# Addition of Cognitive-Behavioral Therapy for Nonresponders to Medication for Obsessive-Compulsive Disorder: A Naturalistic Study

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***Objective:*** The best currently available treatments for obsessive-compulsive disorder (OCD) are serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT). It is generally recommended that patients who have been unsuccessfully treated with SRIs should receive supplementary CBT, although few studies have yet to investigate the proposal's validity. The purpose of the present study is to examine the effectiveness of CBT on a sample of nonselected, pharmacologically treatment-resistant OCD patients.

***Method:*** Thirty-six OCD patients (based on DSM-IV criteria) who had not responded to at least 1 adequate SRI trial conducted in our outpatient clinic were treated from January 2000 through April 2004 with CBT, incorporating exposure and ritual prevention. The therapy was conducted in a naturalistic setting and manualized guidelines were adapted to each patient. Pharmacologic treatment underwent no changes during the trial period. Outcome measures included the Yale-Brown Obsessive Compulsive Scale, the Clinical Global Impressions-Severity of Illness scale, and the Global Assessment of Functioning scale. The primary outcome measure was a rating of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale (CGI-I).

***Results:*** Two patients (5%) refused CBT after 1 session, and 10 patients (28%) dropped out of the study. Three of the 24 remaining patients completed the trial at 6 months (T1) but did not follow through up to 12 months (T2). The 21 patients completing CBT showed statistically significant improvement ($p < .0001$) during follow-up on all outcome measures. At T2, 15 (42%) of 36 patients were rated as being "much improved" or "very much improved," as measured by the CGI-I. Symptom reduction was clinically modest but important, with nearly all patients presenting residual symptoms.

***Conclusion:*** CBT could be usefully added to pharmacologic treatments for severe, real-world, medication-resistant OCD patients.

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The 2 current treatments of choice for obsessive-compulsive disorder (OCD) are (1) serotonin reuptake inhibitors (SRIs), e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and clomipramine and (2) cognitive-behavioral therapy (CBT) incorporating exposure and ritual prevention (E/RP).[1–5] Both treatments are found to be equally effective,[6,7] but neither SRIs nor CBT alone have a 100% success rate. Approximately 50% to 60% of patients who receive medication respond, and those who respond achieve an approximately 40% reduction in symptoms.[8–10] Moreover, pharmacologic treatment can lead to compliance problems, particularly in the long term. CBT has a higher completion or partial response rate (on average, 70% to 90%),[9,11,12] but up to 25% of patients refuse it,[12,13] and 13% to 20% do not complete it.[7,14,15] An expert consensus panel has recommended that patients unsuccessfully treated with SRIs be supplemented with CBT.[16] Yet, to the best of our knowledge, only 3 studies have investigated the validity of this suggestion. Simpson et al.[17] published an open CBT trial, using E/RP for 6 patients who had remained symptomatic after 1 adequate SRI trial. Results showed that the addition of 17 E/RP sessions to SRI treatment led to a significant reduction in OCD symptoms. Similar results were obtained by Kampman et al.[18] in an open study of 14 patients who were nonresponders to 12 weeks of fluoxetine (60 mg/day). Twelve supplemental sessions of CBT, including E/RP and continuation of fluoxetine, resulted in OCD symptom reduction. In a wait-list–controlled, open trial, Tolin et al.[19] showed that 15 sessions of CBT incorporating E/RP represented a

  

Table 1. Drug Dose Requirements for Study Inclusion[a]

| Medication | Minimum Dose |
|---|---|
| Citalopram | 60 mg/d |
| Fluoxetine | 60 mg/d |
| Fluvoxamine | 300 mg/d |
| Paroxetine | 60 mg/d |
| Sertraline | 200 mg/d |
| Venlafaxine | 375 mg/d |
| Clomipramine | 225 mg/d |

[a]Duration at minimum dose: 12 weeks.

helpful treatment for 20 patients with a history of inadequate response to multiple adequate SRI trials. Overall, these results are encouraging, but we believe that it is still unclear whether these findings are applicable to all OCD nonresponder patients treated in routine clinical practice. In fact, the 3 above-cited studies excluded patients with some Axis I comorbidity or with alcohol or substance use/dependence, and only 1 study[19] included severe OCD patients with multiple failed medication trials—i.e., patients who are not so rarely encountered in clinical practice.

The purpose of the present study was to investigate the effectiveness of CBT including E/RP for severe, real-world, medication-resistant nonresponder OCD patients.

## METHOD

### Patients

This study was conducted in an outpatient clinic that specializes in mood and anxiety disorders. Patients included in the study were residents of Rome or of one of Italy's central regions. They were evaluated consecutively from January 2000 through April 2004 and met the following criteria: (1) they were 18 to 65 years of age, (2) they met DSM-IV[20] criteria for OCD, (3) they had suffered from OCD for at least 1 year, and (4) they were nonresponders to at least 1 adequate SRI trial conducted in our clinic (Table 1). We defined nonresponders as patients at trial's end still meeting DSM-IV criteria for OCD and having a Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[21,22] total score of ≥ 16. Exclusion criteria were diagnoses of schizophrenia or mental retardation. All patients gave written informed consent for the anonymous use of their clinical records, and a local ethical committee approved the research project.

Thirty-six patients were enrolled in the study; the sample's demographic and clinical variables are shown in Table 2. Fifteen patients (42%) presented 1 lifetime comorbid Axis I disorder, and 6 patients (16%) had 2 or more of the following: bipolar disorder (13 patients), anxiety disorder (9 patients), major depressive disorder (5 patients), and eating disorder (4 patients).

Twenty-eight percent (N = 10) of the sample had failed to respond to 1 adequate SRI trial, 44% (N = 16) had shown no response to 2 to 4 adequate SRI trials, and 28% (N = 10) were nonresponders to 5 or more adequate SRI trials. All the trials had been conducted in our clinic by a senior research psychiatrist (A.T.). Fifteen patients (42%) had been treated with clomipramine; 17 (47%), with fluvoxamine; 5 (14%), with fluoxetine; 21 (58%), with 2 selective serotonin reuptake inhibitors (SSRIs)—e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; 21 (58%), with clomipramine and an SSRI; and 14 (38%), with clomipramine or an SSRI and augmentation drugs[23]—e.g., atypical antipsychotics, buspirone, trazodone, or L-tryptophan.

Table 2. Baseline Demographic and Clinical Variables of Treatment-Resistant Obsessive-Compulsive Disorder Patients (N = 36)

| Variable | Value |
|---|---|
| Age, mean ± SD, y | 31 ± 8 |
| Men, N (%) | 23 (63) |
| Married, N (%) | 7 (19) |
| Education, mean ± SD, y | 15 ± 3 |
| Employed full time, N (%) | 18 (50) |
| Student/housewife, N (%) | 13 (36) |
| Age at onset, mean ± SD, y | 18.9 ± 6.8 |
| Length of illness, mean ± SD, y | 13.4 ± 9.8 |
| Y-BOCS total score, mean ± SD | 28.2 ± 4.4 |
| Y-BOCS insight item score, mean ± SD | 2.8 ± 1.1 |
| CGI-S score, mean ± SD | 5.5 ± 1.0 |
| GAF score, mean ± SD | 46.6 ± 10.4 |
| Patients with previous hospitalization, N (%) | 4 (11) |
| Alcohol or substance use/dependence, N (%) | 4 (11) |
| Lifetime comorbid Axis I disorder, N (%) | 21 (58) |

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

### Treatments

At the beginning of the study, 6 patients (17%) were taking clomipramine; 4 (11%), fluvoxamine; 1 (3%), fluoxetine, sertraline, or venlafaxine; 11 (31%), clomipramine and an SSRI; and 10 (28%), clomipramine or an SSRI and augmentation drugs. Mean duration of treatment at adequate doses (as defined in Table 1) was 8.3 (SD 4.1) months. Patients with bipolar disorder were taking 1 or more concomitant mood stabilizer(s): lithium (mean dose, 0.67 mEq/L; range, 0.60–0.75 mEq/L) in 4 patients, carbamazepine (mean dose, 660 mg/day; range, 400–900 mg/day) in 5 patients, valproate (mean dose, 675 mg/day; range, 600–900 mg/day) in 4 patients, topiramate (mean dose, 108 mg/day; range, 75–150 mg/day) in 3 patients, and olanzapine (mean dose, 11 mg/day; range, 2.5–20 mg/day) in 2 patients. Eight patients were taking benzodiazepines (mean diazepam-equivalent dose, 4.7 mg/day; range, 3–6 mg/day). Pharmacologic treatment had been effective (i.e., patients no longer met DSM-IV criteria at CBT baseline) for both major depressive disorder and anxiety disorder, for 2 of 4 cases of eating disorder, and for 5 of 13 cases of bipolar



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Table 3. Outcome Measures for Intent-to-Treat Sample (N = 36)

| Scale | Time Point[a] | | | | Comorbidity[a] | | | Comorbidity × Time, |
|---|---|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | F | Yes | No | F | F |
| Y-BOCS score | | | | | | | | |
| Total | 28.2 ± 4.4 | 24.8 ± 5.2 | 22.9 ± 5.9 | 33.73* | 24.7 ± 6.2 | 26.2 ± 7.3 | 0.92 | 1.21 |
| Obsession | 14.6 ± 2.6 | 13.0 ± 2.6 | 12.2 ± 3.0 | 25.12* | 13.2 ± 3.2 | 13.3 ± 3.8 | 0.01 | 2.96 |
| Compulsion | 13.7 ± 4.0 | 11.8 ± 3.9 | 10.7 ± 4.2 | 23.98* | 11.5 ± 4.9 | 12.9 ± 5.8 | 1.29 | 0.16 |
| Insight | 2.8 ± 1.1 | 2.4 ± 1.3 | 2.0 ± 1.4 | 29.07* | 2.5 ± 1.6 | 2.3 ± 1.9 | 0.24 | 2.23 |
| CGI-S score | 5.5 ± 1.0 | 5.0 ± 1.4 | 4.6 ± 1.4 | 27.05* | 5.0 ± 1.6 | 5.2 ± 1.9 | 0.11 | 0.01 |
| GAF score | 46.6 ± 10.4 | 51.4 ± 12.2 | 55.5 ± 13.6 | 36.47* | 52.2 ± 15.4 | 49.7 ± 18.2 | 0.40 | 0.94 |

[a]Values are presented as mean ± SD.
*p Value < .0001.
Abbreviations: CGI = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, T0 = baseline, T1 = 6 months, T2 = 12 months, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

disorder. Pharmacologic treatment for OCD was not changed during the trial period; clinical conditions were monitored by the first author (A.T.) with follow-up visits occurring as required, with a frequency ranging from every week to every few months.

CBT was conducted by 4 cognitive-behavioral psychologists (L.S., G.B., D.D.S., R.F.), all of whom had at least 5 years' experience in treating OCD. CBT consisted of imaginal and in vivo exposure, ritual prevention and/or delay, cognitive therapy, and other ad hoc interventions used to supplement E/RP strategies. Patients were treated in a naturalistic setting, in the sense that the manualized guidelines[24] were adapted to each patient by taking due account of level of insight into the senselessness of OCD symptoms, treatment adherence, and the presence of comorbid Axis I disorder. Therapy sessions were scheduled flexibly and jointly by the therapist and patient. Patients received an average of 4 sessions per month during the first 4 months and then continued with 1 to 4 sessions per month. CBT duration was not fixed in advance, which follows the real-world practice of ending treatment when patients report either feeling better or feeling that therapy is no longer helping them. We provided a mean of 30.4 (range, 6–46) CBT hours, excluding patients who had a single session before withdrawing from the study.

### Procedure

Obsessive-compulsive symptoms were assessed by the Y-BOCS; clinical severity of illness, by the Clinical Global Impressions-Severity of Illness scale (CGI-S)[25]; and overall level of functioning, by the Global Assessment of Functioning (GAF) scale.[26] The scales were administered at baseline (T0) and at 6 (T1) and 12 (T2) months after starting CBT. The Clinical Global Impressions-Improvement scale (CGI-I)[25] was used to evaluate patient improvement at T1 and T2. All assessments were conducted by the first author, who was uninvolved in CBT. The primary outcome measure was a rating of "much improved" or "very much improved" on the CGI-I.

### Statistical Analysis

We conducted an intent-to-treat analysis; missing data for dropouts and noncompleters were replaced by the last observation carried forward. Data were analyzed by using Number Cruncher Statistical Systems software (Number Cruncher Statistical Systems, Kaysville, Utah). The Wilcoxon signed-rank test was used for categorical data (e.g., CGI-S and CGI-I scores), and continuous variables (e.g., Y-BOCS and GAF scores) were analyzed using a repeated-measures analysis of variance (ANOVA), with time as the repeated measure. Significant ANOVAs were followed up with within-group t tests comparing time points T0 with T1 and T1 with T2. All p values (based on 2-tailed tests) were examined at $\alpha = .05$.

## RESULTS

Two patients (5%) refused CBT after 1 session; 10 patients (28%) dropped out during the study—6 before T1 and 4 before T2. Of the 28 patients remaining, 3 completed the trial at 6 months but did not follow through to 12 months. The sample was therefore made up of 28 patients at T1 and 21 patients at T2. Five of the dropout patients (50%) reported that CBT was ineffective for them, 3 (30%) moved to another city, and 2 (20%) were hospitalized for a manic episode.

Table 3 shows the variation of mean Y-BOCS, CGI-S, and GAF scores from T0 to T1 and from T1 to T2. All outcome measures showed statistically significant improvement ($p < .0001$) during follow-up. At final assessment, conducted 12 months after the beginning of CBT, the mean reduction in Y-BOCS total scores was 19%; in Y-BOCS insight subscale scores, 28%; and in CGI-S scores, 16%. General functioning had also improved, as shown by a 19% increase in GAF scores. At T2, 42% (15/36) of the patients were rated as being "much improved" or "very much improved" (CGI-I), and 4 of 36 patients obtained a Y-BOCS total score of < 16. As shown in Table 3, presence of comorbidity did not significantly correlate with outcome measures.

  

## DISCUSSION

Some caveats to our findings must be considered. First, the present clinical study had all the methodological limitations inherent to a naturalistic study; in particular, the study was neither double blind nor placebo controlled. Second, the possibility of type II error cannot be ruled out due to the relatively small sample size. Moreover, we cannot know if the improvement observed was partially or wholly attributable to longer continuance of medication, although the mean duration of SRI treatment before CBT baseline was 8.3 months. Lastly, we used presence/absence of DSM-IV criteria and not ad hoc scales to monitor mood and anxiety symptoms. Thus, we cannot exclude the possibility that the reduction in OCD symptoms observed in patients with bipolar disorder might have been at least partially related to mood fluctuations. In spite of these limitations, our study provides useful information about CBT treatment of a real-world sample of pharmacologically treatment-resistant OCD patients. The study shows that including E/RP in CBT can represent a helpful strategy for treating nonresponders to OCD medication. The combination of SRIs and CBT resulted in a modest yet significant reduction in OCD symptoms and a substantial improvement in insight and overall level of functioning.

The results of the present study are generally consistent with the findings of Simpson et al.,[17] Kampman et al.,[18] and Tolin et al.[19] Indeed, overall, the 4 studies show that CBT supplementation improves OCD symptoms in patients who have failed to respond to 1 or more adequate SRI trials. Nevertheless, the percentage of "improved" patients was greater for Simpson et al.[17] (86%), Kampman et al.[18] (77%), and Tolin et al.[19] (66%) than it was for the present study (42%). Furthermore, the other 3 studies showed a higher mean reduction in Y-BOCS total scores (49% in Simpson et al.,[17] 41% in Kampman et al.,[18] and 39.5% in Tolin et al.[19]) than that observed in the present study (19%). Similarly, at the end of the study, our patients were globally more symptomatic (mean Y-BOCS total score = 22.9 ± 5.9) than the patients in Simpson et al.,[17] Kampman et al.,[18] and Tolin et al.,[19] who had mean ± SD Y-BOCS total scores of 12.2 ± 4.3, 15 ± 6.5, and 15.9 ± 5, respectively. Yet, we believe that the lower degree of improvement shown by patients in the present study could be due to cohort differences, given that our study was conducted on a severely ill patient sample with long-term illness, high frequency of comorbidity, failure to respond to 2 or more adequate trials in 72% of the cases, poor insight into the senselessness of OCD symptoms, and high Y-BOCS and CGI-S baseline scores. In fact, our sample represented the more severe medication-resistant OCD patients treated in clinical practice. The samples examined in the other 3 studies[17–19] had a less severe degree of illness (mean ± SD Y-BOCS total baseline scores were 23.8 ± 2.6 in Simpson et al.,[17] 25.7 ± 5.3 in Kampman et al.,[18] and 25.1 ± 5.4 in Tolin et al.[19]) and, with the exception of the Tolin et al.[19] sample, had failed only 1 SRI trial. Nevertheless, the different findings yielded may also have been due to differences in treatment.

The CBT used in our study was practiced in a naturalistic setting; manual procedures were adapted to each patient's needs, E/RP was supplemented with other cognitive and behavioral interventions as needed, sessions were scheduled flexibly, and treatment duration was not prefixed. These changes in protocol were made in an effort to enhance adherence to treatment and to render the therapy more applicable to the typical clinical setting. Conversely, the number of sessions in the other 3 studies[17–19] was pre-arranged; therapists strictly followed a specific protocol in Simpson et al.,[17] Kampman et al.,[18] and—to a lesser extent—Tolin et al.[19] Sessions were scheduled twice a week in Simpson et al.[17] and in a flexible dose ranging from 1 to 5 per week in Tolin et al.[19] We do not know whether more rigorously structured and manualized sessions and/or a higher number of treatments per week would have been more effective. However, the number of sessions per week in our study was the same as in Kampman et al.[18] and in other studies;[19,27] no relationship between frequency of sessions and treatment outcome emerged.

Our results suggest that the consensus panel advice[16] to use additional CBT incorporating E/RP in nonresponders to OCD medication could be usefully applied to more severe real-world samples—even if these patients have failed 2 or more medication trials, have 1 or more lifetime comorbid Axis I disorders, and have alcohol or substance use/dependence. Nevertheless, the effectiveness of CBT is lower in this population than in treatment-naive patients,[9] and improvement is achieved slowly. All outcome measures for our sample showed gradual but continuous improvement from baseline to 6 months and from 6 months to 12 months of treatment. The most promising results were the increase of insight into the senselessness of OCD symptoms and the improvement of general functioning. OCD symptoms decreased significantly but modestly, with nearly all patients presenting residual symptoms. Our intention is to verify whether clinical changes persist over time; the study is in progress, and follow-up data will be presented in a successive report.

Further, more sophisticated randomized controlled studies with large samples are necessary, both to confirm the effectiveness of supplemental CBT in pharmacologically treatment-resistant OCD patients and to identify outcome predictors for this disabling disorder.

*Drug names:* buspirone (BuSpar and others), carbamazepine (Equetro, Tegretol, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), diazepam (Valium and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva,

and others), sertraline (Zoloft and others), topiramate (Topamax and others), venlafaxine (Effexor and others).

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