Long-Term Follow-Up and Predictors of Clinical Outcome in Obsessive-Compulsive Patients Treated With Serotonin Reuptake Inhibitors and Behavioral Therapy

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Background: The objective of this study was to examine the long-term course of obsessive-compulsive disorder (OCD) in patients treated with serotonin reuptake inhibitors (SRIs) and behavioral therapy and to identify predictors of clinical outcome.

Method: Sixty outpatients meeting DSM-III-R or DSM-IV criteria for OCD were followed up for 1 to 5 years (mean = 2.5 years). All of them received prolonged pharmacologic therapy with an SRI.

Results: Thirty-seven patients (61.7%) completed an adequate behavioral treatment. At long-term assessment, 22 patients (36.7%) exhibited a global Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score greater than 16 or a final reduction in Y-BOCS global score of less than 35% and were considered nonresponders. Patients who completed behavioral therapy showed a significant decrease in Y-BOCS compulsions subscale score ($p = .01$), whereas no significant differences in either Y-BOCS global or obsessions subscale scores between those who did and those who did not undergo behavioral therapy were detected. Obsessions of sexual/religious content were the unique factor related to a poorer long-term outcome.

Conclusion: A substantial number of OCD patients showed persistent disabling symptoms at the long-term follow-up in spite of combined pharmacologic and behavioral treatment. Major benefits from behavioral therapy appeared to be the improvement of ritualistic behaviors. Sexual/religious obsessions predicted poorer long-term outcome, whereas short-term response to SRI treatment failed to achieve predictive value in the long-term course of OCD.

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Initial studies on the long-term course of obsessive-compulsive disorder (OCD), carried out before specific therapeutic approaches were available, highlighted the natural tendency of the disorder to chronicity.[1–3] The presence of moderate or atypical symptoms, brief duration of the disorder before starting treatment, and the absence of abnormal personality traits were associated with a better prognosis.[4]

More recent reports based on extensive use of specific behavioral and pharmacologic approaches have attempted to analyze the long-term efficacy of these therapeutic strategies as well as the existence of outcome predictors. Initial retrospective studies reported persistence of obsessive symptoms of moderate-to-severe intensity in 50% to 80% of patients, mainly treated with behavioral techniques.[5–7] Subsequent prospective studies, based on pharmacologically treated patients, reported similar results.[8–11] In the first study with clear clinical definitions of response, Eisen et al.[12] have recently reported a probability of complete clinical remission of 12% of OCD patients, with partial remission in 47% of patients and subsequent relapses in 48%. Nevertheless, the combined use of pharmacologic and behavioral therapies is reported in less than 20% of the samples described in the literature.

The results obtained to date concerning the existence of outcome predictor variables are scarce and often contradictory. Factors such as age or precocious onset of the disorder do not predict the course of OCD,[8,9] neither do differences appear to exist in the course with regard to

gender, although some authors report a greater tendency in women toward episodic course.[13] Other factors such as the initial severity of the obsessive illness,[13–16] the lack of response to short-term treatment,[5] the presence of familial psychiatric history,[5,17,18] and the comorbidity with chronic tic disorder[17,19] have not been conclusively associated with a specific course pattern.

The aim of the current study was to assess the long-term outcome of a sample of 60 obsessive patients who were exhaustively treated using a standardized pharmacologic and behavioral approach for 1 to 5 years. The questions raised were (1) whether the long-term outcome of these pharmacologically and behaviorally treated patients was different from that in previous reports, (2) whether the response to the initial pharmacologic treatment permitted a forecast of the long-term prognosis of OCD, (3) whether those patients who completed an adequate behavioral therapy protocol were further improved at follow-up compared with those who did not, and (4) whether any sociodemographic and/or clinical variable existed that would have prognostic value in relation to the long-term course of OCD.

METHOD

Subjects

Sixty consecutive outpatients (40 male and 20 female) at the Clinical and Research Unit at the Ciudad Sanitaria y Universitaria de Bellvitge (Barcelona, Spain) from 1993 through 1998 participated in the study. All met DSM-III-R or DSM-IV criteria for OCD[20] and had undergone standardized OCD treatment in our unit for a minimum period of 1 year. All patients gave written informed consent regarding their participation in the study after being informed about its features. Exclusion criteria were past history of psychoactive substance abuse, age under 18 or over 65 years, and severe organic or neurologic pathology, except tic disorder. Comorbidity with other DSM-IV Axis I disorders was not considered an exclusion criterion, provided OCD was the main diagnosis and the primary reason for seeking medical assistance. During the selection period, 4770 outpatients were remitted for examination at the Department of Psychiatry of our hospital, of whom 115 (2.4%) met DSM-IV criteria for OCD. From these patients, 22 were excluded by the exclusion criteria, 17 refused to take part in the study, and 16 patients dropped out from the study before finishing the minimum follow-up period (1 year).

The mean ± SD age of the patients was 30.2 ± 10 years (range, 18–63 years), and the mean age at onset of the disorder was 17.5 ± 7.6 years (range, 5–52 years). At the time of their first assessment in our center, the previous duration of the disorder was 11.9 ± 10.1 years (range, 1–49 years). Only 26.7% (N = 16) of patients had not received adequate previous pharmacologic treatment as defined by the OCD Expert Consensus Guidelines,[21] 36.7% (N = 22) had completed at least one correct therapy, 16.7% (N = 10) had undergone 2 pharmacologic strategies, and 20.0% (N = 12) had proved resistant to 3 or more pharmacologic trials. Seventy percent of the patients (N = 42) were single, and only 33.3% (N = 20) were engaged in remunerated employment.

Clinical Assessment

Two psychiatrists (P.A. and J.M.M.) independently assessed all patients to decide on their inclusion in the study. Information was obtained on both sociodemographic (age, sex, marital status, level of education, and employment situation) and clinical variables (age at onset of the disorder and previous OCD treatments). The severity of OCD was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),[22,23] which establishes the following severity levels: subclinical (score of 0–7), mild (8–15), moderate (16–23), severe (24–31), and extreme (32–40). Obsessive symptomatology was assessed by means of the Y-BOCS Symptom Checklist, considering the 5 factors recently reported as the principal dimensions of obsessive illness: "symmetry/ordering," "hoarding," "contamination/cleaning," "aggressive/checking," and "sexual/religious."[24] The Hamilton Rating Scale for Depression (HAM-D)[25] was used to assess the severity of depressive symptoms.

The presence of past familial psychiatric history in first-degree relatives was established according to Family History Research Diagnostic Criteria.[26] The Structured Clinical Interview for DSM-III-R (SCID-II)[27] was used to assess the presence of personality disorders according to DSM-III-R criteria.

Treatment Across Follow-Up

The severity of obsessive-compulsive and depressive symptoms was assessed at baseline. After this initial assessment, all patients received pharmacologic treatment for OCD that took into account their response to previous therapies. Initial pharmacologic therapies employed were clomipramine, 225 to 300 mg/day (N = 27); fluoxetine, 60 to 80 mg/day N = 10); and fluvoxamine, 300 mg/day (N = 11). In those patients with previous history of resistance to 3 adequate trials of a serotonin reuptake inhibitor (SRI) (N = 12), a combination of clomipramine, 225 mg/day, and fluvoxamine, 300 mg/day, was started. Full doses were maintained for a period of 12 weeks, after which changes in the severity of obsessive symptomatology were assessed using the Y-BOCS. We considered this second assessment as a measurement of the short-term response to pharmacologic treatment. A 35% or greater improvement in global Y-BOCS score or a final Y-BOCS score less than 16 was established as the criterion of clinical response. Patients with mild OCD at baseline (global Y-BOCS score from 8 to 15) were considered responders

only if they exhibited a reduction of 35% or more in global Y-BOCS score, since they already fulfilled the second criterion of response (final Y-BOCS score < 16).

After these first 12 weeks, all patients were offered specific behavioral therapy for OCD, mainly involving exposure and response prevention, carried out by a trained psychotherapist (D.M.), for an average of 20 weekly 1-hour sessions. Stable pharmacologic treatment was maintained during the behavioral therapy. Changes in Y-BOCS obsessive-compulsive severity scores from before start of behavioral therapy were assessed. The same criterion of response used during the first 12 weeks of the study (minimum reduction in global Y-BOCS score of 35% or final Y-BOCS score less than 16) was used.

Those patients who were considered nonresponders after completing behavioral therapy and those who rejected or dropped out of this treatment after the first sessions were switched from their initial serotonergic compound to another SRI. Full doses were then maintained for 12 weeks, after which changes in obsessive-compulsive symptoms were assessed. Treatment was enhanced with low doses of neuroleptics (haloperidol, 1–3 mg/day, or risperidone, 1–3 mg/day) in all patients with associated chronic tic disorder and/or schizoid personality disorder. We applied this treatment strategy (switch to different pharmacologic compound after absence of response to 12 weeks of treatment) throughout the study. All patients received treatment for a minimum period of 1 and a maximum of 5 years. Since we were interested in long-term outcome of OCD patients, we considered 1 year as a reasonable minimum follow-up period and established 5 years as the maximum outcome period to avoid excessive withdrawals.

Statistical Analysis

Student t tests for paired samples were used to analyze changes in Y-BOCS global and subscales scores between baseline and first assessment after 12 weeks of treatment with SRI and between baseline and long-term assessment after 1 to 5 years of treatment.

To study the differences in the long-term follow-up outcome, patients were divided into 2 groups with regard to their response to treatment. A minimum reduction in global Y-BOCS score of 35% or a final Y-BOCS score less than 16 was considered as response to treatment. Patients were classified as responders if they fulfilled either or both of the 2 criteria. A final reduction in Y-BOCS score less than 35% or a final Y-BOCS score of 16 or greater was considered an indicator of nonresponse. Student t tests for independent data and the chi-square test were used to analyze the differences between responding and nonresponding patients, as well as between patients who completed behavioral therapy and those who dropped out or rejected it.

Multiple logistic regression analysis was used to examine the existence of predictors of clinical response. The presence of long-term follow-up response as previously defined was considered the dependent variable. Baseline Y-BOCS global score was forced first into the equation to control for initial severity. The following factors were then introduced as independent variables: age; age at onset of the disorder; duration of OCD; gender; presence of personality disorders; presence of personal and familial psychiatric past history; HAM-D scores at baseline, first, and final assessment; presence of any of the 5 OCD symptom factors (included in the equation as dummy-coded variables); duration of follow-up; history of previous OCD treatment; and short-term response to pharmacologic therapy.

The SPSS statistical package (version 6.0) was used in all analyses. Significance level was set at $p < .05$ (2-tailed).

Table 1. Frequencies of the Major Symptom Categories of the Yale-Brown Obsessive Compulsive Scale Symptom Checklist at Baseline Assessment in 60 Patients With Obsessive-Compulsive Disorder

	Present Symptom[a]		Major Symptom[b]	
Symptom Category	N	%	N	%
Obsessions				
Aggressive	27	45.0	22	36.7
Contamination	17	28.3	15	25.0
Sexual	10	16.7	9	15.0
Hoarding	4	6.7	2	3.3
Religious	2	3.3	1	1.7
Symmetry	13	21.7	11	18.3
Somatic	6	10.0	6	10.0
Compulsions				
Cleaning	15	25.0	15	25.0
Checking	36	60.0	19	31.7
Repeating	14	23.3	3	5.0
Counting	12	20.0	3	5.0
Ordering	16	26.7	10	16.7
Hoarding	2	3.3	2	3.3

[a]At least 1 symptom in a category not considered principal.
[b]At least 1 symptom in the category considered principal. More than 1 principal category was allowed for each patient.

RESULTS

Baseline Clinical Assessment

The mean ± SD Y-BOCS scores at intake were as follows: global, 24.7 ± 6.6 (range, 10–38); obsessions subscale, 13.2 ± 3.5; compulsions subscale, 11.5 ± 4.8. Frequencies of the principal symptom categories of obsessions and compulsions were distributed as shown in Table 1. There was no past psychiatric history prior to the OCD diagnosis in 51.6% of the patients (N = 31), and in those with a psychiatric history, affective disorders were the most frequent diagnosis (38.3%; N = 23). Five of the patients mentioned a past history of or current chronic tic disorder, and 2 had satisfied DSM-III-R or DSM-IV criteria for anorexia nervosa.

In 43.3% of patients (N = 26), past familial psychiatric history was absent. In the remaining 56.7% (N = 34), the

Table 2. Short- and Long-Term Response to Treatment in 60 Patients With Obsessive-Compulsive Disorder[a]

Outcome Variable	Baseline	Short-Term Response to SRI	Long-Term Follow-Up
Y-BOCS score, mean ± SD			
Global	24.7 ± 6.6	17.7 ± 7.8	14.4 ± 9.2
Obsessions	13.2 ± 3.5	9.5 ± 3.8	8.0 ± 4.8
Compulsions	11.5 ± 4.8	8.2 ± 4.6	6.4 ± 5.1
HAM-D score, mean ± SD	13.7 ± 6.1	9.6 ± 5.9	8.6 ± 5.0
Y-BOCS severity level, N (%)			
Subclinical (0–7)	0 (0)	5 (8.3)	18 (30.0)
Mild (8–15)	7 (11.7)	19 (31.7)	17 (28.3)
Moderate (16–23)	14 (23.3)	15 (25.0)	14 (23.3)
Severe (24–31)	33 (55.0)	16 (26.7)	8 (13.3)
Extreme (32–40)	6 (10.0)	5 (8.3)	3 (5.0)
Reduction in Y-BOCS global score, N (%)			
> 75%	...	2 (3.3)	8 (13.3)
50%–74%	...	9 (15.0)	20 (33.3)
25%–49%	...	23 (38.3)	17 (28.3)
< 25%	...	16 (26.7)	8 (13.3)
Worse	...	10 (16.7)	7 (11.7)

[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SRI = serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

most prevalent diagnoses were anxiety disorders other than OCD (20%; N = 12), OCD (15.1%; N = 9), and affective disorders (11.7%; N = 7).

Twenty-six patients (43.3%) met DSM-III-R criteria for at least one personality disorder. Cluster C personality disorders were the most frequent (31.7%)—12 patients with obsessive-compulsive, 4 with avoidant, and 3 with dependent personality disorder. Five patients (8.3%) met criteria for schizoid personality disorder, and 2 (3.3%) received a diagnosis of cluster B personality disorders—1 patient with borderline and another with histrionic personality disorder.

Short-Term Response to Treatment With SRI

Scores on Y-BOCS global ($t = 6.8$, $df = 59$, $p < .01$), obsessions ($t = 7.5$, $df = 59$, $p < .01$), and compulsions ($t = 4.6$, $df = 59$, $p < .01$) subscales were significantly reduced from baseline, as can be seen in Table 2. The mean ± SD percentage of reduction in global Y-BOCS scores was 29.9% ± 24.4%. According to the criteria previously defined, 23 patients (38.3%) could be considered responders.

Long-Term Follow-Up

Patients were followed up and reassessed after a minimum treatment period of 1 year (mean ± SD = 2.5 ± 1.2 years; range, 1–5 years) by one of the psychiatrists who made the initial assessments (P.A.).

The final assessment confirmed a statistically significant improvement in Y-BOCS scores from baseline measures (global: $t = 8.4$, $df = 59$, $p < .01$; obsessions: $t = 8.7$, $df = 59$, $p < .01$; compulsions, $t = 6.5$, $df = 59$, $p < .01$) (Table 2). Mean ± SD reduction in global Y-BOCS score achieved was 43.8% ± 28.9%. Thirty-eight patients (63.3%) met the established criteria for long-term follow-up response.

Treatment Across Follow-Up

During the follow-up period, 28.3% of patients (N = 17) received a single pharmacologic therapy, 30.0% (N = 18) received 2, 23.3% (N = 14) received 3, and 18.3% (N = 11) received more than 3 pharmacologic trials due to the absence of clinical response (less than 35% reduction in global Y-BOCS score or global Y-BOCS scores of 16 or greater). At the time of the long-term assessment, all patients were receiving pharmacologic treatment.

Thirty-seven patients (61.7%) completed an adequate behavioral therapy protocol. Patients not treated behaviorally included 5 (8.3%) who rejected this approach, 10 (16.7%) who started behavioral therapy but dropped out after the first few sessions, and 8 patients (13.3%) in whom prolonged behavioral treatment was considered unnecessary since they achieved a Y-BOCS global score of 8 or less after initial SRI therapy. Patients who received behavioral therapy did not differ significantly in sociodemographic and clinical variables from those who did not.

At long-term follow-up, patients who completed behavioral therapy exhibited a mean ± SD reduction of 44.2% ± 27.2% in Y-BOCS global score, 40.9% ± 27.1% in obsessions subscale score, and 50.2% ± 32.2% in compulsions subscale score. Patients who rejected or dropped out of behavioral therapy reached a reduction of 29.6% ± 28.0% in global Y-BOCS score, 32.9% ± 28.6% in obsessions subscale score, and 25.7% ± 28.6% in compulsions subscale score. Although reductions in Y-BOCS global and obsessions subscale scores were not statistically significantly different between both groups (global Y-BOCS: $t = 1.58$, $p = .1$; obsessions subscale: $t = 1.2$, $p = .2$), improvement in compulsions subscale score was significantly greater in behaviorally treated patients ($t = 2.5$, $p = .01$).

SRI treatment prior to behavioral therapy was not significantly different between patients who responded to behavioral therapy and those who did not ($\chi^2 = .02$, $p = .8$).

Outcome Predictors

Analysis of differences detected a significantly greater frequency of obsessions of sexual/religious content in nonresponding patients ($\chi^2 = 8.5$, $p = .01$). No differences with respect to the other factors considered could be detected. Nevertheless, there was a trend for nonresponding patients to report longer OCD history, fewer previous OCD treatments, higher baseline global and obsessions Y-BOCS scores, and less reduction in global Y-BOCS scores after initial SRI therapy (Table 3).

Table 3. Sociodemographic and Clinical Characteristics of 60 Patients With OCD[a]

Characteristic	Long-Term Assessment of OCD Severity: Responders[b] (N = 38)	Long-Term Assessment of OCD Severity: Nonresponders[c] (N = 22)	Statistical Comparison
Age, y, mean ± SD	29.3 ± 10.6	32.1 ± 10.0	NS (p = .3)
Male/female	26/12	14/8	NS (p = .7)
Never married, N (%)	27 (71.7)	15 (68.2)	NS (p = .4)
Age at onset of OCD, y, mean ± SD	17.9 ± 8.4	16.8 ± 5.6	NS (p = .6)
Duration of illness, y, mean ± SD	10.4 ± 9.0	15.3 ± 11.7	NS (p = .09)
Personality disorders, N (%)	16 (42.1)	10 (45.5)	NS (p = .8)
Familial psychiatric background, N (%)	22 (57.9)	12 (54.5)	NS (p = .8)
Previous OCD treatment, N (%)	25 (65.8)	18 (81.8)	NS (p = .09)
Baseline global Y-BOCS score, mean ± SD	23.5 ± 7.1	26.5 ± 5.4	NS (p = .09)
Baseline Y-BOCS obsessions score, mean ± SD	12.5 ± 3.7	14.5 ± 2.9	NS (p = .06)
Baseline Y-BOCS compulsions score, mean ± SD	11.2 ± 4.9	12.0 ± 4.6	NS (p = .5)
Reduction in Y-BOCS score after 12 wk of pharmacologic treatment, %, mean ± SD	34.4 ± 23.4	22.6 ± 24.8	NS (p = .08)

[a]Abbreviations: NS = not significant, OCD = obsessive-compulsive disorder, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
[b]Minimum Y-BOCS score reduction of 35% or final Y-BOCS score < 16.
[c]Y-BOCS score reduction < 35% and final Y-BOCS score ≥ 16.

These results were confirmed by multiple logistic regression analysis. From all the factors considered, only the presence of obsessions of sexual/religious content showed prognostic value in relation to the long-term outcome of OCD ($R^2 = .17$, $\beta = -.41$, $p = .001$).

DISCUSSION

This study was designed to assess the long-term response of obsessive-compulsive patients to a combined pharmacologic and behavioral approach and to focus on factors that could predict long-term outcome of OCD. On the basis of our data, 36.7% of the patients were resistant to this combined treatment, similar to what has been previously reported in the literature.[8–12] Patients who completed an adequate behavioral therapy exhibited a significantly greater reduction in compulsions, although no differences in obsessions and global OCD intensity were detected with respect to those who did not undergo behavioral therapy. The presence of sexual/religious obsessions was the unique clinical factor that permits prediction of a worse long-term outcome.

Concerning the prognostic value of the initial response to pharmacologic therapy, our results support those of Flament et al.[8] and Bolton et al.,[11] who underlined the lack of correlation between initial response to clomipramine and long-term outcome. This remains a controversial point in the studies concerning OCD course since Leonard et al.[17] reported a worse long-term response in those patients with persistent severe obsessive symptoms after 5 weeks of clomipramine treatment.

A major benefit from behavioral therapy in our OCD group was the improvement of ritualistic behaviors, whereas obsessive thoughts were less modified by this approach. Since patients who were offered behavioral therapy in our study had already been treated with an SRI without a positive clinical response, they can be considered pharmacologic treatment–resistant OCD patients. Current literature provides few data concerning the efficacy of behavioral therapy in previously resistant medicated patients or the combined use of drug and behavioral treatment.[28] Further studies specifically designed to assess this important topic are needed.

The analysis of variables that could predict OCD course detected that the presence of sexual/religious obsessions was the unique factor that showed predictive value and appeared to be associated with a poorer long-term outcome. Analysis of our study parameters indicated that a minimum sample of 27 subjects in each outcome group would have been necessary to achieve 80% power ($\alpha = .05$). Failing to detect other significant predictors may be related to a type II error due to the small number of patients in the nonresponding group.

Response of the different clinical subtypes of OCD to available treatments has not yet been clearly established. Patients with cleaning rituals[14,29] and those with hoarding obsessions and compulsions[24,30] have been reported to have poorer short-term outcome. In the only long-term study concerning this aspect of OCD, Skoog and Skoog[31] reported poorer progress after 4 decades of follow-up in patients with predominant rituals and magical-content obsessions. Recently developed studies have reported good outcome in OCD patients submitted to cognitive therapy, particularly ruminators.[32,33] This new approach might be helpful in patients suffering from sexual/religious obsessions, who appear to be resistant to usual pharmacologic and behavioral therapies, as did our patients with this characteristic.

Some limitations of the study need to be addressed. We did not employ a placebo group since it would not have been ethically correct to keep OCD patients without an active treatment for such a prolonged period; nevertheless, OCD response to placebo has been reported to be low.[34] On the other hand, our sample might not have been large enough to allow us to detect other predictive variables such as some personality disorders, which have been postulated to predict scant response in OCD.[35–38]

Similarly, the small number of patients with comorbid chronic tic disorder did not allow us to analyze the differences related to long-term outcome between patients with and without tics, which would have been interesting from a clinical standpoint. Finally, follow-up period varied among patients from 1 to 5 years, so we do not know whether a more homogenous follow-up would have rendered different outcome results.

Further studies with larger samples of pharmacologically and behaviorally treated patients are required to ascertain the current long-term prognosis of OCD after the development of such specific therapies. On the other hand, in view of the evident heterogeneity of obsessive illness, determining response predictor variables based on these studies could facilitate optimizing existing therapeutic options among different OCD subgroups.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), risperidone (Risperdal).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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