Venlafaxine Versus Clomipramine in the Treatment of Obsessive-Compulsive Disorder: A Preliminary Single-Blind, 12-Week, Controlled Study

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Background: The objective of this study was to investigate, in a single-blind manner over a period of 12 weeks, the efficacy and tolerability of venlafaxine versus clomipramine in the treatment of obsessive-compulsive disorder (OCD).

Method: Patients with a DSM-IV diagnosis of OCD and a Yale-Brown Obsessive Compulsive Scale (YBOCS) score ≥ 16 were randomly assigned to receive venlafaxine, 225 to 350 mg/day (26 patients), or clomipramine, 150 to 225 mg/day (47 patients), for 12 weeks, with dosage adjustments according to tolerability and response to treatment. All patients were medication-free from at least 2 months prior to study enrollment. Efficacy measures were the YBOCS and the Clinical Global Impressions scale (CGI), which were completed at baseline and every 4 weeks.We defined responders as patients who had an improvement from baseline in YBOCS score of ≥ 35% and a CGI score ≤ 2. An investigator who was blinded to patients' current medication administered rating scales independently. Moreover, patients were instructed not to reveal their current treatment to this investigator.

Results: Twenty-five patients in the venlafaxine group and 40 in the clomipramine group completed the 12-week trial. Responder rates at the end of the 12 weeks were 36% for venlafaxine (9/25) versus 50% for clomipramine (20/40) according to the visitwise analysis and 34.6% (9/26) for venlafaxine versus 42.6% (20/47) for clomipramine according to the last-observation-carried-forward analysis, with no statistically significant difference between the 2 drugs. Adverse experiences were reported by 61.5% of patients receiving venlafaxine (16/26) and by 91.5% of those receiving clomipramine (43/47).

Conclusion: Our results indicate that venlafaxine might be as efficacious as clomipramine in the acute treatment of OCD, with fewer side effects.

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Serotonin reuptake inhibitors are effective treatments for obsessive-compulsive disorder (OCD); clomipramine, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline have been proved to be effective against obsessive and compulsive symptoms independent of their antidepressant activity. However, a proportion of patients (between 40% and 60%) fail to respond to pharmacologic treatment with a first-line antiobsessional agent. Moreover, although the newer drugs such as the selective serotonin reuptake inhibitors (SSRIs) are generally considered to be safe and well tolerated, still a proportion of subjects do experience intolerable side effects and discontinue treatment prematurely. The search for new pharmacologic agents in the treatment of OCD stems from these considerations. However, no single drug acting on different neurotransmitter systems has yet proved its efficacy against obsessive-compulsive symptoms.

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that is similar to clomipramine but lacks the latter drug's anticholinergic, antihistaminic, and α-adrenergic blocking effects. Its efficacy and tolerability have been well demonstrated in the treatment of depression.

Initial case reports of patients treated with venlafaxine involved subjects with OCD resistant to other SSRIs or intolerant to their side effects. Zajecka and colleagues[1] described the case of a patient "refractory to other agents" that was treated with venlafaxine, 375 mg/day, and responded by week 5; however, they did not specify the response criterion used to assess the efficacy of venlafaxine. Ananth et al.,[2] a few years later, reported having treated 2 patients—"nonresponders or intolerant to SSRIs"—with venlafaxine, 150 mg/day, with success. Again, the authors did not describe in more detail the previous failed

treatment strategies with SSRIs and did not mention response criteria or duration of venlafaxine treatments. Another single case report was described by Grossman and Hollander[3]; they treated a patient intolerant to clomipramine and paroxetine alone with venlafaxine, 225 mg/day: 5 weeks after treatment initiation, the patient's Yale-Brown Obsessive Compulsive Scale (YBOCS) score had fallen from 24 to 7, and the patient continued to show a positive response 10 months later. The same year, Rauch and colleagues[4] described a series of 10 patients (a combination of drug-naive patients and nonresponders to previous SSRIs) treated with venlafaxine dosages between 150 and 375 mg/day (mean dose = 308 mg/day). They defined responders as patients who had an improvement in YBOCS score ≥ 35% versus baseline and a Clinical Global Impressions scale (CGI) score ≤ 2 at the end of the 12 weeks of treatment; according to these criteria, venlafaxine was effective in 3 patients. Of interest is that the 3 responders were all treatment-naive patients, while the 7 nonresponders had a mean of 2.5 previous failed treatments.[4]

Additional evidence in favor of a potential antiobsessional efficacy of venlafaxine stems from a double-blind, placebo-controlled study of 30 patients (16 taking venlafaxine) conducted over a period of 8 weeks.[5] All patients taking venlafaxine were treated with 225 mg/day; response was assessed by means of the CGI-Improvement scale. Of the 30 patients, 8 (2 taking venlafaxine and 6 taking placebo) discontinued therapy. Venlafaxine proved beneficial in 6 patients, while in 3 subjects OCD symptoms remained unchanged and in 5 others OCD symptoms became worse. Although the CGI scores showed no significant difference between the group taking venlafaxine and the group taking placebo, there was a trend toward greater improvement in venlafaxine-treated patients for the 8 weeks of treatment. The authors concluded that the number of patients who might have benefited from treatment with venlafaxine would have been higher if the study had been carried out for a longer duration than was called for in the protocol (8 weeks) and if higher dosages of venlafaxine than that used (225 mg/day) had been employed. Another bias of this study is that the authors did not mention whether patients included had been previously treated for OCD or were drug-naive.

The objective of the present study was to investigate, in a single-blind manner over a period of 12 weeks, the efficacy and tolerability of venlafaxine versus clomipramine in the acute treatment of OCD. Given the scarcity of data on venlafaxine in the treatment of OCD, we decided to perform a preliminary single-blind study comparing venlafaxine with clomipramine in patients with OCD who previously had never been treated for this condition. According to suggestions by Yaryura-Tobias and Neziroglu,[5] we chose a minimum target dose of 225 mg/day of venlafaxine and considered the possibility of higher dosages (up to a maximum of 350 mg/day) for patients tolerating 225 mg/day and showing no sign of response. For clomipramine, no reports have been made of dose findings in OCD: although some patients have shown responses at doses as low as 75 mg/day, traditionally a dose in the range of 150 to 250 mg/day seems to be most effective.[6] On the basis of such considerations, a minimum target dose of 150 mg/day was chosen; patients tolerating this dose and not showing any sign of response were allowed to increase the dose to a maximum of 225 mg/day.

METHOD

Subjects

Participants were male or female outpatients, 18 years of age or older, who met DSM-IV criteria for a primary diagnosis of OCD. All patients' diagnoses were assessed by means of the Structured Clinical Interview for DSM-IV (SCID)[7] criteria. Other inclusion criteria were as follows: (1) obsessive-compulsive symptoms had to have been present for at least 1 year prior to study entry; (2) patients had to have a YBOCS total score ≥ 16; and (3) a 17-item Hamilton Rating Scale for Depression (HAM-D) score ≤ 14 at the baseline evaluation was required. A current diagnosis of major depressive disorder and/or a HAM-D score of 15 or greater, a present or previous diagnosis of schizophrenia or other psychotic disorders, or an organic brain syndrome or medical illness that would contraindicate the use of venlafaxine or clomipramine excluded potential subjects from the study. Pregnant or nursing women and women of childbearing potential not using adequate contraceptive measures were also excluded. Patients with OCD who were in treatment or who had been previously treated with serotonin reuptake inhibitors (clomipramine or SSRIs) for OCD were excluded from the study.

Patients were recruited from referrals to the Anxiety and Mood Disorders Unit of the University of Turin, Turin, Italy. Written informed consent was obtained for all patients prior to study enrollment after the procedure had been fully explained.

Drug Administration

Patients were randomly assigned to receive venlafaxine, 225 to 350 mg/day (26 patients), or clomipramine, 150 to 225 mg/day (47 patients), for 12 weeks, with dosage adjustments according to tolerability and response to treatment. Patients were assigned to treatment with venlafaxine or clomipramine according to a treatment allocation ratio of 1 to 2.

The dosing schedules were as follows: patients receiving venlafaxine were started with a regimen of 25 mg t.i.d.; the dose was then titrated up to a minimum dose of 75 t.i.d.; patients tolerating this dose and showing no sign of response were allowed to take a maximum dose of

Table 1. Demographic and Baseline Clinical Characteristics of Patients Receiving Venlafaxine or Clomipramine[a]

Variable	Venlafaxine (N = 26)	Clomipramine (N = 47)	χ^2	t	p Value
Males, N (%)	14 (53.8)	21 (44.7)	0.563	…	.453
Age, y	28.88 ± 7.66	30.09 ± 8.71	…	–0.588	.559
Age at onset, y	24.15 ± 8.52	24.51 ± 9.92	…	–0.154	.878
Duration of illness, y	4.73 ± 4.13	5.57 ± 4.79	…	–0.756	.452
YBOCS total score	25.00 ± 4.81	25.70 ± 5.07	…	–0.577	.566
CGI-S score	4.46 ± 0.99	4.57 ± 1.06	…	–0.447	.656

[a]Values shown as mean ± SD unless otherwise noted. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

350 mg/day. Clomipramine was given initially at a dosage of 50 mg/day and increased by 50 mg/day every 2 days to a minimum daily dose of 150 mg; patients tolerating this dose and showing no sign of response were allowed to take a maximum dose of 225 mg/day.

The minimum daily doses of venlafaxine and clomipramine were reached at the end of the first week; if efficacy was insufficient and dose-limiting side effects were absent, dose escalation was permitted after a minimum of 4 weeks at the minimum daily doses and at 2-week intervals thereafter.

Efficacy Measures

Treatment response was measured by the change from baseline to final value within the 12-week comparative phase of the study. The primary measures of efficacy were the YBOCS[8–9] total score and the CGI,[10] which were completed at baseline and every 4 weeks (T0, T1, T2, and T3). For the purpose of the present study, we defined responders as patients who had an improvement from baseline in YBOCS score of ≥ 35% and a CGI score ≤ 2. An investigator who was blinded to patients' current medication administered the rating scales independently. Moreover, patients were instructed not to reveal their current treatment to this investigator.

All adverse experiences volunteered by the patient or observed by the investigator were recorded at each visit by means of the UKU Side Effect Rating Scale.[11] The occurrence of severe side effects (as defined by item 3 of the CGI "efficacy index"), lack of compliance (missing more than 3 consecutive doses of the drug), or withdrawal of patient consent were criteria for premature discontinuation from the study.

Data Analysis

Treatment group comparisons of patient demographic characteristics and baseline severity measurements were done using a chi-square test and the Student t test. Statistical significance was defined as a 2-sided p value ≤ .05. Mean YBOCS total score changes by time (week 12 – baseline) were analyzed within each group using the paired t test; mean changes from baseline were compared across the 2 groups using the unpaired t test. We used 2 different statistical methods to evaluate responders: a visitwise statistical analysis and a last-observation-carried-forward (LOCF) analysis. Responder rates were compared across the 2 groups with the chi-square test.

RESULTS

Sample

Seventy-three patients referred to the Anxiety and Mood Disorders Unit of the University of Turin were included in the study. Twenty-six were assigned to receive venlafaxine and 47, clomipramine.

Twenty-five patients in the venlafaxine group and 40 in the clomipramine group completed the 12-week trial; 1 patient taking venlafaxine dropped out between T2 and T3 for inefficacy, while 7 subjects taking clomipramine dropped out before the end of the study, 3 before T1 and 2 before T2 for intolerance to side effects and 2 between T2 and T3 for inefficacy; of the 5 subjects who dropped out because of adverse effects, 3 withdrew for nausea/vomiting and 2 for orthostatic dizziness, dry mouth, and constipation occurring together.

No group differences in sex distribution, mean age, duration of illness, or YBOCS total score were found between the treatment groups (Table 1).

Efficacy

For the patients who completed the trial, mean ± SD daily dosages for the 2 treatment groups were as follows: 265.0 ± 52.5 mg for venlafaxine and 168.1 ± 28.9 mg for clomipramine.

Patients in both the venlafaxine and the clomipramine group showed a marked and significant improvement over the 12-week study period (paired t test for mean YBOCS total score at week 12 vs. baseline: $t = 6.442$, $df = 24$, $p < .001$ for the venlafaxine group and $t = 10.586$, $df = 39$, $p < .001$ for the clomipramine group). When the YBOCS obsession and compulsion subscores were examined both groups showed a significant improvement at week 12 compared with baseline (paired t test for mean YBOCS obsession subscore: $t = 6.431$, $df = 24$, $p < .001$ for the venlafaxine group and $t = 10.043$, $df = 39$, $p < .001$ for the clomipramine group; paired t test for mean YBOCS compulsion subscore: $t = 4.391$, $df = 24$, $p < .001$ for the venlafaxine group and $t = 7.704$, $d = 39$, $p < .001$

Table 2. Mean Yale-Brown Obsessive Compulsive Scale (YBOCS) Scores at Baseline and During the Study Period: Visitwise Analysis

	Venlafaxine (N = 26)		Clomipramine (N = 47)			
YBOCS Score	Mean	SD	Mean	SD	t test	p Value
Baseline						
Total	25.00	4.81	25.70	5.07	–0.870	.387
Obsessions	12.50	2.37	12.62	2.49	–0.196	.846
Compulsions	12.12	3.50	12.62	2.83	–0.665	.508
Week 4						
Total	23.65	4.46	22.80	5.47	0.678	.500
Obsessions	11.77	2.21	11.25	2.70	0.828	.410
Compulsions	11.88	2.39	11.55	2.83	0.512	.610
Week 8						
Total	19.12	6.73	21.19	5.53	–1.383	.171
Obsessions	9.42	3.24	10.60	2.85	–1.563	.123
Compulsions	9.69	3.54	10.55	2.80	–1.106	.273
Week 12						
Total	18.36	7.11	17.30	6.15	0.636	.527
Obsessions	9.08	3.50	8.55	3.10	0.638	.526
Compulsions	9.28	3.63	8.75	3.09	0.628	.532

Table 3. Responders to a 12-Week, Single-Blind, Randomized, Controlled Trial of Venlafaxine Compared With Clomipramine: Visitwise Analysis

	Venlafaxine		Clomipramine			
Visit	N/Total N	%	N/Total N	%	χ^2	p Value
Week 4	0/26	0	1/44	2.3	0.599	.439
Week 8	6/26	23.1	6/42	14.3	0.854	.355
Week 12	9/25	36.0	20/40	50.0	1.220	.269

for the clomipramine group). Moreover, improvement was evident for all YBOCS single items (e.g., time occupied by obsessive thoughts, interference) and was not related only to a decrease in the resistance score, indicating that improvement was not secondary to anxiety reduction.

Treatment with either venlafaxine or clomipramine produced statistically significant decreases in YBOCS total scores and obsession subscores from the week 4 visit onward, and the response profiles of the 2 drugs were similar (paired t test for mean YBOCS total score at week 4 vs. baseline: $t = 3.367$, $df = 25$, $p = .002$ for the venlafaxine group and $t = 8.760$, $df = 43$, $p < .001$ for the clomipramine group; paired t test for mean YBOCS obsession score at week 4 vs. baseline: $t = 3.453$, $df = 25$, $p = .002$ for the venlafaxine group and $t = 8.496$, $df = 43$, $p < .001$ for the clomipramine group). For the YBOCS compulsion subscore, a significant improvement from baseline was evident in the venlafaxine group from week 8 onward (paired t test at week 4 vs. baseline: $t = 0.503$, $df = 25$, $p = .619$; paired t test at week 8 vs. baseline: $t = 4.162$, $df = 25$, $p < .001$), while in the clomipramine group, a significant improvement was evident from week 4 onward (paired t test at week 4 vs. baseline: $t = 3.916$, $df = 43$, $p < .001$). However, when examining by means of the unpaired t test, no differences between the 2 groups at week 4 or 8 were detected in mean YBOCS compulsion subscores (see Table 2).

Table 4. Responders to a 12-Week, Single-Blind, Randomized, Controlled Trial of Venlafaxine Compared With Clomipramine: Last-Observation-Carried-Forward Analysis

	Venlafaxine		Clomipramine			
Visit	N/Total N	%	N/Total N	%	χ^2	p Value
Week 4	0/26	0	1/47	2.1	0.561	.454
Week 8	6/26	23.1	6/47	12.8	1.296	.255
Week 12	9/26	34.6	20/47	42.6	0.440	.507

Table 5. Side Effects Reported by More Than 5% of Patients (UKU Side Effect Rating Scale)

	Venlafaxine (N = 26)		Clomipramine (N = 47)			
Side Effect	N	%	N	%	χ^2	p Value
Orthostatic dizziness	6	23.1	7	14.9	0.766	.381
Reduced duration of sleep	5	19.2	7	14.9	0.229	.632
Nausea/vomiting	5	19.2	4	8.5	1.780	.182
Sleepiness/sedation	4	15.4	9	19.1	0.162	.687
Reduced salivation	3	11.5	16	34.0	4.403	.036
Constipation	2	7.7	17	36.2	7.051	.008
Asthenia	2	7.7	10	21.3	2.249	.134
No side effects	10	38.5	4	8.5	9.688	.002

Table 2 shows mean YBOCS scores across time in the 2 treatment groups. No differences were detected between the 2 study groups in mean YBOCS total scores or obsession and compulsion subscores.

Responder rates (≥ 35% improvement in YBOCS score vs. baseline and CGI score ≤ 2) across time are shown in Tables 3 and 4: no differences were detected at any time using either the visitwise or the LOCF statistical analysis.

Adverse Experiences

Overall, adverse experiences were reported by 61.5% of patients receiving venlafaxine (16/26) and by 91.5% of those receiving clomipramine (43/47; percentages include patients who dropped out because of adverse events or noncompliance). The most common adverse experiences reported by more than 5% of patients are reported in Table 5.

DISCUSSION

The aim of the present study was to investigate, in a single-blind manner over a period of 12 weeks, the efficacy and tolerability of venlafaxine versus clomipramine in the treatment of OCD.

Previous reports on the efficacy of venlafaxine in OCD patients showed a response rate of 30% at the end of a 12-week period[4] and a response rate of 37.5% at the end of an 8-week period.[5] These 2 studies, however, do not provide sufficient information: the study by Yaryura-Tobias and Neziroglu,[5] although performed under a

double-blind condition, was biased by the short duration and the lack of definite criteria for treatment response; the study by Rauch and colleagues,[4] which used definite and appropriate response criteria (≥ 35% improvement in YBOCS score vs. baseline and CGI score ≤ 2), was performed in an open-label fashion and included a combination of drug-naive patients and nonresponders to previous SSRI treatment; moreover, they used doses in a range between 150 and 375 mg/day, while Yaryura-Tobias and Neziroglu[5] suggested that effective venlafaxine doses are at least 225 mg/day.

On the basis of such considerations, we chose to perform a pilot study in a single-blind manner and in drug-naive patients in order to provide information on the efficacy of venlafaxine in OCD patients; positive results might be considered indicative of the need for a large, double-blind, placebo-controlled study with venlafaxine. We chose clomipramine as the active comparator because of its well-established effectiveness in OCD and its similarity to venlafaxine in the dual action on norepinephrine and serotonin reuptake inhibition.

Overall, patients in both the venlafaxine and the clomipramine groups showed, in our study, a marked and significant decrease in mean YBOCS total scores over the 12-week study period. When mean YBOCS scores were examined at week 12, no differences were found between treatment groups; moreover, response rates at the end of the study were comparable for the venlafaxine and clomipramine groups. These response rates at the end of the 12 weeks (36% and 50% for venlafaxine and clomipramine, respectively, according to the visitwise analysis) are consistent with those generally reported for OCD patients. The difference in response rates between the venlafaxine and the clomipramine groups was smaller (34.6% vs. 42.5%, respectively) when we used the LOCF analysis, which takes into account dropout rates due to intolerance or inefficacy.

Given the equivalent efficacy of venlafaxine and clomipramine in the short-term treatment of OCD, the potential benefit of venlafaxine over clomipramine might be its more favorable safety profile. A higher percentage of patients treated with clomipramine in our study reported at least 1 side effect on the UKU Side Effect Rating Scale (91.5%) as compared with patients taking venlafaxine (61.5%), although the significant differences for more frequent individual side effects were restricted to "reduced salivation" and "constipation" only.

U.S. package labeling for clomipramine recommends a starting dose of 25 mg/day, and the higher starting dose of 50 mg/day employed in our study might have accounted for the higher rate of adverse events and early terminations because of intolerance to side effects that we found in our clomipramine group. However, the Expert Consensus Guideline for the Treatment of OCD[12] considers a starting dose of 50 mg/day to be adequate. Moreover, 50 mg/day has been the starting dose of clomipramine in other comparative studies in OCD.[13,14] Our dropout rate in the clomipramine group is similar to the 13.3% early discontinuation rate in the study by Freeman et al.[13] and lower than the rate of 26% found by Bisserbe and colleagues.[14] Comparative studies that used a 25-mg/day starting dose[15,16] found similar dropout rates: Zohar and Judge[15] started with 25 mg/day for the first 3 days, maintained 50 mg/day for 14 days, and then allowed upward titration according to study investigators; 17% of patients reported adverse experiences leading to withdrawal from the study. Koran and colleagues,[16] in another double-blind, comparative study, reached 100 mg/day at the end of week 2, starting with 25 mg/day for the first 4 days; 16.7% of patients taking clomipramine dropped out before the end of the study because of treatment-emergent adverse experiences. These data suggest that the starting dose of clomipramine does not play a major role in the tolerability of clomipramine treatment.

In conclusion, our results indicate that venlafaxine might be as efficacious as clomipramine in the acute treatment of drug-naive patients with OCD, with fewer side effects. Our study, however, should be considered preliminary and only suggestive of a potential antiobsessive property of venlafaxine; only large double-blind and placebo-controlled studies will elucidate the potential efficacy of venlafaxine in the acute treatment of OCD. Given the positive results of our study, such studies are strongly recommended.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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