Serotonin-Norepinephrine Reuptake Inhibitors in the Treatment of Obsessive-Compulsive Disorder: A Critical Review

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Objective: To critically review the antiobsessional properties of serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine and clomipramine) in the treatment of obsessive-compulsive disorder (OCD) as an alternative to selective serotonin reuptake inhibitors (SSRIs), which are currently considered the first-line treatment of OCD.

Data Sources: A MEDLINE search was performed to identify clinical trials with the SNRIs venlafaxine and clomipramine published from 1996 to 2004 (keywords: *SNRIs, venlafaxine, duloxetine,* and *clomipramine,* each matched individually with the term *OCD*), focusing on the best-designed studies for inclusion.

Data Synthesis: Much of the literature about SNRIs in OCD supports the efficacy of these compounds in the treatment of OCD. However, double-blind, placebo-controlled studies with venlafaxine are lacking, and the most relevant studies consist of active comparison trials between SNRIs and SSRIs. In these studies, SNRIs seem to be as effective as SSRIs in OCD; SNRIs might be preferred for patients with certain types of treatment-resistant OCD or those with particular comorbid conditions. A large number of placebo-controlled and active comparison trials with clomipramine document efficacy in OCD, and meta-analytic studies suggest a small superiority over SSRIs. Compared with clomipramine, the SNRI venlafaxine showed fewer side effects and better tolerability.

Conclusion: The SNRIs may represent a valid alternative to the SSRIs, particularly in specific cases. Double-blind, placebo-controlled studies are, however, needed to confirm the positive findings reported by several studies with venlafaxine.

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Obsessive-compulsive disorder (OCD) is a relatively common disorder, with a lifetime prevalence of about 2.5%,[1] that has long been considered a disabling and treatment-resistant condition. Treatment of OCD has improved substantially over the last 2 decades due to the introduction of the selective serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram, which provide symptom reduction in about 40% to 60% of OCD patients.[6,7] Extensive research has demonstrated that OCD responds selectively to serotonergic agents and that nonserotonergic antidepressants such as desipramine have little effect.[2,3] The selective response of OCD patients to SSRIs has focused attention on the role of the 5-HT system, the main target of these drugs, in the pathophysiology of this disorder. Although it is unlikely that 1 neurotransmitter can be responsible for all the complexities of OCD, efforts to elucidate the pathophysiology of OCD have centered on the role of this system.

For more than 2 decades, the 5-HT hypothesis has provided a frame of reference[4] for understanding the pathophysiology of OCD. The first evidence was the effectiveness of clomipramine, a tricyclic antidepressant that preferentially blocks 5-HT reuptake, compared to other tricyclics or placebo.[5–7] This evidence was subsequently confirmed by the superiority of SSRIs over other agents.[8–12] Nevertheless, since at least 40% of patients do not respond to SSRIs, other treatments have been investigated over the last decade. Increasing attention has been paid to the possible efficacy of the serotonin-norepinephrine reuptake inhibitors (SNRIs) in patients with OCD. The first evidence of the effectiveness of these compounds came from the observation that clomipramine, a tricyclic antidepressant with potent antiobsessional properties, is an inhibitor of the reuptake of norepinephrine as well as serotonin.[13]

SNRIs represent a class of antidepressants that combine the actions of SSRIs with noradrenergic reuptake inhibitors. SNRIs differ from tricyclics in having a more robust effect on 5-HT.[14,15] Unlike tricyclics, the SNRIs venlafaxine and duloxetine do not block α_1-adrenergic, cholinergic, or histaminergic receptors; this profile results in a more favorable tolerability. Venlafaxine, although

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not approved by the U.S. Food and Drug Administration for the treatment of OCD, is the only nontricyclic SNRI studied in patients with this disorder. Venlafaxine is a 2-phenyl-2-ethylamine derivative that is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants and shows different degrees of inhibition of serotonin, norepinephrine (NE), and dopamine (DA) depending on the dose. The inhibition of 5-HT reuptake seems to be prevalent at low doses, while the inhibition of NE reuptake seems to increase with increasing doses. The inhibition of DA reuptake is the least potent and seems to be present only at the highest doses with venlafaxine.[15]

The possible superiority of compounds with dual reuptake mechanisms over single action compounds is, however, still subject to debate.[15,16] Patients who have disorders with high rates of treatment resistance—such as OCD—may theoretically benefit from the use of SNRIs, because the addition of NE reuptake blockade to the 5-HT action might result in a synergistic mechanism of action of these neurotransmitter systems and might boost the efficacy of these compounds.

DATA SOURCES

Articles on the use of venlafaxine and clomipramine in the treatment of OCD published from 1996 to 2004 were located by searching MEDLINE, using the keywords *SNRIs, venlafaxine, duloxetine,* and *clomipramine,* each matched individually with the term *OCD*. For clomipramine, which has a firmly established efficacy in the treatment of OCD based on almost 40 years of research, a comprehensive summary of key studies was included. In addition to reporting the overall results from comparison studies, we have underscored throughout this review clinically significant differences in the efficacy, tolerability, and safety of these medications that might suggest specific circumstances for their use in OCD. Attention was also focused on side effect profiles of venlafaxine compared to clomipramine.

DATA SYNTHESIS

Venlafaxine

For venlafaxine, 3 double-blind studies (2 active comparison studies and 1 placebo-controlled study), 1 single-blind active comparison study, 3 open-label trials, and a case-report series were located in the literature and included in this review. These reports are presented in Tables 1 and 2.

In a recent double-blind, active comparison study, Denys and coworkers[17] randomly assigned 150 OCD patients to venlafaxine (up to 300 mg/day) or paroxetine (up to 60 mg/day) for 12 weeks. Full and partial response were defined, respectively, as decreases of 50% and 35% on the Yale-Brown Obsessive Compulsive Scale (YBOCS).[25] An intent-to-treat last-observation-carried-forward (LOCF) analysis demonstrated improvement in both treatment groups but no significant differences between them. For example, response rates were comparable looking at full response (24% venlafaxine vs. 22% paroxetine) or partial response (37% venlafaxine vs. 44% paroxetine). Of note, the venlafaxine group had undergone significantly more prior medication trials and so could be considered a more refractory group. Side effects were considered mild to moderate in severity, and only a small percentage of patients (5%) dropped out due to adverse effects (6 treated with paroxetine and 2 treated with venlafaxine). The investigators concluded that venlafaxine and paroxetine were equally effective in treating patients with OCD, but the absence of a placebo control group precludes a definitive conclusion based on this study regarding efficacy in OCD. This study may not have provided an optimum test of venlafaxine since high doses were not used (i.e., between 300–450 mg/day); for venlafaxine, both efficacy and side effects are dose related. In a second phase of this study,[18] after the prior drug was tapered for 4 weeks, 43 patients who did not respond in the first phase (nonresponse was defined as less than 25% reduction on the YBOCS) were switched to the alternate antidepressant for 12 additional weeks. Of the 16 patients who received venlafaxine, 3 subjects (19%) were considered responders (response now defined as a decrease of at least 25% on the YBOCS from the phase 2 baseline), whereas 15 (56%) of the 27 patients receiving paroxetine were responders. A statistically significant difference between the 2 groups was observed in favor of paroxetine. However, the small sample size, the absence of a placebo control group, and the use of a different criterion for response limit the interpretation of the findings from this second study.

So far, only 1 double-blind, placebo-controlled trial[20] with venlafaxine has been conducted in OCD patients. Yaryura-Tobias and Nerizoglu randomly assigned 30 OCD patients to venlafaxine (up to 225 mg/day, N = 16) or placebo (N = 14) for 8 weeks; there were 22 completers (14 for venlafaxine, 8 for placebo). At the end of the study, they did not find statistically significant differences in response (Clinical Global Impressions scale [CGI], critical ratings of avoidance) between the active drug and the placebo, but they reported strong trends on these measures in favor of the venlafaxine group. In this study, however, the small size of the sample, the short length of the trial, the low dosages administered, and the lack of standard outcome measures (e.g., YBOCS) represent methodological limitations. It is possible, as the authors suggested, that a statistically significant responder rate would have been shown if the study had continued for additional weeks with increasing doses of venlafaxine.

Table 1. Double-Blind and Single-Blind (placebo-controlled and active comparison) Studies With Venlafaxine in OCD Treatment

Citation	Study Design and Sponsor	Sample Features	Treatment Group Dose and N	Control Group Dose and N	Trial Length	Outcomes	Conclusions
Denys et al, 2003[17]	Double-blind, random assignment, active comparison, ITT. Sponsors: Wyeth, GSK	150 outpatients (139 completers) with DSM-IV OCD Dropouts due to side effects: 6 in the PAR group, 2 in the VEN XR group	VEN XR final dose = 300 mg/d; N = 75	PAR final dose = 60 mg/d; N = 75	12 wk	An ITT, LOCF analysis demonstrated no significant differences between VEN and PAR groups in responder rates (partial response = decrease ≥ 35% on the YBOCS: 37% VEN vs 44% PAR; full response = decrease ≥ 50% on the YBOCS: 24% VEN vs 22% PAR)	VEN (300 mg/d) was equally as effective as PAR (60 mg/d) in treating patients with OCD. The study did not include dosages higher than 300 mg/d of VEN. A methodological limitation of the study is the lack of a placebo control
Denys et al, 2004[18]	Double-blind, random assignment, active comparison, ITT. Sponsors: Wyeth, GSK	43 outpatients (42 completers) with DSM-IV OCD who did not respond to a previous 12-week trial of PAR or VEN (< 25% decrease on the YBOCS) Only 1 dropout due to side effects, but no mention of the group in which it occurred	VEN XR final dose = 300 mg/d; N = 16	PAR final dose = 60 mg/d; N = 27	12 wk	A significant decrease in total YBOCS score from baseline was found in the PAR group ($t = 4.7$, $df = 26$, $p < .000$) but not in the VEN group ($t = 2.0$, $df = 15$, $p = .065$). A statistically significant difference between the 2 treatment groups was observed in favor of PAR ($t = 2.7$, $df = 41$, $p = .017$). While analysis of change in YBOCS showed statistically significant difference between treatments, percent responder analysis did not differ	Small-sample nonresponder crossover study showing that PAR is more efficacious than VEN in patients who were nonresponders or partial responders to a trial of the other medication. Methodological limitations include the lack of a placebo control, differing criteria for response from earlier trial, doses below 300 mg/d of VEN, and the small size of the sample
Albert et al, 2002[19]	Single-blind, random assignment, active comparison, ITT. Sponsor: none specified	73 outpatients (65 completers) with DSM-IV OCD Dropouts due to side effects: 5 in the CMI group, 0 in the VEN group	VEN doses ranging from 225–350 mg/d (mean = 265.0 mg/d); N = 26	CMI doses ranging from 150–225 mg/d (mean = 168.1 mg/d); N = 47	12 wk	No statistically significant differences were found between the 2 drugs in response rates (improvement from baseline in YBOCS ≥ 35% and CGI score ≤ 2) according to the visitwise analysis (36% VEN vs 50% CMI) or to the LOCF analysis (34.6% VEN vs 42.6% CMI). The VEN group reported fewer side effects	Small preliminary study suggesting that VEN 225–350 mg/d might be as efficacious as CMI in the acute treatment of OCD, with fewer side effects. A methodological limitation of the study is the lack of a placebo control
Yaryura-Tobias and Nerizoglu, 1996[20]	Double-blind, placebo-controlled, random assignment. Sponsor: Wyeth-Ayerst	30 outpatients (22 completers) with DSM-IV OCD No mention regarding the cause of the 8 dropouts	VEN doses up to 225 mg/d; N = 16	Placebo N = 14	8 wk	No significant differences were found between the 2 groups according to the outcome measures (CGI, critical ratings of avoidance), even if a positive trend was observed for the VEN group across 7 wk	Small-sample study with no YBOCS measure and with shorter duration and lower dosages than those generally foreseen, so the results are inconclusive

Abbreviations: CGI = Clinical Global Impressions scale, CMI = clomipramine, GSK = GlaxoSmithKline, ITT = intent-to-treat, LOCF = last-observation-carried-forward, OCD = obsessive-compulsive disorder, PAR = paroxetine, VEN = venlafaxine, XR = extended release, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 2. Open-Label Studies With Venlafaxine in OCD Treatment

Citation	Study Design and Sponsor	Sample Features	Dose	Trial Length	Outcomes	Conclusions
Hollander et al, 2003[21]	Unblinded, uncontrolled. Sponsor: private foundation	39 outpatients with DSM-IV OCD; of these, 29 were resistant to prior SRI treatment trials No dropout	VEN doses up to 450 mg/d (mean final = 232.2 mg/d, mean maximum = 288.1 mg/d)	Mean = 18 ± 13 mo	69% of the patients were responders (response = CGI score of 1 or 2) at the end of the trial. 75.9% of the patients who did not respond to 1 or more previous SRI trials were rated as responders. 81.8% of the patients who did not respond to 2 or more previous SRI trials were rated as responders	Open-label trial in which VEN was shown to be beneficial to individuals with OCD, including those who had not responded to prior SSRI trials. Of note, this study had a longer observation period and higher dosages of VEN (up to 450 mg/d) than other VEN studies
Sevincok and Uygur, 2002[22]	Unblinded, uncontrolled. Sponsor: none specified	12 outpatients with DSM-IV OCD No dropout	VEN doses ranging from 150 to 225 mg/d (mean = 210.0 mg/d)	8 wk	75% of patients were judged responders based on ≥ 35% decrease in YBOCS, whereas 50% of patients were judged responders based on CGI scores of 1 or 2	Small sample size, open-label study supporting the efficacy of VEN in the acute treatment of OCD. Statistically significant differences in treatment response were first observed by wk 4
Rauch et al, 1996[23]	Unblinded, uncontrolled. Sponsor: none specified	10 outpatients with DSM-IV OCD No dropout	VEN doses ranging from 150 to 375 mg/d (mean maximum = 308.3 mg/d)	12 wk	30% of patients were judged responders based on ≥ 35% decrease in YBOCS, whereas 40% of patients were judged responders based on CGI scores of 1 or 2	Small sample size, open-label study supporting the potential antiobsessional efficacy of VEN. Of note, patients who were treatment-naive showed the most robust treatment responses
Marazziti, 2003[24]	Unblinded, uncontrolled. Sponsor: none specified	5 outpatients with DSM-IV OCD and previous lack of response to SSRI treatment No dropout	VEN doses ranging from 150 to 225 mg/d	Ranging from 8 to 48 wk	All patients showed a meaningful improvement in OCD symptoms based on YBOCS, HAM-D, and other clinical evaluations; however, these were not administered to every patient	Series of 5 case reports suggesting the efficacy of VEN without particular adverse effects in patients with OCD who did not respond previously to SSRIs. Of note, for the majority of patients, symptom improvement was maintained at 1 y of treatment

Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, OCD = obsessive-compulsive disorder, SRI = serotonin reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, VEN = venlafaxine, YBOCS = Yale-Brown Obsessive Compulsive Scale.

In a 12-week, single-blind trial, Albert and colleagues[19] randomly assigned 73 patients with OCD to venlafaxine (225–350 mg/day; mean dose = 265 mg/day) or clomipramine (150–225 mg/day; mean dose = 168 mg/day). At the end of the study, comparing the efficacy of these 2 compounds, using both visitwise and LOCF analyses, the investigators found no statistically significant differences in responder rates (response was defined as an improvement ≥ 35% on the YBOCS and a CGI[26] score ≤ 2) between these 2 groups and concluded that venlafaxine might be as efficacious as clomipramine in the acute treatment of OCD and have fewer side effects. However, the single-blind nature of the trial and the absence of a placebo control group prevent this study from being considered definitive.

In 2003, Hollander and colleagues[21] reported the results of an open-label clinical trial in which they treated 39 OCD patients, including 29 who were resistant to prior serotonin reuptake inhibitor (SRI) treatment trials, for a mean period of 18 months with dosages of venlafaxine up to 450 mg/day (mean final dosage = 232 mg/day). At the end of the study, 69% of trial completers were responders (CGI score of 1 or 2). Of note, 75.9% of the patients who did not respond to 1 or more previous SRI trials, and 81.8% of those who did not respond to 2 or more SRI trials, were rated as responders. Although this is an open-label study, and therefore subject to treating clinician bias, the results are interesting because it was conducted over an extended time period (18 months) and used higher doses (up to 450 mg/day) than in prior studies. In addition, this dose range had good tolerability, and a high rate of improvement for treatment-resistant patients was reported.

In 2002, Sevincok and Uygur[22] treated 12 OCD patients with venlafaxine for 8 weeks in an open-label trial and reported response rates of 75% based on the YBOCS (decrease ≥ 35%) and 50% based on the CGI (score of 1 or 2) and no dropouts. This confirmed the efficacy of venlafaxine (ranging from 150 to 225 mg/day) in the acute treatment of OCD without serious side effects.

Previously (in 1996), Rauch and coworkers[23] conducted a 12-week open-label trial in which 10 OCD patients received venlafaxine (ranging from 150 to 375 mg/day; mean dose = 308 mg/day). The responder rates for the 9 completers were 30% based on the YBOCS (decrease ≥ 35%) and 40% based on the CGI (score of 1 or 2); a more robust treatment response was reported for the 3 treatment-naive patients than for the 6 in whom previous trials had failed. Finally, Marazziti,[24] in 2003, reported a case series of 5 OCD patients, previously resistant to SSRI trials, who showed symptom improvements (YBOCS, HAM-D, and other clinical evaluations) with dosages of venlafaxine ranging from 150 to 225 mg/day. All patients maintained a clinical response for at least 1 year without reporting significant side effects.

Clomipramine

Clomipramine is a tricyclic antidepressant with potent serotonin reuptake inhibition[27]; however, given the capacity of this compound to also inhibit noradrenergic reuptake, it is an SNRI. In addition, one of the primary metabolites of clomipramine, desmethylclomipramine, is a potent norepinephrine uptake blocker. There is considerable literature available on the use of clomipramine in the treatment of OCD. These reports are presented in Tables 3 to 5.

The antiobsessional property of clomipramine has been established by almost 40 years of research. The first studies[40,41] on its potential anti–obsessive-compulsive effect go back to the second half of the 1960s. By 1980, a series of anecdotal studies[42] demonstrated the efficacy of clomipramine in 184 of 226 patients with OCD at doses ranging from 75 to 300 mg/day. The majority of the studies conducted from 1980 to 1990[2,5,27,42–44] showed, moreover, greater efficacy for clomipramine than for other tricyclics in treating obsessive-compulsive symptoms. In 1991, a large multicenter, double-blind trial[29,45] involved 384 OCD patients randomly assigned to clomipramine or to placebo for a period of 10 weeks. As measured by the YBOCS, symptoms in the clomipramine group decreased by 40% to 45%, whereas the placebo group experienced virtually no change in symptoms (less than 5%). Generally, symptom improvement was observed in clomipramine studies by the fourth to sixth week of treatment[42,43,46–48]; however, as many authors highlighted,[5,49] it may take 12 weeks or longer to see the full benefit of the medication (Table 3).

In 1997, Koran and colleagues[50] compared the efficacy of oral and intravenous clomipramine in a double-blind study and reported a more rapid response in the group treated with the intravenous drug, although at the end of the trial there were no differences between the 2 groups. In a subsequent study,[51] intravenous clomipramine was also found to be efficacious in patients who were previously refractory to or unable to tolerate the oral formulation. In the last 2 decades, several double-blind studies have compared clomipramine with different SSRIs, including sertraline,[52] fluoxetine,[35] and fluvoxamine[30–34] (Table 4), and finally paroxetine.[53] These studies showed equal efficacy between SSRIs and clomipramine, highlighting, however, important differences in the side effect profiles, with clomipramine having a poorer profile due to its anticholinergic effects. Finally, several studies[5,46,47,54–56] have demonstrated that the antiobsessional properties of clomipramine are independent of its antidepressant effect and that the effective dosage (150–250 mg/day) and duration of treatment (from 3 to 12 months) for OCD are different from those effective in the treatment of depressed patients.

In addition, various meta-analytic studies (Table 5) have underscored the antiobsessional property of clomipramine. Greist et al. (1995)[9] conducted the first meta-analytic study of the antiobsessional medications of the time. They found that clomipramine was significantly more effective than fluoxetine, fluvoxamine, and sertraline and that a significantly greater proportion of the clomipramine study participants were rated much or very much improved. Abramowitz's meta-analysis[37] reveals the effectiveness of all SRIs studied, with a modestly greater effect size for clomipramine; this is equalized when side effect profiles are adjusted. In the Eddy et al. study,[38] once again, clomipramine had greater effect sizes than the other SRIs with the caveat that the studies considered are earlier reports and there was a high dropout rate.

In each of the meta-analytic studies, the effect of clomipramine was greater than that for the SSRIs. However, this finding has to be tempered by the "head-on" trials showing no difference. The finding of superiority in effect sizes of clomipramine versus placebo studies compared to the SSRIs, but no superiority in head-on comparisons, poses a dilemma. Several explanations have been proposed. The Ackerman and Greenland study[39] investigated study design and participant characteristics and found that age at onset, pretrial severity, date of publication, duration of trial, and length of single-blind pre-randomization impact on efficacy, but after controlling for these predictive factors, clomipramine still appeared superior. This study is important because many of the randomized trials with clomipramine were conducted many years earlier than those of the other antiobsessional medications. The effect size in these studies was relatively high, presumably related to a very low placebo response. It has been suggested that this was the result of the less complicated clinical presentation of the participants in these early studies compared to those in the contemporary studies. However, controlling for the year in which the different studies were performed, as accomplished in Ackerman and Greenland's study, did not reduce the superiority of clomipramine. This apparent advantage of clomipramine needs to be borne in mind, yet the greater test is the head-on comparison.

Table 3. Double-Blind, Placebo-Controlled Studies With Clomipramine in OCD Treatment

Citation	Study Design and Sponsor	Sample Features	Treatment Group Dose and N	Control Group Dose and N	Trial Length	Outcomes	Conclusions
Thoren et al, 1980[5]	Double-blind, placebo-controlled. Sponsor: none specified	38 inpatients retrospectively diagnosed using RDC criteria (12 screened out); age range 19–61 y; illness duration > 1 y	CMI dose = 150 mg/d; N = 8	Nortriptyline dose = 150 mg/d; N = 8. Placebo N = 8	5 wk	OCD Scale mean reduction: CMI 42%, nortriptyline 21%, placebo 0%. Non–statistically significant difference between nortriptyline and CMI	Small-sample study showing the effectiveness of CMI
Katz et al, 1990[28]	Double-blind, placebo-controlled, random assignment, ITT, multicenter. Sponsor: Ciba-Geigy	282 outpatients diagnosed using DSM-III criteria; HAM-D < 17, YBOCS ≥ 16, and NIMH-OC ≥ 7; age range 18–65 y; excluded diagnoses: depression, anxiety, Tourette's disorder, schizotypal disorder, psychosis; 32 patients not randomized CMI dropouts: 10 adverse reactions; extension, 17 adverse reactions.	CMI dose = 200 mg/d, flexible doses up to 300 mg/d; N = 134	Placebo N = 129 Placebo dropouts: 5 no response; extension, 10 no response	10 wk; extension, 1 y	NIMH-OC score decrease of 4 for CMI vs 0 for placebo. NIMH-OC improvement to a subclinical level, 50% of CMI group vs 4% of placebo group. Physician's Global: 50% CMI group vs 7% of placebo group had CGI ratings of much/very much improved	Large-sample study showing the superiority of CMI over placebo; the improvement achieved with CMI continued for 1 y
Clomipramine Collaborative Study Group, 1991[29]	Double-blind, placebo-controlled, random assignment, ITT, multicenter. Sponsor: Ciba-Geigy	575 outpatients diagnosed using DSM-III criteria; YBOCS ≥ 16 and NIMH-OC ≥ 7; excluded were patients with prior behavioral therapy or CMI treatment 5% of subjects in each group dropped out	CMI dose = 200 mg/d, flexible doses up to 300 mg/d; N = 260	Placebo N = 260	10 wk	YBOCS mean decrease, 40% for CMI vs 4% for placebo; ≥ 35% decrease in YBOCS score, 55% of CMI group vs 7% of placebo group. NIMH-OC mean decrease, 35% vs 3%; NIMH-OC improvement to a subclinical level (rating of at least "much improved"), 49% of CMI group vs 3% of placebo group. Patients' and physicians' reports of therapeutic change: both showed significant improvement	Large-sample study showing the superiority of CMI over placebo. 4 patients (2%) exhibited seizures, 17% of subjects had elevated transaminases, maximum daily dose not to exceed 250 mg due to a 2% frequency of seizures in doses above this level

Abbreviations: CGI = Clinical Global Impressions scale, CMI = clomipramine, HAM-D = Hamilton Rating Scale for Depression, ITT = intent-to-treat, NIMH-OC = National Institute of Mental Health Global Obsessive Compulsive Scale, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 4. Double-Blind, Active-Comparison Studies With Clomipramine in OCD Treatment: Clomipramine Versus Fluvoxamine and Clomipramine Versus Fluoxetine

Citation	Study Design and Sponsor	Sample Features	Treatment Group Dose and N	Control Group Dose and N	Trial Length	Outcomes	Conclusions
Mundo et al, 2001[30]	Double-blind, random assignment, active comparison, ITT. Sponsor: Solvay	227 outpatients (217 in efficacy analysis) with DSM-III-R OCD, minimum score on NIMH-OC: 7, baseline YBOCS score > 25 45 dropouts: 19 FLV vs 26 CMI; adverse events dropouts: 7.8% FLV vs 16.1% CMI	CMI doses of 150–300 mg/d; N = 105	FLV doses of 150–300 mg/d; N = 112	10 wk	The percentage of responders (response ≥ 35% improvement in the YBOCS total score) at the end of the study was similar in both groups (62% FLV vs 65% CMI, LOCF analysis; YBOCS decreased from 26.5 to 14.3 with FLV vs 25.4 to 13.4 with CMI). FLV was better tolerated than CMI; patients treated with CMI had more anticholinergic side effects (dry mouth, constipation, and tremor) and premature withdrawals due to adverse events	Large multicenter trial showing that FLV is as effective as CMI in the treatment of OCD but has a better tolerability. A methodological limitation is the lack of a placebo control group
Koran et al, 1996[31]	Double-blind, random assignment, active comparison, ITT. Sponsor: Solvay	79 outpatients (56 completers) with DSM-III-R OCD; minimum YBOCS score:16 23 dropouts: 8 FLV vs 15 CMI; adverse events dropouts: 5 FLV vs 7 CMI	CMI doses of 100–250 mg/d (mean maximum dose = 201 mg/d); N = 42	FLV doses of 100–300 mg/d (mean maximum dose = 255 mg/d); N = 37	10 wk	Based on ≥ 25% and ≥ 35% decreases in YBOCS, 56% and 44% of patients, respectively, were judged responders in the FLV group compared to 54% and 38% in the CMI group. YBOCS 30.2 FLV vs 30.0 CMI	FLV and CMI were equally effective in reducing OCD symptoms over a 10-wk treatment period but displayed different side effects. A methodological limitation is the lack of a placebo group
Milanfranchi et al, 1997[32]	Double-blind, random assignment, active comparison, ITT. Sponsor: none specified	26 outpatients (25 completers) with DSM-III-R OCD; minimum YBOCS score: 16 1 dropout in CMI group due to urinary infection	CMI doses of 50–300 mg/d; N = 12	FLV doses of 50–300 mg/d; N = 13	9 wk	At endpoint, both YBOCS and CGI scores indicated an equal improvement in the 2 groups (38% in the patients taking FLV and 40% in those taking CMI, as compared with baseline values), but onset was faster in the CMI group. Side effects, in particular anticholinergic side effects, were more prominent in the CMI group	Small-sample study showing that FLV is as effective as CMI in the treatment of OCD but has a better tolerability. CMI, however, showed a faster response than FLV. A methodological limitation is the lack of a placebo control group
Freeman et al, 1994[33]	Double-blind, random assignment, active comparison, ITT. Sponsor: Solvay	66 outpatients (64 in efficacy analysis) with DSM-III-R OCD; minimum YBOCS score: 16 17 dropouts: 6 FLV vs 11 CMI; adverse events dropouts: 5 FLV vs 4 CMI	CMI doses of 100–250 mg/d (mean final dose = 200 mg/d); N = 32	FLV doses of 100–250 mg/d (mean final dose = 200 mg/d); N = 34	10 wk	LOCF analysis showed no significant differences between the 2 groups (YBOCS score reduction: 8.6 FLV vs 7.8 CMI). YBOCS obsession-free interval was longer in the FLV group, particularly among patients with disease duration >12 mo. CMI group reported more anticholinergic effects; FLV group, more headaches and insomnia	Multicenter trial in which FLV was as effective as CMI; FLV produced fewer anticholinergic side effects and caused less sexual dysfunction than CMI. A methodological limitation is the lack of a placebo group
Smeraldi et al, 1992[34]	Double-blind, random assignment, active comparison. Sponsor: none specified	12 outpatients (10 completers) with DSM-III-R OCD; 7 patients had a codiagnosis of major depression 2 dropouts: 1 in the FLV group due to increase in aggresive behavior and 1 in the CMI group	CMI doses up to 200 mg/d; N = 5	FLV doses up to 200 mg/d; N = 5	12 wk	Both treatments induced a marked improvement of the obsessive and compulsive symptoms (YBOCS) without statistically significant differences between the 2 groups (YBOCS 31.8 ± 4.8 to 18.2 ± 2.5 in the FLV group vs 25.4 ± 9.3 to 15.2 ± 12.4 in the CMI group). Improvement in depressive symptoms was noted in both groups as well	Small-sample study showing the equal efficacy of FLV and CMI in the acute treatment of OCD and their equal antiobsessional effects. A methodological limitation is the lack of a placebo control

continued

Table 4. Double-Blind, Active-Comparison Studies With Clomipramine in OCD Treatment: Clomipramine Versus Fluvoxamine and Clomipramine Versus Fluoxetine (cont.)

Citation	Study Design and Sponsor	Sample Features	Treatment Group Dose and N	Control Group Dose and N	Trial Length	Outcomes	Conclusions
Pigott et al, 1990[35]	Double-blind, random assignment, crossover. Sponsor: none specified	12 outpatients with DSM-III-R OCD; 1 y illness; age inclusion criterion of 18–65 y; Global OCD Rating Scale > 4/10	CMI maximum dose = 250 mg/d, mean = 209 mg/d; N = 5	FLUOX maximum dose = 80 mg/d, mean = 75 mg/d; N = 6	10 wk, then 4 wk of washout, then 10 wk	YBOCS significant decrease in both groups, nonsignificant difference between groups. Adverse event rates greater for CMI	Small sample size and no placebo-controlled group. The speed of response to the second drug was not increased, requiring the same amount of time to response, and exacerbations occurred during washout
Lopez-Ibor et al, 1996[36]	Double-blind; random assignment, active comparison. Sponsor: none specified	55 patients with DSM-III-R OCD; CGI > 4; YBOCS > 16; OCD > 6 months; No difference in dropout rates	CMI dose = 150 mg/d; N = 25	FLUOX dose = 40 mg/d; N = 30	8 wk	YBOCS nonsignificant difference between groups; response rate (≥ 25% change in YBOCS score) CMI > FLUOX; (≥ 35% YBOCS change) non–statistically significant difference; CGI CMI > FLUOX	Small sample, no placebo-controlled group, and low doses. CMI better on some indices; both drugs were well tolerated. FLUOX group had 2 point higher YBOCS at baseline

Abbreviations: CGI = Clinical Global Impressions scale, CMI = clomipramine, FLUOX = fluoxetine, FLV = fluvoxamine, ITT = intent-to-treat, LOCF = last-observation-carried-forward, NIMH-OC = National Institute of Mental Health Global Obsessive Compulsive Scale, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 5. Meta-Analyses of Clomipramine in OCD Treatment

Citation	Study Design	Sample Features and Results	Conclusions
Abramowitz, 1997[37]	Double-blind; 32 studies 1975–1995	Effect size, clinician rating/patient rating: CMI vs placebo 1.31/0.66 (N = 8 studies) FLV vs placebo 1.28/0.37 (N = 3 studies) SERT vs placebo 0.37/1.09 (N = 2 studies) FLUOX vs placebo 0.68 (clinician rating only; N = 2 studies) CMI vs non-SRI 0.37/0.70 (N = 6 studies) Clinician rating scales included YBOCS, CGI, CPRS Patient rating scales included LOI, MOCI, NIMH-OC	Side effect contrast most predictive of effect size Non-SRIs ineffective CMI modestly greater effect size than SSRIs, considered completers only in effect size determination
Eddy et al, 2004[38]	Double-blind; 32 studies, 3588 patients 1980–2001	1/3 of patients (3%–50%) excluded from the 6 studies reporting exclusion data; at least 80% of participants (all studies) completed the trial (range, 80%–92%) Effect size, pre–post: CMI 1.55, SERT (highest of SSRIs) 1.36 Effect size, drug vs placebo: CMI 1.35, FLV (highest of SSRIs) 0.86	CMI greater effect sizes than other SRIs; however, CMI studies were conducted earlier than the SSRI studies
Ackerman and Greenland, 2002[39]	Double-blind, placebo-controlled; 25 studies; used meta-regression (effect-size modeling) 1989–1996	YBOCS score change difference: CMI vs placebo –8.19 (N = 7 studies) FLV vs placebo –4.84 (N = 4 studies) FLUOX vs placebo –1.61 (N = 3 studies) SERT vs placebo –2.47 (N = 4 studies) PAR vs placebo –3.0 (N = 1 study) CMI vs SSRI 0.15 (NSD), (N = 6 studies) CMI vs FLV 1.23 (NSD), (N = 4 studies)	CMI superiority persisted after controlling for heterogeneity effects

Abbreviations: CGI = Clinical Global Impressions scale, CMI = clomipramine, CPRS = Comprehensive Psychopathological Rating Scale, FLUOX = fluoxetine, FLV = fluvoxamine, LOI = Leyton Obsessional Inventory, MOCI = Maudsley Obsessive Compulsive Inventory, NIMH-OC = National Institute of Mental Health Global Obsessive Compulsive Scale, NSD = non–statistically significant difference, OCD = obsessive-compulsive disorder, PAR = paroxetine, SERT = sertraline, SRI = serotonin reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.

DISCUSSION

The majority of venlafaxine trials, although mostly conducted without placebo controls, demonstrate the efficacy of this compound in short- and intermediate-term trials and in both treatment-naive and treatment-resistant OCD patients. Venlafaxine was as effective as paroxetine and clomipramine, and it was generally well tolerated by patients. However, due to the absence of a successful double-blind, placebo-controlled trial, and the presence of only double-blind active comparison studies, venlafaxine cannot be considered a first-line medication treatment for patients with OCD at this time.

There are, however, reasons to consider venlafaxine as a valid alternative to SSRIs. In 2 double-blind, active comparison studies,[17,18] venlafaxine was shown to be equally effective to paroxetine and clomipramine, currently considered 2 treatments of reference in the short- and intermediate-term treatment of OCD. In addition, in 1 double-blind trial[17] and in 2 case reports,[24] venlafaxine was shown to be particularly effective in OCD patients who did not previously respond to SRI/SSRI trials. Finally, both double-blind and open-label studies show venlafaxine to be well tolerated. In the majority of the studies, symptom reduction was generally observed within 4 weeks of treatment initiation, and improvement continued gradually during the following weeks. Some but not all meta-analytic studies comparing venlafaxine to SSRIs in the treatment of depression suggest greater efficacy of the SNRIs.[57,58] Venlafaxine seems more effective in OCD at the higher dose range. This may reflect greater noradrenergic activity at high doses and may also support the possible efficacy of SNRIs in patients with prior SSRI treatment resistance or in patients showing a partial response.

Perhaps there are some clinical situations in which venlafaxine might be preferred to SSRIs. For example, venlafaxine might be more efficacious than SSRIs in the presence of particular comorbid conditions such as attention-deficit/hyperactivity disorder (ADHD).[59,60] Also, venlafaxine has been shown in some trials to have a greater likelihood of remission than SSRIs.[58,61–63] Thus, it might be considered a valid alternative in cases with a low rate of response using traditional pharmacologic approaches. In addition, venlafaxine and other SNRIs could conceivably have an advantage over SSRIs in resolving the symptoms of comorbid anxiety and depression, with resultant remission.[64–66]

Another potentially important consideration for the future, for which there is as yet insufficient information, concerns the probable clinical heterogeneity of OCD. It is plausible, even likely, that as more is learned about the condition, different compounds will exhibit different therapeutic profiles. This is also likely to become a reality as pharmacogenetic studies come of age.

With regard to side effects, venlafaxine has shown a profile better than that of clomipramine, and more similar to those of SSRIs, with dosages ranging from 150 to 300 mg/day. However, one peculiar mechanism supporting the efficacy of this compound consists of the "noradrenergic boost" that operates at higher dosages: the possibility of developing more serious side effects, especially hypertension, with increasing doses, especially at the highest doses, when the action on the noradrenergic and dopamine system becomes more consistent, deserves further research.

With regard to clomipramine, its efficacy in treating obsessive-compulsive symptoms has been supported by almost 40 years of research, and this compound still represents one of the most efficacious therapies in the pharmacologic approach to OCD. As demonstrated by double-blind placebo-controlled and active comparison studies with other SSRIs, clomipramine is one of the anti-obsessional treatments with the most abundant data supporting its efficacy in OCD. Various meta-analytic studies demonstrate the equal efficacy, and, in some cases, even a small superiority, of clomipramine compared with other SSRIs, underscoring, however, its less favorable tolerability. In addition to SNRI properties, in fact, clomipramine, like other tricyclic antidepressants, has anticholinergic, antihistaminergic, and anti–α-adrenergic effects. This is consistent with the clinical side effects reported by the patients receiving clomipramine in clinical practice. Clomipramine's main side effects are due to the receptor blockade of the cholinergic, histaminergic, and α-adrenergic system. These neurochemical effects result in constipation, blurred vision, dry mouth, and drowsiness due to M_1 receptor blockade; weight gain and drowsiness due to H_1 receptor blockade; and dizziness and decreased blood pressure due to α_1-adrenergic receptor blockade. Although some patients habituate to most of these side effects over time, others cannot tolerate this side effect profile, reducing compliance. Venlafaxine shows a better side effect profile because of its selectivity.

CONCLUSION

Over the last decade, several studies have demonstrated the efficacy of venlafaxine, an SNRI, in treating patients with OCD. However, given the scarcity of double-blind studies, further trials are needed to confirm these preliminary positive results. Venlafaxine deserves further study in treating OCD patients resistant to prior SRI/SSRI treatments and in patients with comorbid ADHD, anxiety, or depression. Furthermore, SNRIs may have a place in the treatment of patients with comorbid anxiety and depression and in effecting a more complete remission. The one study[19] that directly compared venlafaxine to clomipramine in the treatment of OCD reported

an equal efficacy for both the treatments, but a better tolerability for venlafaxine. The antiobsessional properties of clomipramine have been confirmed by numerous studies in decades of research.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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