A Double-Blind Switch Study of Paroxetine and Venlafaxine in Obsessive-Compulsive Disorder

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Background: The treatment guidelines for obsessive-compulsive disorder (OCD) propose to switch serotonin reuptake inhibitors (SRIs) in case of refractoriness. However, no controlled research has been published yet that prospectively examined the effects of changing SRIs. This article describes the first double-blind switch study of 2 SRIs in patients with OCD.

Method: 150 patients with primary OCD, according to DSM-IV criteria, were randomly assigned in a 12-week, double-blind trial to receive dosages titrated upward to 300 mg/day of venlafaxine (N = 75) or 60 mg/day of paroxetine (N = 75). Primary efficacy was assessed by the change from baseline on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), and nonresponse was defined as less than 25% reduction on the Y-BOCS. After a 4-week tapering phase, 43 nonresponders were switched to 12 additional weeks of the alternate antidepressant, of which 16 patients received venlafaxine and 27 received paroxetine.

Results: Eighteen of 43 patients benefited from a switch to the alternate SRI with a mean ± SD decrease of at least 25% on the Y-BOCS. At the end of 12 weeks, responder rates were 56% for paroxetine (15/27) and 19% for venlafaxine (3/16). An intent-to-treat, last-observation-carried-forward analysis demonstrated a mean decrease on the Y-BOCS of 1.8 ± 3.5 in the venlafaxine group and 6.5 ± 7.1 in the paroxetine group. After 2 consecutive SRI trials, 109 of 150 patients (73%) achieved a Y-BOCS decrease of at least 25%.

Conclusion: The results of the current study show that 42% of the nonresponders benefited from a crossover to the other SRI, and that paroxetine was more efficacious than venlafaxine in the treatment of nonresponders to a previous SRI trial. Switching SRIs in case of refractoriness may be considered a useful strategy for patients with OCD.

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Obsessive-compulsive disorder (OCD) is a common and severe psychiatric disorder. If not treated properly, obsessive-compulsive symptoms are usually chronic with a continual waxing and waning. Fortunately, over the past decades, behavioral treatments and the advent of serotonin reuptake inhibitors (SRIs) have altered the outlook for patients suffering from OCD. Although the efficacy of SRIs has been well established, up to 40% to 60% of OCD patients do not respond well to treatment.[1] In case of nonresponse or partial response, it is recommended by the guidelines to switch SRIs.[2]

While switching SRIs is a common clinical practice in the treatment of OCD, controlled research supporting this practice is scant. Earlier literature suggested that 25% of the OCD patients might benefit from switching SRIs, whereas the expert guidelines estimate that patients who do not respond to one SRI have about a 40% chance of responding to a second SRI, and 10% to a third SRI.[2] To date, no systematic study has been conducted to evaluate the efficacy of switching SRIs in OCD. Although numerous anecdotal examples suggest therapeutic success with a different SRI, it is unclear how many responders and how much improvement a clinician might expect with a second SRI trial in case of nonresponse.

The objective of the present study was to assess the efficacy of switching SRIs in patients with OCD in case of nonresponse. We report the results of a double-blind switch study of patients with OCD who failed to respond to a 12-week trial of paroxetine or venlafaxine (< 25% reduction on the Yale-Brown Obsessive Compulsive Scale [Y-BOCS]) and were crossed over to the alternate drug for another 12 weeks of treatment.

SUBJECTS AND METHOD

This study was part of a larger research protocol studying a treatment algorithm for patients with OCD. The entire study was encompassed in a first phase, which consisted of a double-blind comparison trial of venlafaxine and paroxetine, and a second phase, which was a double-blind switch study. A full description of the first phase has been previously published.[3]

Subjects

One hundred fifty of 300 patients gave written informed consent for participation in this study, which had been approved by the University of Utrecht Medical Ethical Review committee (Utrecht, the Netherlands). Participants were female or male outpatients, between ages 18 and 65 years, who were diagnosed with primary OCD according to the DSM-IV criteria. The diagnosis was ascertained by means of the Mini-International Neuropsychiatric Interview.[4] Only patients with a score of at least 18 on the Y-BOCS, or at least 12 if only obsessions or compulsions were present, were included. Patients with significant depression, as determined by a total score of 15 or more on the 17-item Hamilton Rating Scale for Depression (HAM-D)[5] on admission, were excluded. Female patients with childbearing potential who were not using adequate methods of contraception and pregnant women were excluded, as were patients with organic mental disorders, epilepsy, any structural central nervous system disorder, or stroke within the last year; patients with primary DSM-IV diagnoses of major depression, bipolar disorder, schizophrenia, or any other psychotic condition; and patients with substance related disorders within the past 6 months, primary anxiety disorders, or obvious personality disorders. Concomitant personality disorders were assessed with the Dutch version of the Structured Clinical Interview for DSM-III-R.[6]

Other reasons for exclusion from this study were evidence of clinically significant and unstable cardiovascular, gastrointestinal, pulmonary, renal, hepatic, endocrine, or hematologic conditions; glaucoma, myocardial infarction within the last year, patients at risk for suicide, multiple drug allergies or known allergy for trial compounds, use of antidepressants or antipsychotics 1 month before the screening visit, use of a concomitant psychotropic drug, behavioral or cognitive therapy 3 months prior to the screening visit, and any contraindications to paroxetine or venlafaxine. Patients were judged to be healthy based on the results of a physical examination, an electrocardiogram, and blood and urine screening tests.

Ratings and Treatment Response

Patients were evaluated at weeks 0, 1, 3, 5, 8, 10, and 12 of each phase. Obsessive-compulsive symptoms were measured with the Y-BOCS.[7] Depression was rated with the 17-item HAM-D[5] and anxiety was evaluated with the Hamilton Rating Scale for Anxiety (HAM-A).[8] The Global Assessment of Functioning scale[9] was used as a measure of overall symptomatic and functional impairment. Two trained investigators, blinded to the patient's assigned condition, completed the scales at baseline and at each visit. The primary efficacy parameter was the Y-BOCS score. Response to treatment was prospectively defined as a ≥ 25% decrease in Y-BOCS score.

Study Design

In the first phase, patients were randomly assigned to receive either paroxetine or venlafaxine XR for 12 weeks in a single-center, double-blind controlled, parallel-group study design (Figure 1). Paroxetine treatment was initiated at a dose of 15 mg/day and gradually increased to 60 mg/day in week 7, using a fixed dosing schedule (15 mg/day for weeks 1–2, 30 mg/day for weeks 3–4, 45 mg/day for weeks 5–6, and 60 mg/day for weeks 7–12). Venlafaxine treatment was initiated at a dose of 75 mg/day and gradually increased to 300 mg/day in week 7, using a fixed dosing schedule (75 mg/day for weeks 1–2, 150 mg/day for week 3–4, 225 mg/day for weeks 5–6, and 300 mg/day for weeks 7–12).

Nonresponders in the first phase with a less than 25% decrease in Y-BOCS score were eligible for the second phase. First, venlafaxine and paroxetine were tapered off in 4 weeks according to a fixed dose schedule (venlafaxine: 225 mg/day for week 1, 150 mg/day for weeks 2–3, and 75 mg/day for week 4; paroxetine: 45 mg/day for week 1, 30 mg/day for weeks 2–3, and 15 mg/day for week 4) with the double blind maintained. Next, patients were administered the alternate SRI for another 12 weeks following the identical dosing schedule as in the first phase. It is of note that both patients and clinicians were blind to which drug was taken, but not to the fact that nonresponders were being switched to the alternate drug. The number of visits, assessments, and outcome definitions for phase 2 followed the same protocol as those described for phase 1.

Assessment of Physiologic Measures, Adverse Events, and SRI Blood Levels

Vital signs, including blood pressure and pulse rate, were obtained at each visit. Any adverse event, either reported by the patient or observed by the investigator, was recorded at each visit. Blood for plasma drug level determinations was collected at each assessment, i.e., in weeks 0, 1, 3, 5, 8, 10, and 12. Blood levels of the compounds were determined by high-performance liquid chromatography with fluorescence detection at the laboratory of our psychiatric department.[10]

Statistical Analysis

The primary efficacy parameter, the Y-BOCS score, was analyzed for all patients with at least 1 assessment

Figure 1. Study Design and Number of Responders According to a > 25% Decrease on the Yale-Brown Obsessive Compulsive Scale

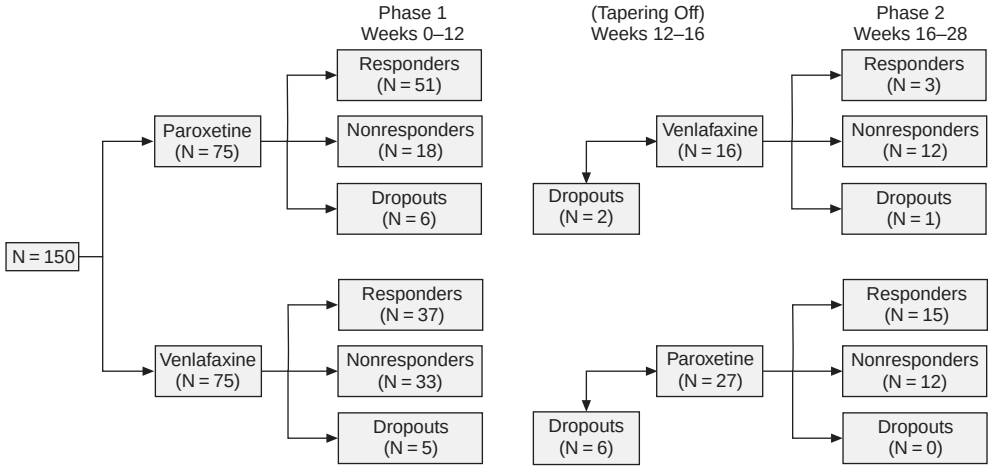

Table 1. Demographic and Baseline Clinical Characteristics of Patient Samples

Characteristic	Paroxetine (N = 27)	Venlafaxine (N = 16)
Sex, N (%)		
Men	11 (41)	8 (50)
Women	16 (59)	8 (50)
Age, mean ± SD, y	36 ± 13	34 ± 11
Age at onset, mean ± SD, y	19 ± 9	18 ± 8
Duration of illness, mean ± SD, y	17 ± 10	17 ± 11
Y-BOCS scores, mean ± SD		
Obsessions	12.8 ± 4.1	13.2 ± 2.9
Compulsions	14.7 ± 2.4	14.7 ± 3.0
Total	27.5 ± 5.3	27.9 ± 4.5
HAM-A score, mean ± SD	10.2 ± 7.8	12.2 ± 8.1
HAM-D score, mean ± SD	8.0 ± 4.2	7.2 ± 5.2
GAF score, mean ± SD	56.4 ± 8.4	57.8 ± 14.6
Comorbid disorders, N (%)		
Mood	6 (22)	1 (6)
Anxiety	2 (7)	2 (13)
Other Axis I	2 (7)	2 (13)
Axis II	8 (30)	5 (31)
Previous behavioral therapy trials, N (%)		
None	16 (59)	7 (44)
1	10 (39)	9 (56)
Previous medication trials, N (%)		
None	13 (48)	7 (44)
1	4 (15)	3 (19)
2	5 (19)	3 (19)
3 or more	5 (19)	3 (19)

Abbreviations: GAF = Global Assessment of Functioning scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

after baseline, following an intent-to-treat (ITT), last-observation-carried-forward (LOCF) procedure. Data analysis was conducted in several stages. First, we analyzed mean changes on the outcome measures in phase 2 (weeks 16–28). Of the 43 patients randomized to receive treatment (ITT) in the second phase, 42 (98%) completed the study and were included in the analysis. Second, we analyzed the mean scores at baseline (week 0) and endpoint (week 28) and the mean change for the outcome measures for the total sample (N = 150) in both phases. Finally, to evaluate the differential efficacy between paroxetine and venlafaxine, the combined paroxetine trials and venlafaxine trials from phases 1 and 2 were compared. Student t tests were calculated to determine if significant differences between venlafaxine and paroxetine were present and a paired t test, using differences in Y-BOCS scores from baseline, was performed to detect a significant treatment effect. A Fisher exact test was used to compare the treatment groups for the rate of responders. An analogous procedure was performed on the HAM-A. The data are presented as mean ± SD and performed at 5% level of significance. All statistical analyses were conducted with the SPSS statistical package version 9.0 (SPSS Inc., Chicago, Ill., 1999).

RESULTS

Of the 150 patients randomized to receive treatment (ITT), 139 (89%) completed the first phase of the study. Eighty-eight patients (63%) were rated as responders and 51 patients (37%) as nonresponders (Figure 1). Forty-three of 51 patients were enrolled in the second phase. Reasons for not enrolling in the switch phase were noncompliance to treatment (N = 4), hospitalization in a clinical setting (N = 2), adverse events (N = 1), and lack of motivation (N = 1).

Demographic and Clinical Characteristics

Sixteen patients were crossed over to the venlafaxine group and 27 to the paroxetine group (Figure 1). Demographic and clinical characteristics for the 2 groups are summarized in Table 1. The patient groups did not differ significantly in age, sex distribution, age at onset, duration

Table 2. Mean ± SD Changes (ITT-LOCF) on Outcome Measures in Phase 2 for Paroxetine and Venlafaxine (N = 43)

	Baseline Score (wk 16)		Endpoint Score (wk 12 and wk 28)		Change			
Scale	Paroxetine (N = 27)	Venlafaxine (N = 16)	Paroxetine (N = 27)	Venlafaxine (N = 16)	Paroxetine (N = 27)	Venlafaxine (N = 16)	df	p
Y-BOCS								
Obsessions	12.6 ± 3.9	11.9 ± 4.5	9.2 ± 4.6	11.3 ± 4.2	3.4 ± 4.0	0.7 ± 2.2	41	.017
Compulsions	13.6 ± 2.8	13.4 ± 3.1	10.4 ± 3.9	12.3 ± 3.5	3.1 ± 3.6	1.1 ± 2.1	41	.045
Total	26.1 ± 5.0	25.3 ± 6.5	19.6 ± 7.2	23.6 ± 7.0	6.5 ± 7.1	1.8 ± 3.5	41	.017
HAM-A	8.0 ± 5.1	9.3 ± 6.7	6.7 ± 5.3	9.1 ± 7.5	1.3 ± 4.0	0.2 ± 4.5	41	.62
HAM-D	6.5 ± 4.4	7.0 ± 5.2	5.4 ± 3.6	7.1 ± 6.7	0.9 ± 5.0	0.1 ± 3.6	41	.27

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3. Comparison of Side Effects in Paroxetine and Venlafaxine

Paroxetine (N = 27)		Venlafaxine (N = 16)	
Side Effect	N (%)	Side Effect	N (%)
Somnolence	15 (54)	Somnolence	6 (38)
Sweating	7 (25)	Sweating	5 (31)
Headache	6 (21)	Constipation	5 (31)
Constipation	6 (21)	Dry mouth	3 (19)
Insomnia	5 (18)	Headache	2 (13)
Nausea	5 (18)	Insomnia	2 (13)
Change in mood	5 (18)	Nausea	2 (13)
Loss of libido	5 (18)	Loss of libido	2 (13)

of illness, baseline ratings, comorbid mood or anxiety disorder or any other comorbid DSM Axis I or Axis II disorder, or previous behavioral therapies.

Response Rates in Phase 2 (N = 43)

Mean scores at baseline (week 16) and endpoint (week 28) and the mean change for the outcome measures are presented in Table 2. An ITT, LOCF analysis demonstrated a mean decrease of 1.8 ± 3.5 in the venlafaxine group and 6.5 ± 7.1 in the paroxetine group, as measured by the reduction in total Y-BOCS scores. A significant decrease in total Y-BOCS score from baseline was found in the paroxetine group ($t = 4.7$, $df = 26$, $p < .000$) but not in the venlafaxine group ($t = 2.0$, $df = 15$, $p = .065$). A statistically significant difference between the 2 treatment groups was observed in favor of paroxetine ($t = 2.7$, $df = 41$, $p = .017$). Eighteen (42%) of 43 patients were rated as responders with a decrease of at least 25% on the Y-BOCS from baseline, of which 3 (19%) of 16 patients responded in the venlafaxine group and 15 (56%) of 27 in the paroxetine group (Fisher exact test, 2-sided, $p = .010$). No statistically significant changes between baseline and endpoint were found in the venlafaxine group on the HAM-A ($t = 0.8$, $df = 15$, $p = .4$) or the HAM-D ($t = 0.3$, $df = 15$, $p = .7$). Similarly, the paroxetine group showed no statistically significant changes on the HAM-A ($t = 0.4$, $df = 26$, $p = .65$) or HAM-D ($t = 1.3$, $df = 26$, $p = .2$).

Taking into account the baseline scores at the beginning of the study (week 0), an ITT, LOCF analysis demonstrated a mean decrease on the Y-BOCS of 4.3 ± 5.3 in the paroxetine → venlafaxine group and 7.9 ± 7.0 in the venlafaxine → paroxetine group, as measured by the reduction in total Y-BOCS scores. Twenty-one (49%) of 43 patients were rated as responders, of which 5 (31%) of 16 were in the paroxetine → venlafaxine group and 16 (59%) of 27 were in the venlafaxine → paroxetine group (Fisher exact test, 2-sided, $p = .116$).

Dropouts, Tolerability, and Plasma Drug Concentrations in Phase 2

The most prevalent side effects are presented in Table 3. The profile of adverse events is comparable for both drugs, and the majority of all side effects were mild or moderate in severity in both treatment groups. Adverse experiences were reported by 98% of the patients, but only 1 patient dropped out due to adverse side effects (sexual dysfunction). No clinically significant laboratory abnormalities were found in phase 2 of the study, and no serious adverse events associated with vital sign changes were observed. Plasma levels of drugs and metabolites were recorded throughout the study, but no evidence for a relationship between treatment outcome and plasma levels was observed.

Response Rates After Phases 1 and 2 for the Total Sample (N = 150)

Mean scores at baseline (week 0) and endpoint (week 12 and week 28) and the mean change for the outcome measures for the total sample are presented in Table 4. All outcome measure decreases were statistically significant between baseline and endpoint for both treatment groups, without any difference observed between the treatment groups (Y-BOCS: $t = 1.6$, $df = 137$, $p = .14$; HAM-A: $t = 0.17$, $df = 127$, $p = .87$; HAM-D: $t = 0.2$, $df = 127$, $p = .83$). The number of responders after the first, the second, and 2 consecutive SRI treatments, according to the definitions of response proposed by the International Treatment Refractory OCD Consortium, is depicted in Table 5.[11]

Comparison of the Combined Paroxetine and Venlafaxine Trials Throughout the Study

Mean scores at baseline and endpoint and the mean change for the outcome measures for the combined paroxetine (N = 102) and venlafaxine (N = 91) trials are presented in Table 6. A significant decrease in total Y-BOCS

Table 4. Mean ± SD Changes (ITT-LOCF) on Outcome Measures in Phases 1 and 2 for the Total Sample (N = 150)

	Baseline Score (wk 0)		Endpoint Score (wk 28)		Change			
Scale	Paroxetine → Venlafaxine (N = 75)	Venlafaxine → Paroxetine (N = 75)	Paroxetine → Venlafaxine (N = 75)	Venlafaxine → Paroxetine (N = 75)	Paroxetine → Venlafaxine (N = 75)	Venlafaxine → Paroxetine (N = 75)	df	p
Y-BOCS								
Obsessions	12.5 ± 3.8	13.4 ± 3.1	8.2 ± 4.2	8.7 ± 4.7	4.4 ± 3.6	4.7 ± 4.5	137	.86
Compulsions	12.8 ± 4.0	13.4 ± 3.2	8.6 ± 4.3	8.9 ± 4.6	4.2 ± 3.0	4.5 ± 3.5	137	.86
Total	25.3 ± 5.6	26.9 ± 4.9	16.7 ± 7.7	16.5 ± 7.1	8.6 ± 4.9	10 ± 6.2	137	.14
HAM-A	11.1 ± 7.5	11.7 ± 6.7	6.4 ± 5.3	6.9 ± 5.1	4.7 ± 6.5	4.9 ± 5.6	127	.87
HAM-D	7.5 ± 5.0	8.6 ± 4.8	5.1 ± 6.7	5.8 ± 4.2	2.6 ± 6.7	2.8 ± 5.2	127	.83

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Table 5. Treatment Response After the First, the Second, and 2 Consecutive SRI Trials (N = 150)

Stages of Response	Y-BOCS Score	First SRI Trial, % (N) Wk 0–12 (N = 150)	Second SRI Trial, % (N) Wk 16–28 (N = 43)	2 SRI Trials, % (N) Wk 0–28 (N = 150)
I Recovery	< 8	10 (15)	NA	10 (15)
II Remission	< 16	23 (35)	25 (11)	31 (46)
III Full response	> 35% decrease	41 (62)	28 (12)	50 (76)
IV Partial response	25%–35% decrease	17 (26)	14 (6)	22 (33)
V Nonresponse	< 25% decrease	34 (51)	56 (24)	14 (21)
Dropout		7 (11)	(8)[a] + 2 (1)	13 (20)

[a]Eight nonresponders from phase 1 did not wish to participate in phase 2.
Abbreviation: NA = not applicable.

Table 6. Comparison (ITT-LOCF) of the Combined Paroxetine and Venlafaxine Trials Throughout the Study (N = 193)

	Baseline		Endpoint		Change			
Scale	Paroxetine (N= 102)	Venlafaxine (N = 91)	Paroxetine (N = 102)	Venlafaxine (N = 91)	Paroxetine (N = 102)	Venlafaxine (N = 91)	df	p
Y-BOCS								
Obsessions	12.5 ± 3.8	13.2 ± 4.2	8.6 ± 4.4	10.0 ± 4.7	4.0 ± 3.8	3.2 ± 4.6	183	.19
Compulsions	13.0 ± 3.7	13.4 ± 3.1	9.3 ± 4.4	10.4 ± 4.7	3.7 ± 3.2	3.0 ± 3.5	183	.18
Total	25.5 ± 5.4	26.6 ± 5.2	17.9 ± 7.8	20.4 ± 8.4	7.6 ± 5.7	6.2 ± 7.3	183	.13
HAM-A	10.3 ± 7.1	11.4 ± 6.7	6.3 ± 4.8	7.6 ± 5.5	3.5 ± 6.6	4.0 ± 5.5	183	.58
HAM-D	7.3 ± 4.9	8.3 ± 4.9	5.0 ± 5.8	6.1 ± 5.9	2.3 ± 6.0	2.2 ± 5.0	183	.90

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

score from baseline was found in the paroxetine group ($t = 13.18$, $df = 97$, $p < .00$) and in the venlafaxine group ($t = 8.0$, $df = 88$, $p < .00$), without a statistically significant difference between the 2 treatment groups ($t = 1.5$, $df = 183$, $p = .13$). On the other hand, the percentage decrease of the total Y-BOCS score was statistically significantly larger in the paroxetine group (31.6% ± 25.0%) than in the venlafaxine group (23.7% ± 23.7%) ($t = 2.0$, $df = 183$, $p = .45$), as was the number of responders (66 [65%] of 102) in the paroxetine group than in the venlafaxine group (39 [43%] of 91) (Fisher exact test, $p = .002$).

CONCLUSION

To our knowledge, this study represents the first double-blind switch trial of SRIs to provide evidence that patients with OCD unresponsive to a first SRI trial benefit from another. Forty-two percent of the nonresponders improved with a second SRI, and eventually, after 2 consecutive drug treatments, more than 70% of patients were rated as responders.

Although previous literature on the subject is sparse, our results are in line with other reports and within the expectations. In a placebo-controlled sertraline trial, 33% of patients benefited from a switch to a second SRI.[12] In a review article by Koran and Saxena,[12] Ravizza et al. reported a 20% chance of responding after switching to another SRI, and 33%–40% after switching to clomipramine. In a recently published 12-week, single-blind switch study, 3 of 8 patients responded to venlafaxine; 3 of 11, to clomipramine; and 1 of 9, to citalopram.[13] A failure to respond to clomipramine treatment resulted in a mere 20% probability of response to subsequent fluoxe-

tine treatment.[14] In brief, our data substantiate the general clinical experience that the lack of response to one or more SRIs does not preclude response to another, but also that the chance of achieving a response diminishes each time an SRI has been prescribed. Whereas 63% of the patients responded to the first SRI trial, only 42% responded to the second.

While a direct evaluation of the comparative efficacy of paroxetine and venlafaxine has not been addressed as a primary aim in this study, it should be noted that in phase 2, paroxetine was clearly superior to venlafaxine. In contrast to paroxetine, which is a selective serotonin reuptake inhibitor (SSRI), venlafaxine has a dual action, inhibiting both the uptake of serotonin and of norepinephrine at higher doses (150 and 225 mg). Some reports suggest that venlafaxine carries an advantage in efficacy over SSRIs in the treatment of depression by virtue of this dual action.[15] The additional reuptake inhibition of norepinephrine has also been suggested to explain the added anxiolytic efficacy of venlafaxine.[16] In OCD, venlafaxine has been rated by the guidelines as a second- or third-line treatment.[2] However, the results of our study demonstrate that paroxetine is more efficacious than venlafaxine in case of a nonresponse or partial response to a previous SRI trial. Therefore, although venlafaxine has proven to be effective in OCD, our data do not support the use of venlafaxine as a second-line treatment.[3] Moreover, the analysis on the combined data shows on the whole a higher response rate for paroxetine relative to venlafaxine. In general, throughout the whole study, 67% of the patients responded to paroxetine whereas 44% responded to venlafaxine. This is somewhat surprising, since OCD is considered an anxiety disorder, and venlafaxine is considered to be efficacious in a number of other anxiety disorders such as social phobia and generalized anxiety disorder.[15,17] In this regard, it is also of note that venlafaxine was not statistically significantly superior to paroxetine in reducing the HAM-A scores. At any rate, our results corroborate the general idea that the additional norepinephrine reuptake–blocking effects of venlafaxine do not result in a higher response rate in OCD.[18,19] This finding contrasts with the superior efficacy of venlafaxine over SSRIs in the treatment of depression and lends further support to the notion that depression and OCD, despite extensive comorbidity, are distinct clinical disorders with a different neurobiology and pharmacologic need.

A methodological limitation of the present study to be considered is the lack of a placebo control. We decided against using a placebo-controlled design because of ethical considerations about withholding effective therapy from chronically ill patients. Also, although a trend for greater placebo response in more recent studies has been noted, placebo responses have been reported to be low in medication trials with OCD.[20] In addition, we may assume that the patients in the switch trial are not particularly vulnerable to placebo response, as they failed to respond to the first SRI trial. Another methodological problem is our definition of nonresponse: a threshold of 25% decrease on the Y-BOCS may be considered too low. However, it has been demonstrated that for most patients a 20% to 35% decrease in mean Y-BOCS score represents a clinically meaningful change in symptom severity.[1] In addition, in most clinical trials, a less than 25% decrease on the Y-BOCS is usually considered partial response or nonresponse. Besides, our definition of nonresponse is in line with the recently proposed operational criteria of the International Treatment Refractory OCD Consortium.[11] Another limitation due to the design of the study is that we assume that the improvement in the second phase is entirely accounted for by the switch of SRIs, whereas it may be partially an effect of continuing SRI treatment for 28 weeks. Finally, it should be mentioned that our study sample is not typical of the patients seen in a clinical practice, as it was drawn from an academic psychiatric department specialized in anxiety disorders.

In summary, the results of this double-blind study indicate that switching SRIs in case of nonresponse is a useful strategy in OCD. Approximately 40% of the nonresponders benefited from treatment with another SRI. Given the chronic course of the disorder and the large amount of nonresponsive patients, it is puzzling why controlled switch trials in OCD are not more widely used. In fact, the systematic, controlled assessment of sequential pharmacotherapies may provide confirmation for a clinical practice already common in OCD.

Drug names: citalopram (Celexa), clomipramine (Anafranil), fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor, Effexor XR).

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