients were defined as responders if they had a score decrease of at least 35% on the Y-BOCS. Depression was rated using the 17-item Hamilton Scale for Depression (HAM-D),[14] and anxiety was evaluated using the Hamilton Anxiety Scale (HAM-A).[15] The Brown Assessment of Beliefs Scale (BABS) was used to assess delusional characteristics of obsessions.[16] The Sheehan Disability Scale[17] was used

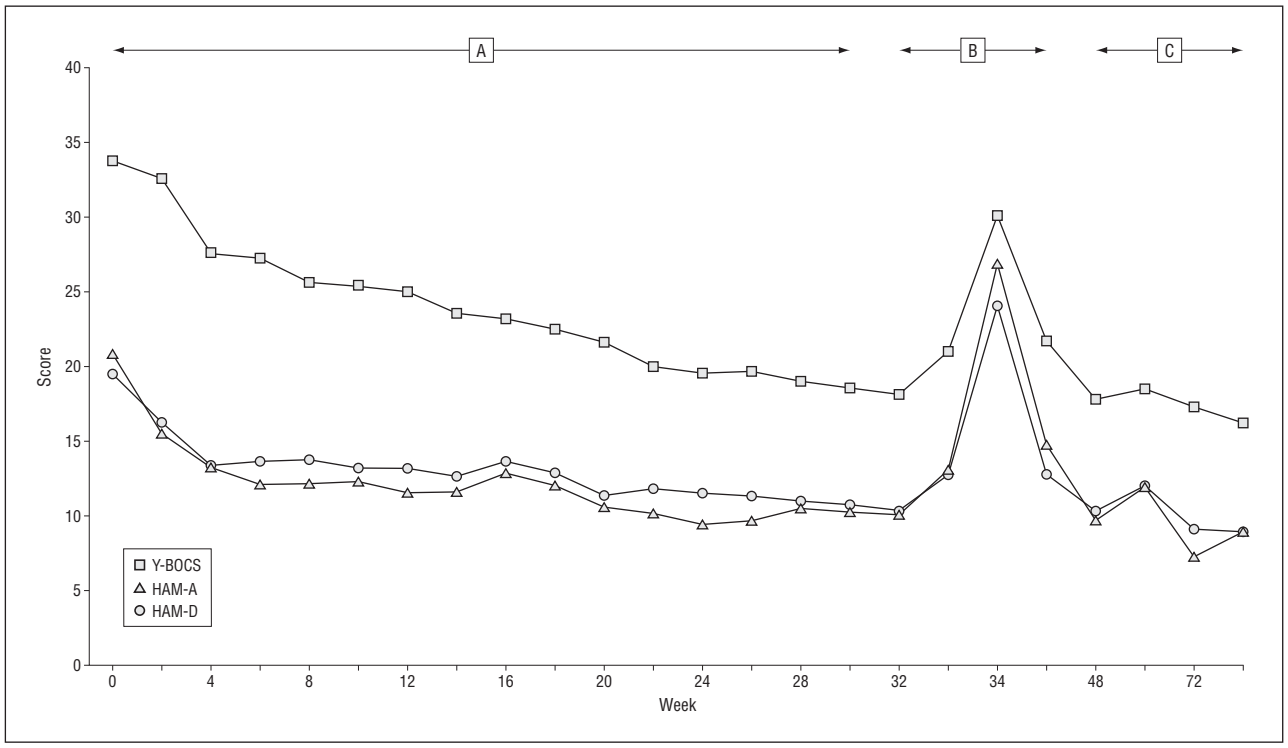

Figure. Change in absolute Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Anxiety Scale (HAM-A), and Hamilton Scale for Depression (HAM-D) scores across the study (84 weeks). A, Change in the open phase (32 weeks). B, Summed increases (weeks 32-34) and decreases (weeks 34-36) during the crossover phase. C, Changes in the maintenance phase (weeks 36-84).

to assess overall symptomatic and functional impairment; the Sheehan Disability Scale consists of 3 separate ratings that evaluate the effect of symptoms on work, social life, and family life. A trained blinded investigator (M.F.) completed the scales at baseline and at each visit. Information on adverse events was derived during each visit by questioning the subjects in general terms, by spontaneous reports of the subjects, or by observation. Any change in behavior reported by the patient was rated as an adverse event.

STATISTICAL ANALYSIS

The sample size was based on the assumption that a mean (SD) reduction of 9 (6) points on the Y-BOCS (based on drug studies[1]) is a clinically relevant response and that a placebo response in this treatment-refractory group will be close to zero. Therefore, 16 patients were judged to be sufficient to assess the potential efficacy of this procedure with a type I error of 0.05 and a type II error of 0.80.

In the open phase, the primary outcome measure (the Y-BOCS score) was analyzed for all patients using paired *t* test. Categorical analyses determined the number of responders based on at least a 35% decrease in the Y-BOCS score. Pearson product moment correlation χ^2 test, Fisher exact test, or 1-way analysis of variance was used to compare clinical characteristics and responder rates for the treatment groups. In the blinded sham-controlled phase, the absolute difference between active and sham stimulation in the entire group was calculated by comparing the end point of weeks 3 and 4 in the on-off group and of weeks 1 and 2 in the off-on group with the end point of weeks 1 and 2 in the on-off group and of weeks 3 and 4 in the off-on group using paired *t* test. To control for period effects, we used a mixed-model regression analysis in line with that by Díaz-Uriarte[18] with Y-BOCS weekly comparison scores as dependent variables and with period and treatment as independent variables. Dependency between data at weeks 1 and 2 vs at weeks 3 and 4 is modeled by a compound symmetry covariance matrix specification. The interaction term treatment × period tests for carryover effects. An analogous procedure was performed for the HAM-A and the HAM-D. Data are presented as the mean (SD) at a 2-tailed 5% level of significance. All statistical analyses were conducted using commercially available statistical software (SPSS, version 16.0; SPSS Inc, Chicago, Illinois).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

One hundred one patients were screened for eligibility, and 16 were included in the study (**Figure**). The demographic and clinical characteristics of the sample are summarized in **Table 1**. Patient 4 fulfilled *DSM-IV* criteria for OCD and avoidant personality disorder. To cover different subtypes of OCD, we deliberately included patients with a wide diversity of content and type of obsessive-compulsive symptoms.

OUTCOME MEASURES OF THE OPEN PHASE

Stimulation in the open phase resulted in a mean Y-BOCS score decrease of 15.7 (10.8) (95% confidence interval [CI], 9.9-21.5) points (46%) ($P<.001$) (**Table 2**). A categorical analysis revealed 9 patients with at least a 35% score decrease on the Y-BOCS, with a mean decrease of 23.7 (7.0) points (72%) compared with a mean decrease of 5.4 (3.1) points (24%) in the nonresponder

Table 1. Baseline Demographic and Clinical Characteristics of the Sample

Patient No./Sex/ Age, y	Age at Onset of OCD, y	Duration of OCD, y	Axis I Comorbidity	Obsessions	Compulsions	Drug Therapy (mg)	No. Previous Drug Trials	No. Previous CBT Trials	Score Y-BOCS	Score HAM-A	Score HAM-D
1/F/54	21	33	. . .	Believing in magic numbers	Counting, walking with right foot over lines	Clomipramine hydrochloride (75), quetiapine fumarate (200)	6	8	38	21	25
2/M/44	10	34	MDD	Fear of contamination, intrusive images of sex and violence	Washing, cleaning, seeking reassurance	Clomipramine (125)	9	4	34	17	19
3/M/51	13	38	MDD	Fear of contamination	Washing	Fluvoxamine maleate (300)	8	5	36	23	20
4/F/26	5	21	Dysthymia	Perfectionism	Obsessional slowness, recurring acts	Fluoxetine hydrochloride (60)	4	5	40	12	22
5/M/40	13	37	MDD	Fear of harming others, fear of contamination	Checking, washing	Citalopram hydrobromide (60)	6	3	33	32	27
6/F/54	4	40	MDD	Fear of contamination	Washing, cleaning	. . .	6	3	31	35	29
7/F/21	13	8	. . .	Fear of contamination, fear of harming others	Checking, mental compulsions	Paroxetine (60), risperidone (1.5)	8	4	30	14	5
8/F/34	14	20	. . .	Fear of contamination, perfectionism	Washing, cleaning	. . .	13	6	35	20	19
9/M/35	16	19	MDD	Need for symmetry, perfectionism	"Just right" behavior	. . .	7	4	38	20	21
10/F/32	18	14	. . .	Believing in magic numbers, fear of predictions	Seeking reassurance	Clomipramine (125), haloperidol (5)	8	2	30	18	15
11/F/45	20	25	Panic disorder	Fear of dirt, need for symmetry	Cleaning, ordering	Paroxetine (60), quetiapine (250)	5	1	38	17	11
12/M/59	13	46	. . .	Fear of coincidence and illogical things	Seeking reassurance, hoarding	Citalopram (60), quetiapine (300)	4	2	33	18	14
13/M/35	14	21	. . .	Somatic obsessions	Checking	Mirtazepine (45)	9	6	35	22	18
14/M/42	12	30	. . .	Fear of contamination	Washing, cleaning	Citalopram (60), quetiapine (300)	6	3	28	24	14
15/M/55	35	20	MDD	Fear of contamination, intrusive images of sex and violence, need for symmetry	Washing, cleaning	. . .	3	4	29	23	30
16/M/54	6	48	. . .	Need to know everything	Hoarding	Clomipramine (225), quetiapine (600)	5	1	32	18	23

Abbreviations: CBT, cognitive behavior therapy; ellipsis, not applicable; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Scale for Depression; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

group. In the open phase, 6 of 16 patients reached a final Y-BOCS score below 10 (mean decrease, 81%), 3 patients reached a final Y-BOCS score between 10 and less than 20 (mean decrease, 51%), 3 patients reached a final Y-BOCS score between 20 and 30 (mean decrease, 22%), and 4 patients reached a final Y-BOCS score greater than 30 (mean decrease, 10%). No patients worsened under stimulation. To test which electrode contacts were to be used, all patients started with monopolar stimulation, with ventral contacts 0 and 1 set negative and case (ie, battery) set positive, at which setting no changes were observed in any patients. In all patients, active contacts were then switched to dorsal contacts 2 and 3 after 2 weeks of stimulation, after which the improvements described herein were achieved. Contacts used were limited to a change from contacts 0 and 1 to contacts 2 and 3 at 2 weeks after implantation. Voltage ranged from 3.5 V to a maximum of 5.0 V, with a mean voltage setting of 4.3 V. With the voltage set at 3.5 V, the mean life span of the batteries is estimated to be 2 years. With amplitudes higher than 3.7 V, the mean life span of the batteries is between 1 year and 2 months and 2 years.

There were no differences in demographic and clinical characteristics between responders and nonresponders except for the content of OCD symptoms. Patients experiencing egosyntonic obsessive-compulsive symptoms such as perfectionism, need for symmetry, seeking reassurance, and hoarding (patients 4, 9, 10, and 16) had a mean score decrease of 10% on the Y-BOCS. At baseline, these 4 patients scored significantly higher on the BABS, 11.5 (2.5) vs 6.6 (5.8) (P=.04) (BABS, 95% CI, 0.3-9.5). Baseline scores, end point scores, and the mean changes on the HAM-A, HAM-D, BABS, and Sheehan Disability Scale are listed in Table 2. A significant decrease was observed in all outcome measures.

OUTCOME MEASURES OF THE DOUBLE-BLIND, SHAM-CONTROLLED PHASE

In the original protocol, a crossover period of 3 months was planned, but after the noted effects of stimulation in the open phase, it was deemed impossible to acquire continuing patient cooperation for 3 months of sham stimulation. Even with this shortened crossover period,

Table 2. Changes in Obsessive-Compulsive Disorder, Anxiety, Depression, Delusional Characteristics of Obsessions, and Overall Symptomatic and Functional Impairment During the Open and Maintenance Periods

	Mean (SD)		Change During Open Period		Start of Maintenance Period, Mean (SD)				Change During Maintenance Period	
Variable	Baseline	After 8 mo of Stimulation	Mean (SD) [95% CI] {%}	*P* Value	12 mo	15 mo	18 mo	21 mo	Mean (SD) [95% CI] {%}[a]	*P* Value
Y-BOCS total score	33.7 (3.6)	18.0 (11.4)	15.7 (10.8) [9.9-21.5] {46}	<.001	17.8 (10.1)	18.5 (12.2)	17.3 (10.9)	16.2 (8.6)	17.5 (8.3) [13.1-22.0] {52}	.001
Obsessions score	16.9 (1.9)	8.3 (5.8)	8.6 (5.6) [5.5-11.5] {50}	<.001	8.2 (5.6)	9.3 (6.6)	8.3 (5.2)	7.1 (4.9)	9.8 (4.9) [7.2-12.4] {58}	.001
Compulsions score	16.9 (1.8)	9.7 (5.7)	7.2 (5.5) [4.1-10.0] {43}	<.001	9.5 (4.9)	9.7 (5.9)	9.0 (5.8)	8.2 (4.7)	8.7 (4.7) [6.2-11.2] {52}	.001
HAM-A score	20.9 (5.9)	10.1 (8.3)	10.8 (8.1) [6.4-15.0] {51}	<.001	9.7 (5.8)	11.9 (8.8)	7.3 (8.3)	8.9 (5.4)	12.0 (9.3) [7.1-17.0] {57}	.001
HAM-D score	19.5 (6.7)	10.5 (7.8)	9.0 (6.2) [5.6-12.3] {46}	<.001	10.3 (7.3)	12.0 (8.1)	9.1 (6.1)	10.6 (6.0)	10.7 (9.1) [5.8-15.5] {55}	.001
BABS score	7.8 (5.6)	4.1 (5.0)	3.7 (5.5) [0.8-6.6] {47}	.02	4.1 (5.0)	5.1 (3.4)	3.7 (5.5)	3.2 (3.4)	4.6 (3.7) [2.7-6.6] {59}	.001
Sheehan Disability Scale score										
Work	8.9 (1.1)	6.0 (3.5)	2.9 (3.1) [1.2-4.6] {32}	.002	5.4 (3.5)	5.4 (3.5)	5.2 (3.2)	4.1 (3.2)	4.8 (3.0) [3.2-6.4] {54}	.001
Social life	9.0 (1.0)	5.2 (3.3)	3.7 (2.5) [1.9-5.5] {41}	.001	4.6 (3.2)	4.7 (3.3)	4.8 (3.0)	4.7 (2.6)	4.3 (2.5) [3.0-5.7] {49}	.001
Family life	7.9 (1.5)	5.0 (3.5)	2.9 (2.7) [1.4-4.3] {17}	.001	4.5 (2.9)	4.5 (3.6)	4.9 (3.2)	4.0 (2.7)	3.9 (2.6) [2.5-5.3] {49}	.001

Abbreviations: BABS, Brown Assessment of Beliefs Scale; CI, confidence interval; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Scale for Depression; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a]Mean change vs baseline.

Table 3. Changes in Obsessive-Compulsive Disorder, Anxiety, and Depression During the Double-Blind Crossover Period

			Start of Crossover Period		Change Between Weeks 1-2 and Weeks 3-4	
Variable	Baseline	After 8 mo of Stimulation	Weeks 1-2	Weeks 3-4	Mean (SD) [95% CI]	*P* Value
(n=6)			**After Stimulation On**	**After Stimulation Off**		
Y-BOCS total score	34.2 (3.6)	23.3 (9.9)	25.8 (9.3)	30.7 (4.5)	4.9 (7.6) [–12.9 to 3.2]	.18
Obsessions score	17.5 (1.7)	11.8 (4.7)	13.0 (4.5)	15.3 (2.3)	2.3 (3.6) [–6.1 to 1.4]	.18
Compulsions score	16.7 (2.0)	11.5 (5.2)	12.8 (4.7)	15.3 (2.4)	2.5 (4.2) [–6.9 to 1.9]	.20
HAM-A score	21.3 (7.7)	12.0 (8.0)	14.3 (6.9)	26.3 (9.2)	12.0 (10.8) [–23.3 to –0.7]	.04
HAM-D score	19.7 (5.4)	10.8 (7.0)	12.7 (5.4)	23.5 (3.6)	10.8 (6.0) [–17.1 to –4.5]	.007
(n=8)			**After Stimulation Off**	**After Stimulation On**		
Y-BOCS total score	33.4 (3.6)	18.7 (10.6)	29.5 (11.4)	17.6 (10.1)	11.9 (9.3) [4.0 to 19.7]	.009
Obsessions	16.4 (2.1)	8.7 (5.5)	15.2 (5.9)	8.0 (5.4)	7.2 (5.5) [2.6 to 11.8]	.007
Compulsions	17.0 (1.7)	10.0 (5.3)	14.2 (5.6)	9.6 (4.8)	4.6 (4.0) [1.2 to 8.0]	.02
HAM-A score	21.5 (4.9)	14.2 (5.8)	27.4 (12.0)	15.2 (13.5)	12.2 (8.4) [5.0 to 19.2]	.005
HAM-D score	21.0 (6.5)	14.6 (5.8)	24.6 (9.9)	12.9 (10.1)	11.7 (8.4) [4.7 to 18.7]	.005

Abbreviations: CI, confidence interval; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Scale for Depression; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

patient 7 refused to participate in the double-blind, sham-controlled phase because of the risk of losing the improvements gained during the open phase (Y-BOCS score decrease, 90%). Patient 9 refused to participate because of disappointment owing to the lack of efficacy (Y-BOCS score decrease, 23%). Therefore, 14 of 16 patients entered phase 2 of the study. The mean Y-BOCS score difference between active and sham stimulation in the whole sample was 8.8 (9.1) (95% CI, 3.6-14.1) points ($P=.003$) (**Table 3**). Because we found no carryover effect ($P=.32$ for treatment × period interaction), the effect of stimulation on Y-BOCS score was assessed using a mixed-model regression analysis with treatment and period as independent variables. After correction for period effects, treatment (stimulation) caused a substantial (mean, 8.3 [2.3] points [25%]) and statistically significant ($P=.004$) reduction in the Y-BOCS total score. Adding prerandomization Y-BOCS score as a covariate (to adjust for initial differences between sequence groups) had no effect on the treatment effect estimate or its SD. The mean difference in HAM-A scores between active and sham stimulation was 12.1 (9.1) (95% CI, 6.8-17.3) ($P<.01$); the mean difference in HAM-D scores between active and sham stimulation was 11.3 (7.2) (95% CI, 7.1-15.5) ($P<.01$). Because of hypomania (or abrupt worsening of symptoms), the blinded status of the stimulators was lifted for most but not all patients. The status of the stimulators remained unclear for patients 4, 11, 12, and 16, in whom the effect of stimulation was not subjectively noticeable.

OUTCOME MEASURES OF THE MAINTENANCE PHASE

As summarized in Table 2, the improvement observed in the open phase was sustained over the 12-month maintenance phase, in which all outcome measures showed a statistically significant mean reduction vs preoperative baseline values. The Y-BOCS scores throughout the study and at the end point were significantly associated

Table 4. Number of Patients Reporting Transient and Permanent Adverse Events

Adverse Event	Transient	Permanent
	Surgery Related	
Wound infection at incision	1 (Patient 11)	0
Tiredness	4 (Patients 2, 5, 7, and 11)	0
Feeling of numbness at incision site	7 (Patients 2, 4, 6, 8, 9, 11, and 12)	0
Nausea	1 (Patient 7)	0
Headaches	2 (Patients 9 and 16)	0
Increase in depressive symptoms	2 (Patients 5 and 9)	0
	Device Related	
Feeling of extension leads, mainly with stress	7 (Patients 2-5, 7, 10, and 12)	1 (Patient 8)
Feeling of electric current around neurostimulator	3 (Patients 3, 6, and 14)	0
Feeling of neurostimulator in chest	0	3 (Patients 7, 8, and 10)
	Stimulation Related	
Hypomanic symptoms	8 (Patients 2, 4, 5, and 11-15)	0
Headaches	3 (Patients 2, 3, and 5)	0
Cold shivers	2 (Patients 3 and 4)	0
Sexual intrusions	1 (Patient 3)	0
Stomachaches	4 (Patients 3, 5, 6, and 14)	0
Dizziness	1 (Patient 5)	0
Taste reduction	3 (Patients 5, 8, and 16)	0
Feeling that the face is asymmetric	1 (Patient 5)	0
Itch in right arm	1 (Patient 5)	0
Menstruation after 1 y of menopause	1 (Patient 6)	0
Menstruation after 4 y of contraceptive injection	1 (Patient 7)	0
Less blood flow during menstruation	1 (Patient 6)	0
Increase in allergy	1 (Patient 7)	0
Difficulty to reach an orgasm, only at higher voltages	1 (Patient 13)	0
Increased libido	0	7 (Patients 2-5, 12, 14, and 15)
Increase in sneezing	1 (Patient 16)	0
Nausea	2 (Patients 7 and 10)	0
Difficulty falling asleep	3 (Patients 4, 8, and 12)	0
Micturition problems, enuresis, polyuria	0	2 (Patients 1 and 12)
Forgetfulness	1 (Patient 8)	5 (Patients 2, 5, 12, 14, and 16)
Difficulty finding words	0	3 (Patients 8, 14, and 16)
Paresthesias in hands or feet	3 (Patients 4, 11, and 16)	0

with HAM-A scores ($\rho = 0.772$) and with HAM-D scores ($\rho = 0.745$) ($P = .001$ for both), suggesting a strong relationship between change in obsessive-compulsive and anxiety measures and mood symptoms.

TOLERABILITY AND ADVERSE EVENTS

All reported adverse events are listed in **Table 4** regardless of their relationship with the treatment procedure. The most prominent transient adverse event related to stimulation was elevated mood or hypomania. This occurred shortly after the switch of the contact points from 0 or 1 to 2 or 3 and lasted for 2 days. Elevated mood or hypomania never required the addition of a mood stabilizer, and the adverse event was rated as mild. Elevated mood was frequently reported during reactivation of the stimulation after an off period. Permanent adverse events were related to stimulation and disappeared during the off periods. Increased libido was reported by 7 patients, but this was not experienced as uncomfortable. Mild forgetfulness was reported by 5 patients and word-finding problems by 3 patients. An extensive neuropsychological test battery was performed in the DBS-treated sample and in a control sample at fixed time points (before and after surgery, at the double-blind crossover phase, and at the end of the maintenance phase). Given the extensiveness of the data, the outcomes of the neuropsychological effects will be published in a separate article.

COMMENT

To our knowledge, this study is the first double-blind, sham-controlled trial to demonstrate that bilateral stimulation of the nucleus accumbens can be an effective and safe treatment in treatment-refractory patients with OCD. All patients underwent electrode implantation in the same target area, and stimulation settings were applied uniformly throughout the study. During the treatment period of 21 months, obsessive-compulsive symptoms decreased by 52%, and 9 of 16 patients responded, with a mean improvement of 72%. Anxiety and depressive symptoms decreased by half. The surgical procedure and stimulation were well tolerated. Permanent adverse events were limited to mild forgetfulness and word-finding problems. Increased libido was reported by several patients but may be interpreted as a return to normal functioning rather than an adverse event.

Our results are consistent with previous studies on DBS in patients with treatment-refractory OCD. Greenberg et

al[6] described 26 patients with OCD in whom stimulation targeting was progressively more posterior over time, moving from the internal capsule to the ventral striatum. On average, they observed a 12.5-point decrease on the Y-BOCS, a 53% decrease in HAM-A scores, and a 40.0% decrease in HAM-D scores, with better results obtained with more posteriorly located electrodes, comparable to our surgical target. In a 2008 study by Mallet et al,[7] 16 patients with OCD underwent bilateral stimulation in the subthalamic nucleus. The mean Y-BOCS score change between sham and active stimulation was 8.9 points. Contrary to our results, neither anxiety and depression scales nor functional impairment (measured by the Sheehan Disability Scale) showed improvement in their study. Transient hypomania has been a consistent finding in DBS for OCD,[5,7] as was also seen in our study. We did not observe deterioration of depression or suicidal ideation, as had been previously reported.[7]

In the blinded sham-controlled phase, patients who were assigned to the stimulation on-off group differed from patients who were assigned to the stimulation off-on group. The patients whose stimulators were turned off in the first 2 weeks immediately experienced an increase in symptoms and then rapidly regained clinical improvement during the ensuing blinded active stimulation. Patients who continued having active stimulation during the first 2 weeks showed a minor increase in obsessive-compulsive symptoms, probably due to uncertainty and doubt about entering the blinded phase of the study. In this group, the baseline Y-BOCS scores at the start of the crossover period were higher, which was in part explained by the higher proportion of nonresponders from the open phase. Four of 6 were nonresponders in the on-off group and 2 of 8 in the off-on group. These factors, along with the small sample size, may have contributed to the nonsignificant difference between active and sham stimulation in the on-off group. The score changes on the HAM-A and HAM-D were statistically significant, suggesting a more robust and immediate effect on anxiety and mood than on obsessive-compulsive symptoms.

The beneficial effects on mood and anxiety, along with improvement in obsessions and compulsions, are striking. All patients, even nonresponders, experienced substantial mood improvement. Therefore, no patients requested to discontinue stimulation, despite the lack of response of obsessive-compulsive symptoms. It is likely that improvement of obsessive-compulsive symptoms depends on changes in mood and anxiety. We observed in our sample a fixed pattern in treatment response and in time at onset of response. Symptoms decreased in a sequential order (depressive symptoms first, anxiety symptoms second, obsessions third, and compulsions fourth) and in a fixed sequence (mood improved within seconds, anxiety within minutes, and obsessions within days, while compulsions took weeks and even months to improve). Finally, avoidance failed to decrease spontaneously and required CBT to disappear. For most patients in this study, compulsive behavior and avoidance had been present for decades; they gradually became part of a "normal" daily pattern and a force of habit. Cognitive behavior therapy proved particularly effective in decreasing compulsive behavior and avoidance. Without stimulation (such as in the placebo-controlled phase), the gained successes with the addition of CBT disappeared rapidly, suggesting that efficacy of CBT depends on stimulation. Our observation of an immediate profound effect with nucleus accumbens stimulation, along with the reported specific effect of subthalamic nucleus stimulation on compulsions observed in the French sample,[7] hints at the involvement of 2 different anatomical circuits in OCD. One circuit might be associated with a mood and anxiety spectrum responding to accumbens stimulation, and another circuit could be related to a compulsive habit spectrum responding to subthalamic nucleus stimulation.

Obsessions and compulsions are heterogeneous symptoms, and a large body of work has delineated subtypes of OCD.[19] We found a clear relationship between DBS nonresponse and type of obsessive-compulsive symptoms. Patients with perfectionism, hoarding, or symmetry did not respond well to the treatment. Patients with this subtype of OCD believe in the worthiness and soundness of their symptoms and were more likely to describe their obsessions and compulsions as egosyntonic, in harmony with their needs and goals and consistent with themselves. The robustness of their obsessions and the lack of insight into the meaninglessness of their obsessions were expressed in higher BABS scores, the only baseline score that was significantly different from baseline scores of other patients. High baseline scores on the BABS predicted nonresponse in our sample and may be of value for patient selection in DBS.

The great appeal of DBS vs lesions is that it permits focal and adjustable modulation of the brain. In our sample, improvement was observed using only dorsal electrode contacts 2 and 3, with active stimulation more in the area of the nucleus accumbens core around the border of the internal capsule and bed nucleus stria terminalis rather than in the shell of the nucleus accumbens, as previously published.[9] The difference in location of the center of the brain tissue volume that is being stimulated between the lower and upper contacts with the 3389 electrode is 4 mm and seemed to determine nonresponse or response in our sample. This finding demonstrates the significance and importance of exact targeting with DBS. In future studies, larger samples are needed to further narrow the "target space" so that the most efficient DBS parameters may be used.

A limitation of this study is that the double-blind periods were short, giving rise to the possibility of a carryover effect, which may have led to an underestimation of the effect of stimulation. This study was originally planned in a sham-controlled design with 3-month periods of on-off stimulation. We changed the 3-month duration to 2 weeks because, once a considerable improvement had been experienced in the open phase, patients did not tolerate off phases owing to massive worsening of symptoms. These findings are consistent with observations by German investigators treating major depression with nucleus accumbens stimulation.[20] Another aspect that may have led to an underestimation of the effect of stimulation is that rating scales such as the Y-BOCS do not fully reflect improvement in patients with severe OCD. The Y-BOCS typically attributes a maximum score of 4 points to duration of symptoms of 8 hours or more. Patients with OCD described herein sometimes experi-

enced 14 to 16 hours a day of obsessions or compulsions. Because the Y-BOCS fails to detect changes beyond 8 hours, reductions remain unnoted by the Y-BOCS. New scales designed to capture changes in severe obsessive-compulsive symptoms are needed.

In summary, the results of this study indicate that bilateral stimulation of the nucleus accumbens may be an effective and safe treatment in patients with highly refractory OCD and support the therapeutic potential of DBS in patients with incapacitating chronic psychiatric disorders. Further research is necessary to optimize this therapy with respect to patient selection and management, target location, and investigation of new potential indications.

Submitted for Publication: November 10, 2009; final revision received February 19, 2010; accepted April 27, 2010.
Correspondence: Damiaan Denys, MD, PhD, Departments of Psychiatry and Neurosurgery, Academic Medical Center, University of Amsterdam, PO Box 75867, 1070 AW Amsterdam, the Netherlands (d.denys@amc.nl).
Financial Disclosure: Dr Schuurman is an independent consultant for Medtronic Inc on educational matters and received travel grants from the company.
Funding/Support: This study was supported by an unrestricted investigator-initiated research grant by Medtronic Inc (Drs Denys and Schuurman), which provided the devices used herein, and by grant 916.66.095 from the Netherlands Organization for Scientific Research ZON-MW VENI program (Dr Denys).
Role of the Sponsors: The funders of this study had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.
Additional Contributions: Maarten Koeter, PhD, provided statistical advice.

REFERENCES

1. Denys D. Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. *Psychiatr Clin North Am*. 2006;29(2):553-584, xi.
2. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet*. 1999;354(9189):1526.
3. Nuttin BJ, Gabriëls LA, Cosyns PR, Meyerson BA, Andréewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, Demeulemeester HG. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*. 2003;52(6):1263-1274.
4. Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, Giordani B. Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2005;57(5):510-516.
5. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology*. 2006;31(11):2384-2393.
6. Greenberg BD, Gabriëls LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, Giftakis JE, Rise MT, Machado AG, Baker KB, Stypulkowski PH, Goodman WK, Rasmussen SA, Nuttin BJ. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry*. 2010;15(1):64-79.
7. Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, du Montcel ST, Yelnik J, Chéreau I, Arbus C, Raoul S, Aouizerate B, Damier P, Chabardès S, Czernecki V, Ardouin C, Krebs MO, Bardinet E, Chaynes P, Burbaud P, Cornu P, Derost P, Bougerol T, Bataille B, Mattei V, Dormont D, Devaux B, Vérin M, Houeto JL, Pollak P, Benabid AL, Agid Y, Krack P, Millet B, Pelissolo A; STOC Study Group. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *N Engl J Med*. 2008;359(20):2121-2134.
8. Denys D, Zohar J, Westenberg HG. The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. *J Clin Psychiatry*. 2004;65(suppl 14):11-17.
9. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkötter J. The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat*. 2003;26(4):293-299.
10. First MB, Spitzer RL, Gibbon MG, Williams JB. *Structured Clinical Interview for* DSM-IV *Axis I Disorders (SCID-I): Clinical Version*. Washington, DC: American Psychiatric Press; 1997.
11. Maffei C, Fossati A, Agostoni I, Barraco A, Bagnato M, Deborah D, Namia C, Novella L, Petrachi M. Interrater reliability and internal consistency of the structured clinical interview for *DSM-IV* axis II personality disorders (SCID-II), version 2.0. *J Pers Disord*. 1997;11(3):279-284.
12. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale, II: validity. *Arch Gen Psychiatry*. 1989;46(11):1012-1016.
13. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. *Arch Gen Psychiatry*. 1989;46(11):1006-1011.
14. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
15. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.
16. Eisen JL, Phillips KA, Baer L, Beer DA, Atala KD, Rasmussen SA. The Brown Assessment of Beliefs Scale: reliability and validity. *Am J Psychiatry*. 1998;155(1):102-108.
17. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996;11(suppl 3):89-95.
18. Díaz-Uriate R. Incorrect analysis of crossover trials in animal behavior research. *Anim Behav*. 2002;63:815-822.
19. Leckman JF, Bloch MH, King RA. Symptom dimensions and subtypes of obsessive-compulsive disorder: a developmental perspective. *Dialogues Clin Neurosci*. 2009;11(1):21-33.
20. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, Schlaepfer TE. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry*. 2010;67(2):110-116.