High-Dose Sertraline Strategy for Nonresponders to Acute Treatment for Obsessive-Compulsive Disorder: A Multicenter Double-Blind Trial

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Objective: To evaluate the efficacy and safety of high-dose sertraline for patients with obsessive-compulsive disorder (OCD) who failed to respond to standard sertraline acute treatment.

Method: Sixty-six nonresponders to 16 weeks of sertraline treatment who met DSM-III-R criteria for current OCD were randomly assigned, in a double-blind continuation phase of a multicenter trial, either to continue on 200 mg/day of sertraline or to increase their dose to between 250 and 400 mg/day for 12 additional weeks. Efficacy measures included the Yale-Brown Obsessive Compulsive Scale (YBOCS), the National Institute of Mental Health Global Obsessive Compulsive Scale (NIMH Global OC Scale), and the Clinical Global Impressions-Severity of Illness and -Improvement (CGI-I) scales. Data were collected from July 26, 1994, to October 26, 1995.

Results: The high-dose (250–400 mg/day, mean final dose = 357, SD = 60, N = 30) group showed significantly greater symptom improvement than the 200-mg/day group (N = 36) as measured by the YBOCS ($p = .033$), NIMH Global OC Scale ($p = .003$), and CGI-I ($p = .011$). Responder rates (decrease in YBOCS score of ≥ 25% and a CGI-I rating ≤ 3) were not significantly different for the 200-mg/day versus the high-dose sertraline group, either on completer analysis, 34% versus 52%, or on endpoint analysis, 33% versus 40%. Both treatments showed similar adverse event rates.

Conclusion: Greater symptom improvement was seen in the high-dose sertraline group compared to the 200-mg/day dose group during continuation treatment. Both dosages yielded similar safety profiles. Administration of higher than labeled doses of selective serotonin reuptake inhibitors may be a treatment option for certain OCD patients who fail to respond to standard acute treatment.

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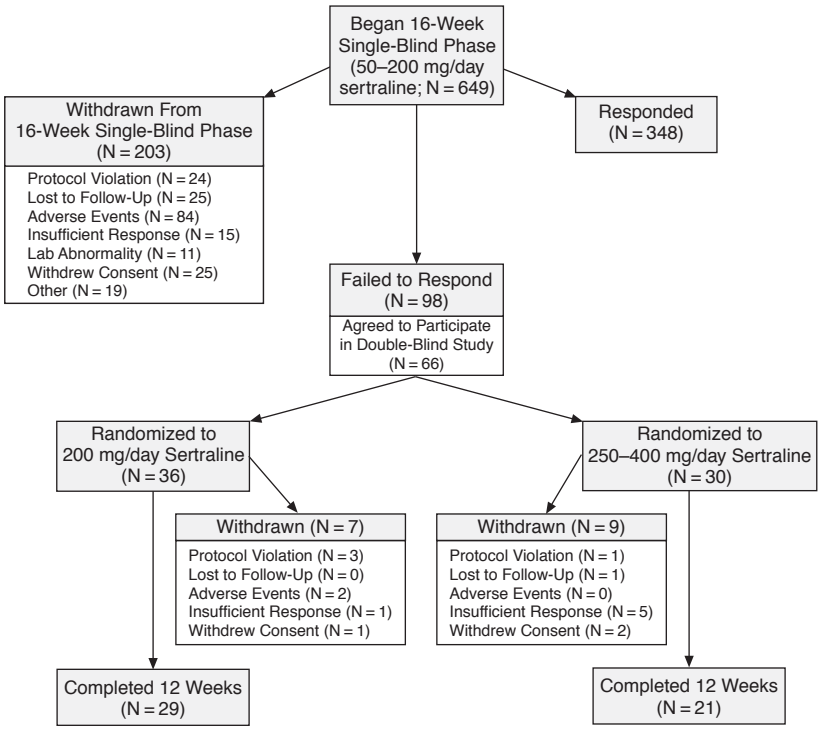
Pharmacologic treatment of obsessive-compulsive disorder (OCD) continues to be a challenge. Although placebo-controlled trials have established the efficacy of potent serotonin reuptake inhibitors (SRIs),[1,2] the proportion of responders to acute treatment is often below 40%.[3,4] Thus, a number of studies have examined additional treatment strategies. Case series and small open-label trials have yielded encouraging results for augmentation of selective SRIs with olanzapine,[5–7] aminoglutethimide,[8] and tryptophan plus pindolol[9] and for clomipramine with trazodone[10] and citalopram.[11] However, these results have not yet been confirmed with controlled trials.

Placebo-controlled trials examining augmentation of SRIs for OCD have failed to find efficacy for desipramine,[12] buspirone,[13] lithium,[14] and clonazepam.[15] Positive results have been reported for augmentation with D_2 antagonists, which were initially demonstrated to be effective in patients with a history of comorbid tics,[16] though a subsequent trial with the atypical antipsychotic risperidone suggests that non–tic-related OCD may respond as well.[17] A recent trial also reported efficacy for pindolol as an augmentation strategy in SRI treatment-refractory OCD,[18] but a second trial comparing fluvoxamine to flu-

Figure 1. Subject Flow From Entry Into 16-Week Single-Blind Phase Through Completion of 12-Week Double-Blind Study



voxamine plus pindolol failed to produce any advantage from the addition of pindolol.[19]

An alternative to augmentation is use of high doses of the initial SRI treatment, perhaps achieving thereby some of the same beneficial effects associated with intravenous drug administration. Moreover, increasing the dosage of the current drug avoids drug interactions that might be a concern with adding a second drug. Case reports suggest that some patients who have not responded to standard therapeutic doses may respond at much higher doses.[20,21] Sertraline, due to its well-tolerated safety profile, seemed suited to test this strategy in a controlled trial; we report here the results of the first such study.

METHOD

Patients

Patients who met DSM-III-R criteria for current OCD using the Structured Clinical Interview for DSM-III-R[22] were recruited at 17 U.S. centers that specialized in the treatment of obsessive-compulsive and other anxiety disorders. Sixty-six male and female outpatients who did not respond to 16 weeks of single-blind treatment with sertraline participated (Figure 1). Failure to respond across the acute phase of treatment was defined by either a decrease of less than 25% from baseline on the Yale-Brown Obsessive Compulsive Scale (YBOCS)[23,24] or a Clinical Global Impressions-Improvement scale (CGI-I)[25] rating of no more than minimally improved. Data were collected from July 26, 1994, to October 26, 1995.

At baseline of the acute phase study, patients had to have a minimum total score of 20 on the YBOCS and a score of at least 7 on the National Institute of Mental Health Global Obsessive Compulsive Scale (NIMH Global OC Scale).[26] Exclusion criteria consisted of (1) a 24-item Hamilton Rating Scale for Depression[27] total score ≥ 17; (2) a female outpatient who was currently pregnant or nursing or of childbearing potential and not using a medically accepted form of contraception; (3) a current diagnosis of organic mental disorder, major depressive disorder, bipolar disorder, Tourette's disorder, or severe Axis II personality disorder or a principal diagnosis of trichotillomania, somatoform disorder, panic disorder, social phobia, or generalized anxiety disorder; (4) current or past diagnosis of schizophrenia, delusional disorder, or other psychosis; (5) a DSM-III-R–defined diagnosis in the past 6 months of alcohol or substance abuse and/or dependence; (6) positive urine drug screen; (7) presence of any medical contraindications to treatment with sertraline; (8) any history or evidence of malignancy other than excised basal cell carcinoma; (9) any acute or unstable medical illness; (10) participation in an investigational

drug study within 28 days prior to entering the study; (11) use of sertraline within 2 months prior to entry into the open-label phase, failure to respond to an adequate trial of sertraline in the past, or participation in an investigational study of sertraline; (12) concomitant use of any psychotropic medication (other than chloral hydrate for sleep); (13) concurrent behavioral therapy for OCD; (14) therapy with a monoamine oxidase inhibitor within 2 weeks, depot neuroleptic within 6 months, fluoxetine within 5 weeks, or regular daily neuroleptic, anxiolytic, or antidepressant drug in the 2 weeks prior to the first administration of sertraline; (15) any liver function test more than twice the upper limit of normal on the first day of washout; and (16) being illiterate or, in the investigator's judgment, unable or unlikely to follow the study protocol.

The Institutional Review Boards associated with each site approved the protocol and informed consent documents. Each patient provided written informed consent after the procedures had been fully explained prior to study participation.

Procedures

During acute treatment, patients with moderate-to-severe OCD were treated with 16 weeks of single-blind sertraline titrated from 50 mg/day to a maximum dose of 200 mg/day. Of 649 patients who began acute phase single-blind treatment, 348 (54%) responded (defined as a 25% or greater decrease in YBOCS scores and a CGI-I rating ≤ 3 ["minimally improved"]).[28] A total of 203 patients were withdrawn from the 16-week single-blind phase, primarily because of adverse events (N = 84), lost to follow-up (N = 25), consent withdrawal (N = 25), protocol violation (N = 24), insufficient response (N = 15), and lab abnormalities (N = 11).

Of the 98 acute study nonresponders who completed the 16-week treatment, 67% (66/98) agreed to participate in the double-blind phase. At the end of the acute treatment phase, these nonresponders were randomly assigned on a 1:1 ratio to an additional 12 weeks of double-blind treatment with either a fixed dose of 200 mg/day of sertraline or a flexible dose of sertraline, titrated between 250 and 400 mg/day. Figure 1 presents the flow of subjects from the 16-week single-blind phase through the completion of the 12-week double-blind study.

Patients assigned to the high dose of sertraline were titrated to their maximum tolerated dose in 50-mg/day increments weekly over the first 3 weeks of treatment. If medication dosage needed to be decreased due to side effects, the dosage could subsequently be titrated upward again to a higher dose if tolerated. Patients assigned to the 200-mg/day treatment were administered a fixed dose of 200 mg/day throughout the 12-week study period. Identical appearing blister-packaged medication was administered to both treatment groups to preserve the blind design, while allowing dose titration.

Assessments were conducted at the end of the acute (single-blind) phase, weekly for 4 weeks, and then every other week until week 12 of the double-blind high-dose trial.

Efficacy Measures

The following primary efficacy measures were completed by the clinician at each of the assessment visits: YBOCS, NIMH Global OC Scale, and CGI-Severity of Illness scale (CGI-S)[25] and CGI-I ratings. In addition to the total score of the YBOCS, we also separately examined the obsessive and compulsive subscales of the YBOCS. Furthermore, in exploratory analyses, we examined items 2 (interference with functioning due to obsessive thoughts) and 7 (interference with functioning due to compulsive behaviors) to assess impairment in functioning. For each of these 2 items, a score was created indicating impairment in functioning was "present" (moderate-to-severe interference with functioning based upon a score of 2 to 4) or "absent" (mild to no interference with functioning based upon a score of 0 or 1).

Treatment response was defined as a decrease in the YBOCS score of ≥ 25% and a CGI-I rating ≤ 3 from single-blind acute phase baseline to endpoint (last observation carried forward, LOCF) during the 12 weeks of double-blind treatment.

Safety assessments evaluated at each visit included assessment of adverse experiences, as well as measurement of blood pressure, heart rate, and body weight. In addition, an electrocardiogram (ECG) and laboratory assessments including complete blood cell count, platelets, blood chemistries, and urinalysis were performed at weeks 4, 8, and 12 of the double-blind trial.

Statistical Analyses

The primary analysis was a random regression analysis that compared the 2 sertraline treatment groups using all available data (observed cases) from baseline (of the randomization phase) to week 12 of the double-blind treatment phase on the YBOCS, NIMH Global OC Scale, CGI-S, and CGI-I. A random regression model was used specifying random intercept and random slope terms. The model included main effect terms for treatment, time, and the treatment-by-time interaction. The dependent variables in these random regression analyses were change from baseline to each assessment during the 12-week treatment period, with the baseline value (of the double-blind trial) included as a covariate to equate for any differences at the beginning of the randomization phase. For the CGI-I, the dependent variable was the score at each assessment during the 12-week treatment period. Random regression analyses were also performed for the 2 YBOCS subscales (obsessive and compulsive subscales).

Exploratory analyses of treatment differences on the "presence" versus "absence" of functional impairment

due to obsessions and compulsive behavior were performed using χ^2 or Fisher exact test, where appropriate, at each assessment visit. Response rates were compared with Fisher exact test. All tests were 2-tailed, and statistical significance was declared at an alpha of 0.05.

RESULTS

Baseline Clinical and Demographic Characteristics

Of the 30 patients assigned to 250 to 400 mg/day of sertraline, 60% (N = 18) were men, 90% (N = 27) were white, and the mean age was 38.1 (SD = 10.1) years. For the 36 patients assigned to 200 mg/day of sertraline, 47% (N = 17) were men, 89% (N = 32) were white, and the mean age was 38.2 (SD = 12.0) years. The mean duration of illness was 21.2 (SD = 11.4) years for the 200-mg/day group and 19.6 (SD = 9.3) years for the high-dose group. In the 250- to 400-mg/day group, 43% (N = 13) had been previously treated with a selective serotonin reuptake inhibitor (SSRI) and 33% (N = 10) had previously received a tricyclic antidepressant (30% [N = 9] clomipramine), while 47% of the 200-mg/day group (N = 17) had previously received SSRI treatment and 28% (N = 10) had received tricyclics (25% [N = 9] clomipramine).

At baseline of the double-blind randomized trial (end of 16-week single-blind phase), the mean (SD) YBOCS score was 25.1 (4.6) for the 200-mg group and 24.7 (4.8) for the 250- to 400-mg group. There were no significant differences between the 2 groups at baseline (week 16) on the YBOCS, NIMH Global OC Scale, or CGI-S.

Study Treatment

For all patients randomly assigned to the flexible high-dose group, the mean final (LOCF) daily dose of sertraline was 357 (SD = 60, N = 30) mg/day. Among completers, the mean final daily dose of sertraline was 377 (SD = 32, N = 21) mg/day. For the 200-mg group, the mean final dose was 347- (SD = 98, N = 36) mg equivalents per day of sertraline plus placebo. The mean final dose for completers in the 200-mg group was 366- (SD = 68, N = 29) mg equivalents per day of sertraline plus placebo. There were no significant differences between the 2 groups in the mg equivalents for either the full sample (t = 0.03, df = 64, p = .98) or the completer sample (t = 0.06, df = 49, p = .96).

Efficacy

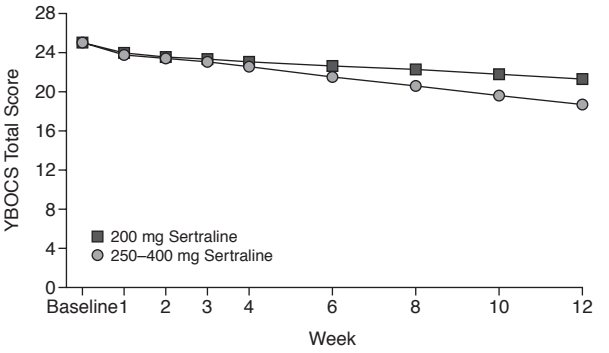
Random regression analyses revealed significant differences in rate of change (treatment-by-time interactions) between the 2 treatment groups on the YBOCS (F = 4.6, df = 1,399; p = .033), NIMH Global OC Scale (F = 9.0, df = 1,399; p = .003), and CGI-I (F = 6.5, df = 1,399; p = .011). The difference in rate of change for the CGI-S was nearly significant (F = 3.7, df = 1,399; p = .057). Across all 4 measures, the group that received the high dose of sertraline demonstrated a faster rate of symptom improvement across the 12 weeks of treatment compared to the 200-mg/day sertraline treatment group (Figures 2–5). By week 12 of double-blind treatment, effect sizes (mean differences divided by pooled SDs) for the 4 outcome measures were 0.38 (YBOCS), 0.27 (NIMH Global OC Scale), 0.50 (CGI-S), and 0.33 (CGI-I), all favoring the high-dose group (Table 1).

Random regression analyses on the YBOCS subscales revealed a significantly faster rate of change (F = 5.5, df = 1,399; p = .02) for the high-dose group on the obsessive subscale, but not on the compulsive subscale (F = 2.7, df = 1,399; p = .10).

Results for functional impairment due to obsessive thoughts (item 2 of the YBOCS) and compulsive behaviors (item 7 of the YBOCS) revealed significant differences at week 6 (χ^2 = 3.9, df = 1, p = .05), week 8 (Fisher exact test, p = .01), week 10 (χ^2 = 5.3, df = 1, p = .02), and week 12 (χ^2 = 3.8, df = 1, p = .05), with the high-dose group demonstrating a significantly greater proportion of patients with little or no impairment in functioning due to obsessive thoughts. A similar pattern of results was evident with impairment in functioning due to compulsive behavior, but statistical significance (Fisher exact test, p = .04) was only achieved at week 8.

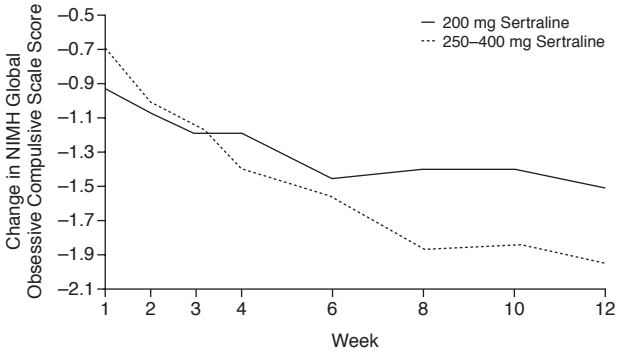
There were no significant differences between treatment groups on response rates. Thirty-three percent of patients (12/36) receiving 200 mg/day and 40% of those receiving the high dose (12/30) met responder criteria by treatment endpoint (χ^2 = 0.31, df = 1, p = .58). Of those who completed treatment, 34% (10/29) and 52% (11/21), respectively, met response criteria (χ^2 = 1.60, df = 1, p = .21).

Figure 2. YBOCS Total Scores at Baseline and Each Assessment Visit: Adjusted Means From Random Regression Analysis[a,b]



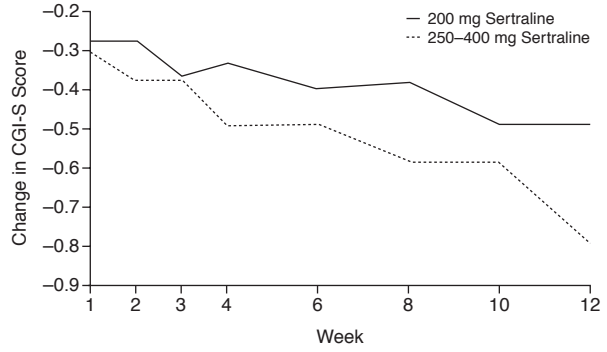
[a]Adjusted means derived from random regression analysis specifying time as a categorical variable. All means adjusted for double-blind phase baseline scores.
[b]200-mg slope = –0.22; 250- to 400-mg slope = –0.36; p = .033.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 3. Change in NIMH Global Obsessive Compulsive Scale Scores From Baseline to Each Assessment Visit: Adjusted Means From Random Regression Analysis[a,b]



[a]Adjusted means derived from random regression analysis specifying time as a categorical variable. All means adjusted for double-blind phase baseline scores.
[b]200-mg slope = –0.05; 250- to 400-mg slope = –0.11; p = .003.

Figure 4. Change in CGI-S Scores From Baseline to Each Assessment Visit: Adjusted Means From Random Regression Analysis[a,b]



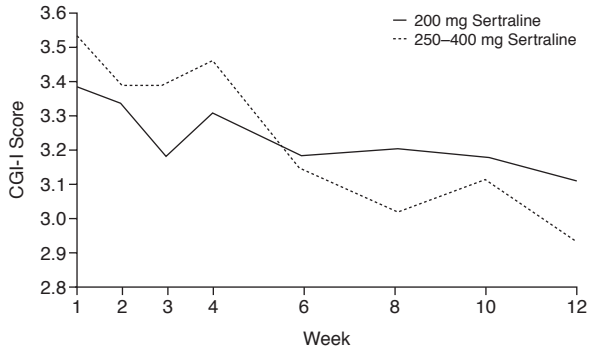
[a]Adjusted means derived from random regression analysis specifying time as a categorical variable. All means adjusted for double-blind phase baseline scores.
[b]200-mg slope = –0.02; 250- to 400-mg slope = –0.04; p = .011.
Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

Safety and Discontinuations

In the 200-mg sertraline group, 7 patients were discontinued and did not complete the continuation phase, while 9 patients discontinued in the high-dose group. Reasons for discontinuation are given in Figure 1.

Eighty-six percent of patients (N = 31) in the 200-mg/day group and 80% of the high-dose patients (N = 24) experienced at least 1 treatment-emergent adverse event. There were no significant differences among the treatment groups in adverse events occurring with greater than or equal to 10% frequency in either group (Table 2). Six percent of patients (N = 2) in the 200-mg/day group and

Figure 5. CGI-I Scores at Each Assessment Visit: Adjusted Means From Random Regression Analysis[a,b]



[a]Adjusted means derived from random regression analysis specifying time as a categorical variable. All means adjusted for double-blind phase baseline scores.
[b]200-mg slope = –0.02; 250- to 400-mg slope = –0.05; p = .057.
Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

none of the patients in the high-dose group discontinued treatment because of adverse events. The most common adverse events in the high-dose group were insomnia (20.0%), diarrhea (16.7%), nausea (13.3%), and somnolence (13.3%). In each case, these adverse events occurred at a lower rate than the rates listed in the 2001 *Physicians' Desk Reference*[29] description for standard dose (50–200 mg/day) sertraline treatment of OCD (28%, 24%, 30%, and 15%, respectively).

There were no significant differences between the groups in clinically significant laboratory tests, vital signs, or ECG abnormalities. None of the high-dose patients and only 2 200-mg/day patients experienced a laboratory abnormality.

DISCUSSION

There were 4 main findings of this study. First, 36% of patients with OCD (N = 24) who failed to respond to an initial 16 weeks of treatment with sertraline achieved a clinical response over the course of an additional 12 weeks of sertraline treatment. Second, among acute phase nonresponders, continuation treatment with a high dose (250–400 mg) of sertraline resulted in significantly greater and more rapid improvement in OCD symptoms compared to the maximal labeled dose of sertraline (200 mg). This finding is consistent with results of studies of intravenous SRI (clomipramine) administration in OCD.[30] This also suggests that some patients who do not respond with doses up to 200 mg/day of sertraline may benefit from higher doses. Third, a faster rate of change for the high-dose group was observed on the obsessive subscale of the YBOCS, but not on the compulsive subscale, and exploratory analyses revealed that a high dose of sertra-

Table 1. Efficacy Measures Across 12 Weeks of Sertraline Treatment Among Patients With Obsessive-Compulsive Disorder

	Sample Size, N		YBOCS, Mean (SD)		YBOCS Obsessive Subscale, Mean (SD)		YBOCS Compulsive Subscale, Mean (SD)		National Institute of Mental Health Global Obsessive Compulsive Scale, Mean (SD)		CGI-S, Mean (SD)		CGI-I, Mean (SD)	
Visit	200 mg/d	250–400 mg/d	200 mg/d	250–400 mg/d	200 mg/d	250–400 mg/d	200 mg/d	250–400 mg/d	200 mg/d	250–400 mg/d	200 mg/d	250–400 mg/d	200 mg/d	250–400 mg/d
Baseline (acute)	36	30	27.2 (4.1)	26.2 (3.8)	13.3 (2.1)	13.0 (2.4)	13.9 (2.3)	13.2 (2.2)	9.5 (1.5)	9.6 (1.4)	4.8 (0.7)	4.8 (0.7)	NA	NA
Baseline (double-blind)	36	30	25.1 (4.6)	24.7 (4.8)	12.2 (2.6)	12.1 (2.8)	12.9 (2.5)	12.7 (2.5)	8.8 (1.3)	9.2 (1.7)	4.6 (0.7)	4.7 (0.8)	3.5 (0.6)	3.7 (0.7)
Week 1	36	30	24.3 (4.6)	24.2 (4.9)	11.8 (2.7)	11.8 (3.0)	12.5 (2.5)	12.4 (2.5)	8.6 (1.5)	8.9 (1.7)	4.6 (0.8)	4.5 (0.8)	3.4 (0.5)	3.5 (0.6)
Week 2	36	29	23.7 (4.9)	23.0 (6.4)	11.6 (2.7)	11.1 (3.5)	12.0 (2.6)	11.9 (3.2)	8.5 (1.6)	8.7 (2.1)	4.6 (0.8)	4.4 (0.9)	3.3 (0.6)	3.4 (0.8)
Week 3	34	26	23.2 (5.4)	22.8 (6.3)	11.5 (2.8)	11.2 (3.5)	11.7 (2.8)	11.6 (3.1)	8.4 (1.7)	8.7 (2.2)	4.5 (0.9)	4.5 (0.9)	3.2 (0.8)	3.4 (0.9)
Week 4	35	26	23.0 (5.9)	22.5 (5.9)	11.3 (3.1)	10.9 (3.6)	11.7 (3.1)	11.6 (2.6)	8.4 (1.8)	8.5 (2.1)	4.5 (0.9)	4.4 (1.0)	3.3 (0.8)	3.5 (0.8)
Week 6	34	26	22.1 (6.1)	21.8 (7.2)	10.8 (3.2)	10.6 (4.2)	11.3 (3.1)	11.2 (3.3)	8.1 (2.0)	8.2 (2.4)	4.4 (0.9)	4.3 (1.0)	3.2 (0.7)	3.2 (1.0)
Week 8	32	21	22.1 (6.6)	19.6 (6.8)	10.8 (3.4)	9.3 (4.0)	11.3 (3.3)	10.2 (3.1)	8.1 (2.0)	7.4 (2.1)	4.5 (0.9)	4.1 (1.0)	3.2 (0.8)	2.9 (1.0)
Week 10	30	21	21.6 (6.9)	19.5 (6.7)	10.6 (3.5)	9.3 (4.0)	11.0 (3.5)	10.2 (3.1)	8.1 (2.1)	7.5 (2.2)	4.4 (1.0)	4.1 (0.9)	3.1 (0.8)	3.0 (0.9)
Week 12	30	21	21.8 (7.2)	19.2 (6.4)	10.8 (3.8)	9.1 (3.9)	11.0 (3.5)	10.9 (3.2)	8.0 (2.3)	7.4 (2.2)	4.4 (1.0)	3.9 (1.0)	3.1 (0.8)	2.8 (1.0)

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, NA = not applicable, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 2. Treatment-Emergent Adverse Events That Occurred in 10% or More of Patients Treated With Either 200 mg or 250–400 mg of Sertraline

Adverse Event	200-mg Group (N = 36) N (%)	250- to 400-mg Group (N = 30) N (%)	p Value[a]
Insomnia	5 (13.9)	6 (20.0)	.53
Somnolence	1 (2.8)	4 (13.3)	.17
Nervousness	2 (5.6)	3 (10.0)	.65
Amnesia	1 (2.8)	3 (10.0)	.32
Agitation	0 (0.0)	3 (10.0)	.09
Diarrhea	4 (11.1)	5 (16.7)	.72
Nausea	4 (11.1)	4 (13.3)	1.00
Respiratory tract infection	9 (25.0)	2 (6.7)	.06
Headache	8 (22.2)	3 (10.0)	.32
Tremor	0 (0.0)	3 (10.0)	.09
Dizziness	4 (11.1)	1 (3.3)	.37
Fatigue	5 (13.9)	3 (10.0)	.72
Pain	4 (11.1)	1 (3.3)	.37
Arthralgia	1 (2.8)	3 (10.0)	.32

[a]p Values are from Fisher exact test.

line resulted in significantly less impairment in functioning due to obsessive thoughts from weeks 6 to 12 of the double-blind trial. Fourth, and importantly, the higher doses of sertraline were generally well tolerated and produced similar rates of adverse events compared to the 200-mg/day dose, although there were somewhat higher rates of tremor and agitation seen on the higher doses.

The current study adds to a growing literature of controlled trials suggesting various augmentation strategies for OCD nonresponders.[16–18] The response rates for those patients who completed treatment with either 200 mg/day of sertraline (34%) or 250–400 mg/day of sertraline (52%) are similar to a previously reported completer response rate for risperidone (50%) as an SRI augmentation agent for OCD nonresponders.[17] Although continuation treatment is an option with acute phase nonresponders, the response rates achieved in the current study, as well as in other treatment studies of OCD,[1] remain relatively low, especially when compared to those seen in other anxiety or affective disorders. Patients continuing on sertraline 200 mg/day experienced a further 3.3-point decrease in YBOCS score, while those receiving higher doses achieved a 5.5-point reduction. However, these improvements left the patients with substantial severity of symptoms reflected in their final YBOCS scores of 21.8 and 19.2, respectively, after 28 weeks of treatment. Thus, further treatment strategies need to be developed and tested. A sequential strategy that incorporates multiple medications, as well as cognitive-behavioral therapy,[31] may be promising.

Despite the encouraging finding of greater change in OCD symptoms for the high-dose group, it is important to note that many patients benefited from simply continuing a longer course of treatment at the approved maximal labeled dose of sertraline. Indeed, in the current trial, 33%

of patients treated with 200 mg/day who failed to respond to the initial 16 weeks of treatment achieved response status with an additional 12 weeks of treatment. In addition, the rate of discontinuation was higher in the high-dose group compared to the 200-mg group. Furthermore, there was no clinical or statistically significant difference in response rates between high and standard doses at endpoint. Among completers, however, a more clinically meaningful, but not statistically significant, difference (52% for high-dose group vs. 34% for 200-mg/day group) began to emerge. We should note that the statistical power to detect differences in response rates in this study was limited. To detect a difference between 52% and 34%, 118 subjects per group would be needed at a statistical power of 0.80 ($\alpha = 0.05$, 2-tailed). Moreover, even relatively small improvements in OCD symptoms may translate into clinically meaningful improvements in quality of life and functioning, particularly for those patients who have been incapacitated by OCD symptoms for many years.

If clinicians choose to implement doses that are higher than the approved labeled maximum doses of sertraline for OCD, clinical wisdom suggests that periodic attempts to reduce the dose to standard levels (50–200 mg/day) to assess whether high doses are necessary in the longer term may be prudent. It should be noted, however, that the superiority of high-dose sertraline did not become apparent for 6 to 8 weeks in the current trial. Thus, the advantage of the high dose may not be seen if the dose is reduced prematurely. The proper long-term maintenance strategy in order to prevent relapse for patients taking high-dose sertraline is not known at this time and clearly needs additional study before any firm recommendations can be made. Studies have demonstrated that cognitive-behavioral therapy can help maintain improvements obtained with SRI treatment after medication is discontinued.[32]

Adverse events were reported by 80% of patients receiving 250–400 mg/day of sertraline and 86% of patients receiving 200 mg/day. However, none of the patients in the high-dose group and 6% in the 200-mg/day group discontinued prematurely because of adverse experiences. In addition, no adverse events were significantly more common with the high dose compared to the 200-mg/day dose, although statistical power was limited to detect differences. These data from the first controlled comparison of high and usual doses of sertraline in a psychiatric disorder suggest that higher than labeled doses of sertraline may be generally well tolerated with an acceptable safety profile. In understanding the adverse event data, it is important to note that 12.9% of patients (84/649) who entered the initial 16-week single-blind acute treatment phase discontinued due to adverse events.[28] Patients highly intolerant of sertraline were therefore not likely to be enrolled in the double-blind phase. Our data do suggest, however, that those patients who are initially tolerant during acute treatment continue to be tolerant during continuation treatment, even if the dosage is increased to high levels.

A limitation of this study is the relatively modest sample size. Furthermore, not all patients who failed to respond during the acute phase elected to participate in this 12-week high-dose trial. Therefore, selection bias in the recruitment of patients into the study may have influenced the overall response rates or the comparative differences between groups.

Another limitation is that this study's inclusion/exclusion criteria constrain the generalizability of the results. In particular, comorbid major depressive disorder was an exclusion criterion, yet almost 30% of individuals in the community with OCD have a lifetime history of major depressive disorder.[33] Finally, only 12-week outcomes were evaluated; therefore, the efficacy and tolerability of high-dose sertraline over a longer period of time remains an open question.

In summary, this double-blind, multicenter study suggests that continued treatment with a 200-mg dose or a high dose (250–400 mg) of sertraline for OCD nonresponders is safe and well tolerated. A substantial percentage of patients who did not respond during initial acute treatment achieved a clinical response during continuation treatment with sertraline at daily doses of 200 mg (33% responder rate) or 250 to 400 mg (40% responder rate). Furthermore, a high dose of sertraline in nonresponders to 16 weeks of treatment resulted in greater and faster improvement in OCD symptoms. Further study of high-dose (and other) treatment strategies for patients with OCD who fail to respond to standard acute treatment is indicated.

Drug names: aminoglutethimide (Cytadren), buspirone (BuSpar and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), pindolol (Visken and others), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others).

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