Clomipramine vs Desipramine Crossover Trial in Body Dysmorphic Disorder

Selective Efficacy of a Serotonin Reuptake Inhibitor in Imagined Ugliness

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Background: Body dysmorphic disorder (preoccupation with an imagined or slight defect in appearance) is a common and disabling disorder associated with high rates of delusional symptoms and suicide attempts. Although preliminary studies suggest that serotonin reuptake inhibitors may be effective for body dysmorphic disorder, to date no controlled treatment studies have been published.

Methods: Forty patients were enrolled and 29 were randomized into a 16-week, double-blind, crossover-design study of clomipramine, a potent serotonin reuptake inhibitor, and active control desipramine, a selective norepinephrine reuptake inhibitor. Outcome measures included specific ratings of body dysmorphic disorder severity, delusionality, and functional impairment.

Results: Clomipramine was superior to desipramine in the acute treatment of body dysmorphic disorder symptoms as measured by assessment of patients’ obsessive preoccupation with perceived body defects, repetitive behaviors in response to this preoccupation, and global ratings of symptom severity. Treatment efficacy was independent of the presence or severity of comorbid diagnoses of obsessive-compulsive disorder, depression, or social phobia. Likewise, clomipramine was equally effective regardless of whether the patients had insight or held their dysmorphic misperception with delusional intensity. Clomipramine was also superior to desipramine in improving functional disability.

Conclusions: Clomipramine is more effective than desipramine in the treatment of body dysmorphic disorder and is effective even among those patients who are delusional.

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SUBJECTS AND METHODS

SUBJECTS

Patients were eligible if they were between 18 and 65 years of age, met DSM-III-R criteria for BDD, and suffered clinically significant distress or impairment in functioning due to BDD. Exclusion criteria included DSM-III-R psychotic disorders (other than delusional disorder, somatic type), bipolar I disorder, major depression with psychotic features, or current substance abuse; clinically significant suicidal ideation; known hypersensitivity to clomipramine or desipramine; or medical illness that would entail any risk while receiving clomipramine or desipramine. Patients were free of psychiatric medications for 2 weeks (6 for fluoxetine, monoamine oxidase inhibitors, or investigational drugs) prior to participation, and no concurrent psychotropic medications or cognitive or behavioral therapies were allowed during the study.

Forty subjects qualified for the study (see Table 1 and Table 2 for their profiles). On average, patients reported first experiencing BDD symptoms as teenagers, although onset was reported as early as age 5 years and as late as age 31 years; most had suffered with BDD for many years. They were concerned about a mean (SD) of 2.5 (1.3) different aspects of their appearance. The perceived defects primarily involved the head and face (n = 33), including hair (n = 14), complexion (n = 9), nose (n = 8), and eyes (n = 5). Patients also expressed dissatisfaction with their bodies (n = 19), including skin or veins (n = 6), legs (n = 5), and torso (n = 5).

None of the patients had received an adequate trial of clomipramine or desipramine in the past. Of those completing minimum treatment, 7 (30%) reported never having tried an antidepressant; 3 (13%) had inadequate trials of clomipramine, none had tried desipramine, and 6 (26%) had tried a tricyclic or monoamine oxidase inhibitor; 4 (17%) had received neuroleptics; and 12 (32%) had tried at least 1 SRI. None had a sustained therapeutic response to BDD treatment, although many had inadequate trials.

MEASURES

Primary Outcome Measures

Three clinician-rated primary outcome measures were used.

1. The BDD modification of the Yale-Brown Obsessive Compulsive Scale (BDD-YBOCS) was used to assess the severity of past-week BDD thoughts and behaviors. Piloted in the DSM-IV OCD Field Trial,2 it has demonstrated reliability, validity, and sensitivity.11 The 10-item version was used for consistency with the YBOCS literature. (2) A modification of the National Institute of Mental Health Global Obsessive-Compulsive Scale (BDD-NIMH) provided a global rating of BDD severity on a 15-point scale. (3) The Clinical Global Impression Scale, a standard scale with 7-point severity and improvement items, was applied specifically to BDD symptoms (BDD-CGI).13

Assessment of Comorbid Diagnoses

Lifetime and current Axis I disorders were diagnosed by the Structured Clinical Interview for DSM-III-R (SCID-I),16 a semistructured clinical interview. Depression severity was assessed by the 24-item Hamilton Depression Rating Scale (HAM-D).17 Obsessive-compulsive disorder severity was assessed by the YBOCS.11,12 Social anxiety severity was assessed by 2 self-administered, true-false questionnaires that do not explicitly measure social phobia, but are widely used to assess social anxiety with demonstrated reliability and validity: the 28-item Social Avoidance and Distress Scale,18 which measures social discomfort or avoidance and the 30-item Fear of Negative Evaluation Scale,19 which quantifies concerns about being judged negatively.

Assessment of Insight

Insight was assessed using the BDD modification of the Fixity of Beliefs Questionnaire,10 a direct adaptation of the Fixity of Beliefs Questionnaire for OCD. The first item was used because it explicitly addresses insight without including less relevant issues such as bizarre ness. Although the BDD version has not been assessed, the OCD version of item 1 was judged to have acceptable reliability and validity in the DSM-IV OCD Field Trial.9 Twelve patients were categorized as delusional and 10 as not delusional; 1 could not be categorized.

Assessment of Functional Disability

The Schneier Disability Profile,20 which is sensitive to the effects of social avoidance, was used to assess functional disability. It is a clinician-rated questionnaire that assesses ability to function in major life areas including work/school, family, marriage/dating, friendships, activities of daily living, and suicidal behavior.

PROCEDURE

After a telephone screen, potential participants had an in-person assessment. They were given a full explanation of the study, signed written informed consent, and were interviewed by a study psychiatrist to establish that they met all control desipramine, a selective norepinephrine reuptake inhibitor. Using these 2 tricyclic antidepressants with similar adverse effect profiles enhances the treatment blind and isolates clomipramine’s specific efficacy for BDD by controlling for nonspecific anxiolytic and antidepressant effects.

In BDD insight is often poor, and greater delusional severity is a key difference between BDD and OCD.2,3 In the DSM-IV OCD field trials, 30% of patients were completely or mostly lacking in insight regarding their OCD, but 49% of those with comorbid BDD were completely or mostly convinced their defect was real; these patients were significantly less insightful regarding their BDD than their OCD. Delusionality is of special interest because it may complicate pharmacological treatment.

In this study, we tested these hypotheses. (1) Clomipramine is more effective than desipramine in acute BDD treatment. (2) Comorbid diagnosis of major depression, social phobia, or OCD does not influence treatment outcome. (3) Delusional BDD is as likely to respond to clomipramine as nondelusional BDD. (4)
Clomipramine was more effective than desipramine in reducing functional disability.

### RESULTS

#### EFFICACY OF CLOMIPRAMINE VS DESIPRAME IN BDD

Clomipramine was superior to desipramine in the acute treatment of BDD symptoms as measured by all primary outcome measures (BDD-YBOCS, BDD-NIMH, and BDD-CGI). Thus, the first hypothesis was fully supported.

The patients’ obsessive preoccupation with perceived body defects and repetitive behaviors in response to this preoccupation, as measured by the mean (SD) BDD-YBOCS scores, were significantly lower following clomipramine treatment than following desipramine treatment (Figure 1): 16.2 (8.5) (low-moderate range) following clomipramine treatment, 20.7 (7.7) (mid-
moderate range) following desipramine treatment, and 25.4 (7.2) (severe range) at baseline. There was a significant relationship between baseline and final BDD-YBOCS scores (covariate effect: $F_{1,19} = 18.65, P < .001$). Response rates were 65% for clomipramine and 35% for desipramine, based on 25% improvement on the BDD-YBOCS ($P = .09$).

Clomipramine was also significantly more effective than desipramine in reducing overall BDD severity as measured by the BDD-NIMH (Figure 2): mean (SD) scores were 5.6 (1.8) following clomipramine treatment, 8.02 (3.1) following desipramine treatment, and 8.85 (2.1) at baseline. There was a significant relationship between baseline and final BDD-NIMH scores (covariate effect: $F_{1,19} = 4.64, P = .04$). Clomipramine was more effective than desipramine regardless of the order in which the drugs were taken (main effect for order was not significant). However, those patients who were treated with clomipramine first showed a smaller difference in their response to the 2 treatment conditions than those who were treated with desipramine first (medication 3 or-der interaction: $F_{1,21} = 5.71, P = .03$). This may be due to a carryover in the clomipramine treatment response resulting in a slow worsening in symptoms while receiving desipramine, compared with the rapid alleviation of symptoms in patients who had been taking desipramine and were switched to clomipramine. Alternatively, this interaction could be due to a difference in response to the drug taken first vs the drug taken second. Response rates were 70% for clomipramine and 30% for desipramine based on 25% improvement on the BDD-NIMH ($P = .02$).

Clomipramine was also significantly more effective than desipramine in decreasing the severity of patients’ overall illness as measured by BDD-CGI improvement ratings (Figure 3): mean (SD) scores were 2.5 (0.8) following clomipramine treatment and 3.4 (1.1) following desipramine treatment. The main effects for sequence and the medication 3 sequence interaction were not significant. Response rates were 44% for clomi-
mine and 22% for desipramine based on a score of 1 or 2 on the BDD-CGI improvement scale (P = .27).

Clomipramine was superior to desipramine at the end of phase 1 on 2 of the 3 key measures, BDD-NIMH (F1,22 = 12.06, P = .002) and BDD-CGI (F1,22 = 5.24, P = .03), but not on the BDD-YBOCS (F1,22 = 1.85, P = .19). Clomipramine resulted in significant improvement on all primary outcome measures both at the end of phase 1 and at the clomipramine end point. Results for desipramine were mixed: improvement was not significant on the BDD-NIMH (phase 1 or clomipramine end point) or on the BDD-CGI after phase 1; improvement was significant on the BDD-YBOCS (phase 1 and clomipramine end point) and on the BDD-CGI at clomipramine end point. Overall, clomipramine effected much greater improvement than desipramine.

**ADVERSE EFFECTS**

Adverse effects for clomipramine and desipramine were similar. They included dry mouth (84% for clomipramine and 62% for desipramine), sedation or tiredness (80% and 52%), constipation (72% and 52%), sweating (44% and 28%), and tremor (44% and 14%). Desipramine tended to produce greater insomnia (41% vs 28% for clomipramine). None of these differences reached statistical significance. Despite adverse effects, no patients dropped out of the study while receiving clomipramine in either arm; 4 patients dropped out while receiving desipramine owing to adverse effects.

**COMORBID DIAGNOSIS AND TREATMENT OUTCOME**

Twenty-two (76%) of the 29 subjects randomized into the study had at least 1 current comorbid diagnosis. Eighteen (62%) had at least 1 of the key comorbid diagnoses: 13 (45%) suffered from depression, 7 (24%) had social phobia, and 7 (24%) had OCD (see Table 2). As predicted, overall comorbid diagnoses (depression, social phobia, OCD, or none) did not affect treatment outcome as measured by the BDD-CGI. In addition, the severity of comorbid symptoms at baseline was not related to clomipramine treatment efficacy. Specifically, there was no correlation between post-clomipramine BDD-CGI improvement ratings and baseline severity of depression, obsessions and compulsions, or social anxiety.

However, there were some important specific differences in treatment efficacy for comorbid symptoms. Depressive symptoms were reduced more by clomipramine treatment than by desipramine treatment (t12 = 2.43, P = .02); mean (SD) HAM-D scores were 9.33 (6.75) vs 14.00 (7.99) at end point and 18.06 (9.38) at baseline. For patients with comorbid diagnoses of depression, clomipramine also reduced depressive symptoms more than desipramine (t12 = 2.54, P = .03); HAM-D scores were 10.85 (6.93) vs 18.00 (6.28) at end point, and 21.27 (10.19) at baseline. Obsessive-compulsive symptoms also decreased more on clomipramine than desipramine (t12 = 3.01, P = .007); YBOCS scores were 15.88 (8.88) vs 21.25 (7.73) at end point and 25.69 (7.13) at baseline.

**DEGREE OF INSIGHT AND TREATMENT OUTCOME**

Clomipramine was more effective than desipramine among both delusional and nondelusional patients; however, there is a statistically significant interaction suggesting that clomipramine was slightly more effective among patients who had no insight while the reverse was true for desipramine. This interaction was found for all 3 primary outcome measures and was independent of baseline severity (Table 3). The more delusional the patient was at baseline, the more he or she improved after clomipramine treatment (significant negative correlation between baseline delusional and BDD-CGI improvement after clomipramine treatment: r = −0.56, P = .007).

Compared with baseline, clomipramine resulted in significant improvement in fixity of beliefs both after phase 1 (t10 = 2.50, P = .03) and at clomipramine end point (t12 = 2.96, P = .007); desipramine did not significantly improve fixity of beliefs at either time point.
Table 3. Interaction Between Delusional Palities of Beliefs and Drug Treatment*

<table>
<thead>
<tr>
<th>Measure</th>
<th>After Clomipramine†</th>
<th>After Desipramine†</th>
<th>ANCOVA, Drug × Insight Interaction</th>
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<td></td>
<td>Nondelusional</td>
<td>Delusional</td>
<td>Nondelusional</td>
</tr>
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<td>BDD-CGI improvement</td>
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<td>2.13 (0.69)</td>
<td>3.20 (1.30)</td>
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<td>BDD-NIMH</td>
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<td>5.25 (1.59)</td>
<td>7.50 (2.82)</td>
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<tr>
<td>BDD-YBOCS</td>
<td>16.90 (7.73)</td>
<td>15.67 (9.92)</td>
<td>19.25 (8.46)</td>
</tr>
</tbody>
</table>

* Data are presented as mean (SD) unless otherwise indicated. ANCOVA indicates analysis of covariance; BDD-CGI, Clinical Global Impression Scale modified for body dysmorphic disorder; BDD-NIMH, National Institute of Mental Health Global Obsessive-Compulsive Scale modified for body dysmorphic disorder; and BDD-YBOCS, Yale-Brown Obsessive Compulsive Scale Modified for BDD.
† After clomipramine treatment, all measures were lower for delusional than nondelusional patients. After desipramine treatment, all measures were lower for nondelusional than delusional patients.

Figure 4. Change in functional impairment over time as measured by the Schneier Disability Profile score (N = 20, $F_{1,17} = 17.43, P = .001$).

**EFFECT OF TREATMENT ON FUNCTIONAL DISABILITY**

Clomipramine was more effective than desipramine in improving functional disability as measured by the Schneier Disability Profile (Figure 4): mean (SD) scores were 8.6 (6.1) after clomipramine treatment, 12.4 (6.9) after desipramine treatment, and 13.2 (6.6) at baseline. There was a significant relationship between baseline and final Schneier Disability Profile scores (covariate effect: $F_{1,17} = 13.29, P = .002$).

**COMMENT**

The potent SRI clomipramine was significantly superior to the selective norepinephrine reuptake inhibitor desipramine on all primary outcome measures of BDD severity and symptoms.

Fixity of BDD beliefs did not limit treatment outcome; while receiving clomipramine delusional patients improved at least as much as nondelusional patients and perhaps more. This is of clinical importance, suggesting that delusional patients may not require neuroleptic treatment and thus might be spared possible adverse effects associated with long-term neuroleptic use. This extends the work of Phillips et al., who found that 71% of delusional patients responded to open fluvoxamine treatment vs 61% of nondelusional patients, and that delusionaly responded to treatment. We also found that clomipramine significantly improved fixity of beliefs whereas desipramine did not. Note that item 1 of the BDD Fixity of Beliefs Scale needs to be validated as the OCD version has been. These delusionality findings deserve further investigation.

This study is strengthened by the use of desipramine, an active control, which serves not only to protect the double-blind (since both agents have similar adverse effect profiles) but also controls for nonspecific antidepressant and anxiolytic effects. However, desipramine is not a perfect control. Although it is unlikely that BDD would respond to placebo, since it is not responsive to a broad range of other treatments (including tricyclics, neuroleptics, monoamine oxidase inhibitors, and benzodiazepines), a trial vs placebo, the “gold standard” control, would clearly establish that clomipramine is not simply better than desipramine. In addition, while a crossover design is a strong one since patients serve as their own controls, there are also problems inherent in crossover designs, such as potential carryover effects. Notably, our results were confirmed based on the study’s first arm alone and so cannot be attributed to crossover-design artifacts. It would be valuable to follow up this research with a placebo-controlled parallel-design study. It is also possible that a longer trial would lead to an even greater reduction in symptoms and a greater percentage of responders with clomipramine. Lack of a maintenance phase after the acute crossover trial is also a limitation. Thus, a longer trial and long-term maintenance data would be useful. Also, the mean (SD) dose of clomipramine, 138 (87) mg/d, was rather low owing to flexible dosing to minimize adverse effects. Higher doses might have resulted in a greater percentage of treatment responders to clomipramine but at the cost of more dropouts. Although patients experienced adverse effects typical of tricyclic antidepressants while receiving clomipramine, they tolerated these well and no patients dropped out while receiving clomipramine.

Because clomipramine was superior to desipramine in alleviating BDD symptoms, the data demonstrate that clomipramine has a specific anti-BDD effect; patients’ BDD does not improve simply because of clomipramine’s antidepressant and antianxiety effects. This is further supported by the absence of an effect of baseline comorbidity or severity on BDD outcome. These findings are similar to the selective efficacy for SRIs in OCD treatment and differ from findings for other mood and...
anxiety disorders. Along with overlap in clinical symptoms, course of illness, and comorbidity, our results suggest that BDD may be closely related to OCD. The greater effectiveness of clomipramine compared with desipramine in treating depression in patients with BDD suggests that their depression may be secondary to their BDD.

There is also evidence for greater improvement of functional disability with clomipramine treatment than with desipramine treatment. This is noteworthy given the very high level of functional disability inherent in BDD, especially when demonstrable over such a short time period.

In conclusion, the positive findings of this first controlled study in BDD are a significant initial step in establishing the efficacy of clomipramine in the treatment of this debilitating disorder, even among delusional patients.

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