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

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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

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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. 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.

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 ISRCTN23253677 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. 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 a 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, 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 obsessional-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 (Soleta, 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, 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), and anxiety was evaluated using the Hamilton Anxiety Scale (HAM-A). The Brown Assessment of Beliefs Scale (BABS) was used to assess delusional characteristics of obsessions. The Sheehan Disability Scale was used...
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) 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 \( r \) 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 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 \( \times \) 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

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Age at Onset of OCD, y</th>
<th>Duration of OCD, y</th>
<th>Comorbidity</th>
<th>Obsessions</th>
<th>Compulsions</th>
<th>Drug Therapy (mg)</th>
<th>Previous CBT Trials</th>
<th>Previous Drug Trials</th>
<th>Y-BOCS</th>
<th>HAM-A</th>
<th>HAM-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/34</td>
<td>21</td>
<td>33</td>
<td>...</td>
<td>Believing in magic numbers</td>
<td>Counting, walking with right foot over lines</td>
<td>Clomipramine hydrochloride (75), quetiapine fumarate (200)</td>
<td>6</td>
<td>8</td>
<td>38</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>2/M/44</td>
<td>10</td>
<td>34</td>
<td>MDD</td>
<td>Fear of contamination, intrusive images of sex and violence</td>
<td>Washing, cleaning, seeking reassurance</td>
<td>Clomipramine (125)</td>
<td>9</td>
<td>4</td>
<td>34</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>3/M/51</td>
<td>13</td>
<td>38</td>
<td>MDD</td>
<td>Fear of contamination</td>
<td>Washing</td>
<td>Fluvoxamine maleate (300)</td>
<td>8</td>
<td>5</td>
<td>36</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>4/F/26</td>
<td>5</td>
<td>21</td>
<td>Dysthymia</td>
<td>Perfectionism</td>
<td>Obsessional slowness, recurring acts</td>
<td>Fluoxetine hydrochloride (60)</td>
<td>4</td>
<td>5</td>
<td>40</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>5/M/40</td>
<td>13</td>
<td>37</td>
<td>MDD</td>
<td>Fear of harming others, fear of contamination</td>
<td>Checking, washing</td>
<td>Citalopram hydrobromide (60)</td>
<td>6</td>
<td>3</td>
<td>33</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>6/F/64</td>
<td>4</td>
<td>40</td>
<td>MDD</td>
<td>Fear of contamination, fear of contamination</td>
<td>Washing, cleaning</td>
<td>...</td>
<td>...</td>
<td>6</td>
<td>3</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>7/F/21</td>
<td>13</td>
<td>8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Paroxetine (60), risperidone (1.5)</td>
<td>8</td>
<td>4</td>
<td>30</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>8/F/34</td>
<td>14</td>
<td>20</td>
<td>...</td>
<td>Fear of contamination, perfectionism</td>
<td>Washing, cleaning</td>
<td>...</td>
<td>13</td>
<td>6</td>
<td>35</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>9/M/35</td>
<td>16</td>
<td>19</td>
<td>MDD</td>
<td>Need for symmetry, perfectionism</td>
<td>&quot;Just right&quot; behavior</td>
<td>...</td>
<td>7</td>
<td>4</td>
<td>38</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>10/F/32</td>
<td>18</td>
<td>14</td>
<td>...</td>
<td>Believing in magic numbers, fear of predictions</td>
<td>Seeking reassurance</td>
<td>Clomipramine (125), haloperidol (5)</td>
<td>8</td>
<td>2</td>
<td>30</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>11/F/45</td>
<td>20</td>
<td>25</td>
<td>Panic disorder</td>
<td>Fear of dirt, need for symmetry</td>
<td>Cleaning, ordering</td>
<td>Paroxetine (60), quetiapine (250)</td>
<td>5</td>
<td>1</td>
<td>38</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>12/M/59</td>
<td>13</td>
<td>46</td>
<td>...</td>
<td>Fear of coincidence and illogical things</td>
<td>Seeking reassurance, hoarding</td>
<td>Citalopram (60), quetiapine (300)</td>
<td>4</td>
<td>2</td>
<td>33</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>13/M/55</td>
<td>14</td>
<td>21</td>
<td>...</td>
<td>Somatic obsessions</td>
<td>Checking</td>
<td>Mirtazapine (45)</td>
<td>9</td>
<td>6</td>
<td>35</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>14/M/42</td>
<td>12</td>
<td>30</td>
<td>...</td>
<td>Fear of contamination</td>
<td>Washing, cleaning</td>
<td>Citalopram (60), quetiapine (300)</td>
<td>6</td>
<td>3</td>
<td>28</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>15/M/55</td>
<td>35</td>
<td>20</td>
<td>MDD</td>
<td>Fear of contamination, intrusive images of sex and violence, need for symmetry</td>
<td>Washing, cleaning</td>
<td>...</td>
<td>3</td>
<td>4</td>
<td>29</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>16/M/64</td>
<td>6</td>
<td>48</td>
<td>...</td>
<td>Need to know everything</td>
<td>Hoarding</td>
<td>Clomipramine (225), quetiapine (600)</td>
<td>5</td>
<td>1</td>
<td>32</td>
<td>18</td>
<td>23</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Change During Open Period</th>
<th>Start of Maintenance Period, Mean (SD)</th>
<th>Change During Maintenance Period</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 8 mo of Stimulation</td>
<td>Mean (SD) [95% CI] [%]</td>
<td>12 mo</td>
<td>15 mo</td>
</tr>
<tr>
<td>Y-BOCS total score</td>
<td>33.7 (3.6)</td>
<td>16.0 (11.4)</td>
<td>15.7 (10.8) [9.9-21.5] [46]</td>
<td>&lt;.001</td>
<td>17.8 (10.1)</td>
</tr>
<tr>
<td>Obsessions score</td>
<td>16.9 (1.9)</td>
<td>8.3 (6.8)</td>
<td>8.6 (6.6) [5.5-11.5] [50]</td>
<td>&lt;.001</td>
<td>8.2 (5.6)</td>
</tr>
<tr>
<td>Compulsions score</td>
<td>19.6 (1.9)</td>
<td>9.8 (5.7)</td>
<td>7.2 (5.5) [4.1-10.0]</td>
<td>&lt;.001</td>
<td>9.5 (4.9)</td>
</tr>
<tr>
<td>HAM-A score</td>
<td>20.9 (5.9)</td>
<td>10.1 (8.3)</td>
<td>10.8 (8.1) [6.4-15.0] [51]</td>
<td>&lt;.001</td>
<td>9.7 (5.8)</td>
</tr>
<tr>
<td>HAM-D score</td>
<td>19.5 (6.7)</td>
<td>10.5 (7.8)</td>
<td>9.0 (6.2) [5.6-12.3] [46]</td>
<td>&lt;.001</td>
<td>10.3 (7.3)</td>
</tr>
<tr>
<td>BABS score</td>
<td>7.8 (5.6)</td>
<td>4.1 (5.0)</td>
<td>3.7 (5.3) [0.8-6.6] [47]</td>
<td>&lt;.001</td>
<td>4.1 (5.0)</td>
</tr>
<tr>
<td>Sheehan Disability Scale score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td>8.9 (1.1)</td>
<td>6.0 (3.5)</td>
<td>2.9 (3.1) [1.2-4.6] [32]</td>
<td>.002</td>
<td>5.4 (3.5)</td>
</tr>
<tr>
<td>Social life</td>
<td>9.0 (1.0)</td>
<td>5.2 (3.3)</td>
<td>3.7 (2.5) [1.9-5.5] [41]</td>
<td>.001</td>
<td>4.6 (3.2)</td>
</tr>
<tr>
<td>Family life</td>
<td>7.9 (1.5)</td>
<td>5.0 (3.5)</td>
<td>2.9 (2.7) [1.4-4.3] [17]</td>
<td>.001</td>
<td>4.5 (2.9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Change Between Weeks 1-2 and Weeks 3-4</th>
<th>Change During Crossover Period</th>
<th>Value 12 mo</th>
<th>15 mo</th>
<th>18 mo</th>
<th>21 mo</th>
<th>Mean (SD) [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=6)</td>
<td></td>
<td>Week 1-2 vs Week 3-4</td>
<td>Start of Crossover Period</td>
<td>After Stimulation On</td>
<td>After Stimulation Off</td>
<td>4.9 (7.6) [−12.9 to 3.2]</td>
<td>.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y-BOCS total score</td>
<td>34.2 (3.6)</td>
<td>23.3 (9.9)</td>
<td>25.8 (9.3)</td>
<td>30.7 (4.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsessions score</td>
<td>17.5 (1.7)</td>
<td>11.8 (4.7)</td>
<td>13.0 (4.5)</td>
<td>15.3 (2.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsions score</td>
<td>16.7 (2.0)</td>
<td>11.5 (6.2)</td>
<td>12.8 (4.7)</td>
<td>15.3 (2.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-A score</td>
<td>21.3 (7.7)</td>
<td>12.0 (8.0)</td>
<td>14.3 (6.9)</td>
<td>26.3 (9.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D score</td>
<td>19.7 (5.4)</td>
<td>10.8 (7.0)</td>
<td>12.7 (5.4)</td>
<td>23.5 (3.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td>After Stimulation Off vs After Stimulation On</td>
<td>4.9 (7.6) [−12.9 to 3.2]</td>
<td>.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y-BOCS total score</td>
<td>33.4 (3.6)</td>
<td>18.7 (10.6)</td>
<td>29.5 (11.4)</td>
<td>17.6 (10.1)</td>
<td>11.9 (9.3) [4.0 to 18.7]</td>
<td>.009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsessions score</td>
<td>16.4 (2.1)</td>
<td>8.7 (5.5)</td>
<td>15.2 (5.9)</td>
<td>8.0 (5.4)</td>
<td>7.2 (5.5) [2.6 to 11.8]</td>
<td>.007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsions score</td>
<td>17.0 (1.7)</td>
<td>10.0 (5.3)</td>
<td>14.2 (5.6)</td>
<td>9.6 (4.8)</td>
<td>4.6 (4.0) [1.2 to 8.0]</td>
<td>.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-A score</td>
<td>21.5 (4.9)</td>
<td>14.2 (5.8)</td>
<td>27.4 (12.0)</td>
<td>15.2 (13.5)</td>
<td>12.2 (8.4) [5.0 to 19.2]</td>
<td>.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D score</td>
<td>21.0 (6.5)</td>
<td>14.8 (5.8)</td>
<td>24.6 (9.5)</td>
<td>12.9 (10.1)</td>
<td>11.7 (8.4) [4.7 to 18.7]</td>
<td>.005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, 90%). 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 [23%]) 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

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with HAM-A scores (p = 0.772) and with HAM-D scores (p = 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
We did not observe deterioration of depression or sui-
finding in DBS for OCD,5,7 as was also seen in our study.
The Sheehan Disability Scale) showed improvement in
change between sham and active stimulation was 8.9
points. Contrary to our results, neither anxiety and de-
pression 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 suici-
dal 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 pa-

tients 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 symp-
toms and then rapidly regained clinical improvement dur-
ing the ensuing blinded active stimulation. Patients who
continued having active stimulation during the first 2 weeks
showed a minor increase in obsessive-compulsive symp-
toms, probably due to uncertainty and doubt about enter-

ing the blinded phase of the study. In this group, the base-
line Y-BOCS scores at the start of the crossover period were
higher, which was in part explained by the higher propor-
tion 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 sig-
ificant, 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 strik-
ing. All patients, even nonresponders, experienced sub-
stantial mood improvement. Therefore, no patients re-
quested to discontinue stimulation, despite the lack of
response of obsessive-compulsive symptoms. It is likely
that improvement of obsessive-compulsive symptoms de-

pends 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 se-
quential order (depressive symptoms first, anxiety symp-
toms second, obsessions third, and compulsions fourth)
and in a fixed sequence (mood improved within sec-

onds, anxiety within minutes, and obsessions within days,
while compulsions took weeks and even months to im-
prove). Finally, avoidance failed to decrease spontane-
ously 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 “nor-
mal” daily pattern and a force of habit. Cognitive behav-
ior therapy proved particularly effective in decreasing com-
pulsive behavior and avoidance. Without stimulation
(such as in the placebo-controlled phase), the gained suc-
cesses with the addition of CBT disappeared rapidly, sug-
gest ing that efficacy of CBT depends on stimulation. Our
observation of an immediate profound effect with nucleus
accumbens stimulation, along with the reported spe-
cific effect of subthalamic nucleus stimulation on com-
pulsions observed in the French sample,7 hints at the in-
v olvement of 2 different anatomical circuits in OCD. One
circuit might be associated with a mood and anxiety spec-
trum responding to accumbens stimulation, and an-
other circuit could be related to a compulsive habit spec-
trum responding to subthalamic nucleus stimulation.

Obsessions and compulsions are heterogeneous symp-
toms, 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 symp-
toms. Patients with perfectionism, hoarding, or symme-
try did not respond well to the treatment. Patients with
this subtype of OCD believe in the worthiness and sound-
ness of their symptoms and were more likely to describe
their obsessions and compulsions as egosyntonic, in har-
mony with their needs and goals and consistent with
themselves. The robustness of their obsessions and the
lack of insight into the meaninglessness of their obses-
sions were expressed in higher BABS scores, the only base-
line 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 elec-
trode contacts 2 and 3, with active stimulation more in
the area of the nucleus accumbens core around the bor-
der of the internal capsule and bed nucleus stria termi-
nalis 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 stimu-
lated between the lower and upper contacts with the 3389
electrode is 4 mm and seemed to determine nonre-
ponse or response in our sample. This finding demon-
strates the significance and importance of exact target-
ing with DBS. In future studies, larger samples are needed
further narrow the “target space” so that the most ef-
cient DBS parameters may be used.

A limitation of this study is that the double-blind pe-
riods were short, giving rise to the possibility of a car-
yover effect, which may have led to an underestima-
tion of the effect of stimulation. This study was originally
planned in a sham-controlled design with 3-month pe-
riods of on-off stimulation. We changed the 3-month du-
ration to 2 weeks because, once a considerable improve-
ment had been experienced in the open phase, patients
did not tolerate off phases owing to massive worsening
of symptoms. These findings are consistent with obser-
vations by German investigators treating major depres-
sion with nucleus accumbens stimulation.20 Another as-
pect 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
d 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.

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